06-82859

Libertad y Orden

REPUBLICA DE COLOMBIA

DIVISION DE PROPIEDAD INDUSTRIAL

PCT

PATENTE DE INVENCION

Industria y Comercio
SUPERINTENDENCIA

06-82859

TITULO Compuestos azufrados como inhibidores de la Serina proteasa NS3 del virus de la hepatitis C

SOLICITANTE SCHERING CORPORATION

DIRECCION 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530, EUA

APODERADO JUAN FAISAL

BOGOTÁ, agosto 22 de 2006

P7006.000176

OLARTERAISBECK 061176

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-082859- -00000-0000
Fec 2006-08-22 16:09:15 Dep 2020 NUECREACIONES
Tra 11 PATENTEIYII
Ene 379 FASENACIONALII
Act 411 PRESENTACION Folios 1432

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	

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2005/005795 Fecha Febrero 24, 2005

Publicación Internacional No. WO 2005/087731 Fecha Septiembre 22, 2005

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

Clasificación Internacional (51) C07D 209/52, 206/56, 491/04, C07K 5/08, 7/02, A61K 31/403, 31/407, A61P 31/12 //(C07D 491/04, 307:00, 209:00.

Prioridad SI [X] NO [ ]

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US	Febrero 27, 2004	60/548,670

(9) **Comprobante de pago No.** 06-63.712 **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).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] 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.

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5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Act: 411 PRESENTACION Folios: 1 a 32

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 000176089-2

RECIBO OFICIAL DE CAJA : 06 - 63,712
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._____

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S D.

Ref.: Nueva solicitud de Patente de Invención titulada: "COMPUESTOS AZUFRADOS COMO INHIBIDORES DE LA 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 EL ANTERIOR ESCRITO DIRIGIDO A

27 FUE PRESENTADO PERSONALMENTE
ANTE EL SEÑOR NOTARIO VEINTISIETE
DE SANTAFE DE BOGOTA POR.

C.C. Y T.P.

Y AFIRMO BAJO LA GRAVEDAD DEL JURAMENTO QUE EL CONTENIDO DE ANTERIOR
DOCUMENTO ES CIERTO Y QUE LA FIRMA Y HUELLA
ALLI CREA FUE PUESTA POR EL.

EL DECLARANTE

HOY 21 JUL. 2006 HUELLA

MARIA EUGENIA ROJAS DE URUETA
NOTARIA VEINTISIETE
REPUBLICA DE COLOMBIA

Comercio

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
Resolucion No 2117 del 7 Oct 1987

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

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

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

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

CERTIFIED

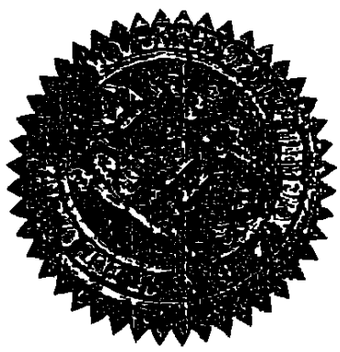
5. AT TRENTON, NEW JERSEY

6. THE 29TH DAY OF AUGUST 2003

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

8. NO. A180345

9. SEAL/STAMP:



10. SIGNATURE

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Power of Attorney

The undersigned,
SCHERING CORPORATION

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

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

Poder

El suscrito,

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

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

Signature/Firma: _____

Edward H. Mazer, Senior Legal Director

Date/Fecha: August 7, 2003

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

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 119 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 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 LaCarte
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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60/548,670 27 February 2004 (27 02 2004) US

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(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

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Declaration under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4 17(iii)) for all designations*

Published:
— *with international search report*

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

(54) Title: SULFUR 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

WO 2005/087731 A1

SULFUR 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 application Serial No. 60/548,670 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.

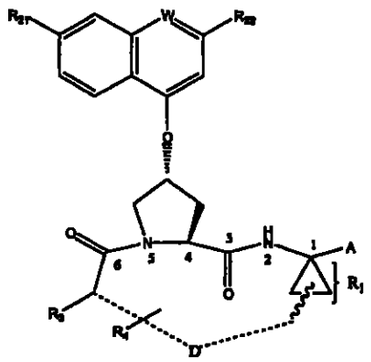
Inhibitors of HCV protease that have been reported include antioxidants (*see*, International Patent Application Publication No. WO 98/14181), certain peptides and peptide analogs (*see*, International Patent Application Publication No. WO 98/17679, Landro et al. (1997) Biochem. 36:9340-9348, Ingallinella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

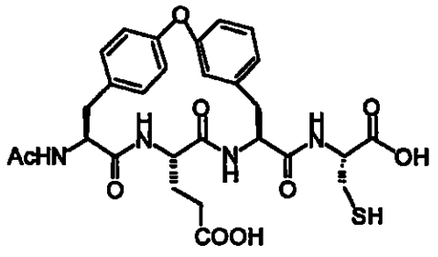
HCV has been implicated in cirrhosis of the liver and in induction of hepatocellular carcinoma. The prognosis for patients suffering from HCV infection is currently poor. HCV infection is more difficult to treat than other forms of hepatitis due to the lack of immunity or remission associated with HCV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

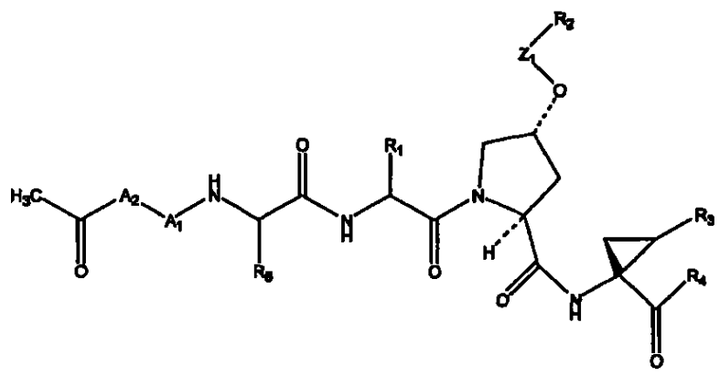


Reference is made to A. Marchetti *et al*, *Synlett*, S1, 1000-1002 (1999) describing the synthesis of bicylic analogs of an inhibitor of HCV NS3 protease. A compound disclosed therein has the formula:

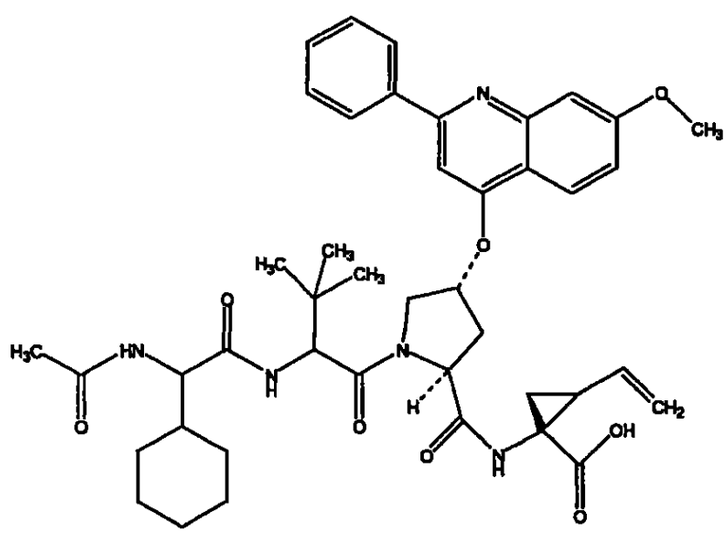


Reference is also made to W. Han *et al*, *Bioorganic & Medicinal Chem. Lett*, (2000) 10, 711-713, which describes the preparation of certain α-ketoamides, α-ketoesters and α-diketones containing allyl and ethyl functionalities.

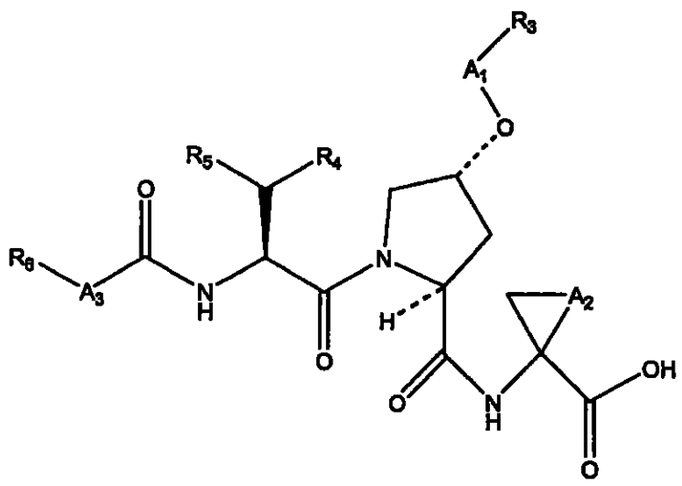
Reference is also made to WO 00/09558 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:



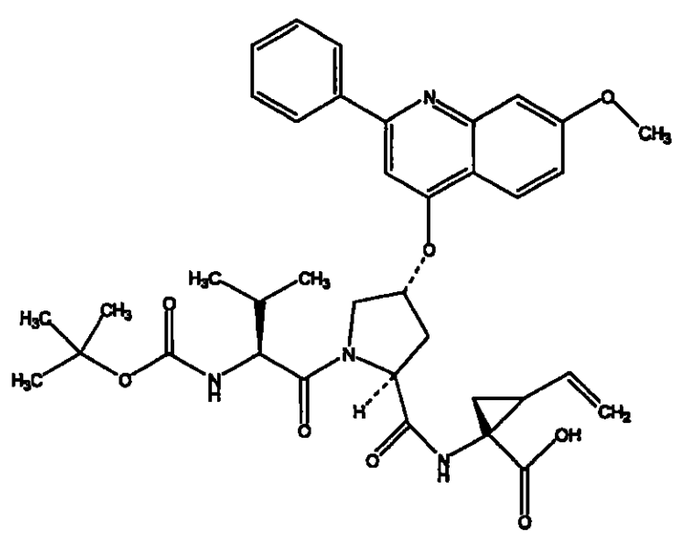
where the various elements are defined therein. An illustrative compound of that series is:



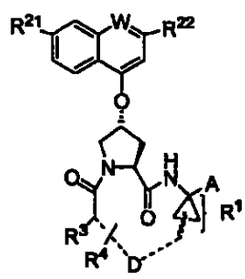
Reference is also made to WO 00/09543 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:



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



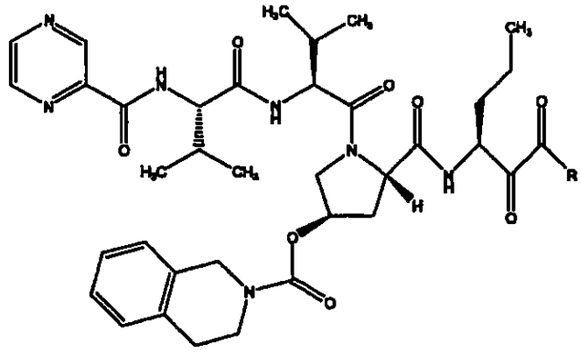
Reference is also made to U.S. 6,608,027 (Boehringer Ingelheim, Canada) which discloses NS3 protease inhibitors of the type:



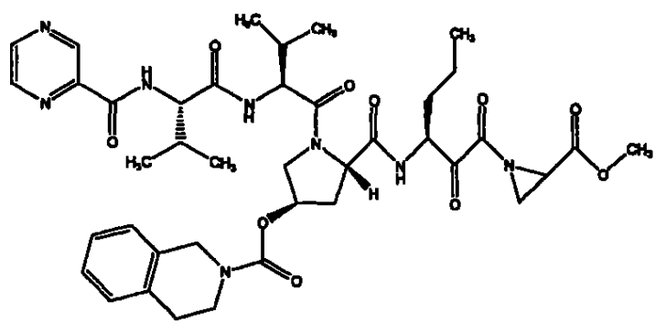
wherein the various moieties are defined therein.

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.

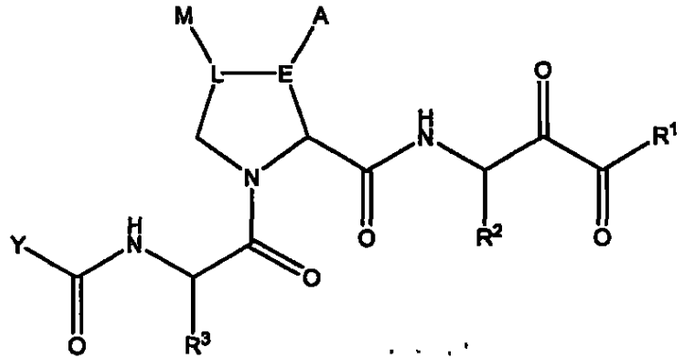
There is a need for methods for modulating the activity of serine proteases, particularly the HCV NS3/NS4a serine protease, using the compounds provided herein.

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, as well as pharmaceutically acceptable salts, solvates or esters of said compounds, said compounds having the general structure shown in structural Formula I:

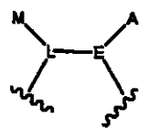


Formula I

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 molety:



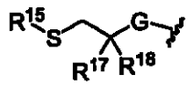
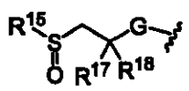
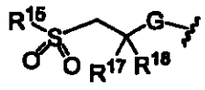
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

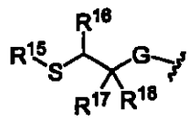
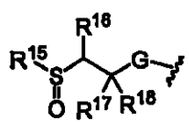
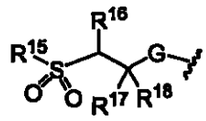
E is C(H) or C(R);

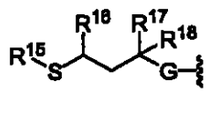
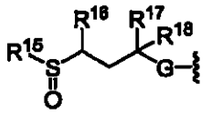
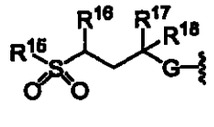
L is C(H), C(R), $CH_2C(R)$, or $C(R)CH_2$;

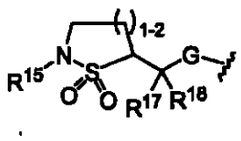
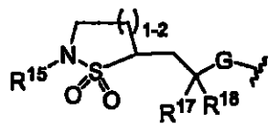
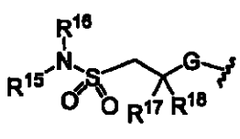
R, R', R^2, and R^3 can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, cycloalkyl-, heteroalkyl-, heterocyclyl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocyclyl)alkyl-, aryl-alkyl-, and heteroaryl-alkyl-; or alternately R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


,

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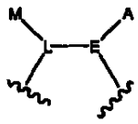

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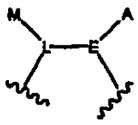

,

and

.

wherein G is NH or O; and R^{15}, R^{16}, R^{17} and R^{18} 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) R^{15} and R^{16} 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.

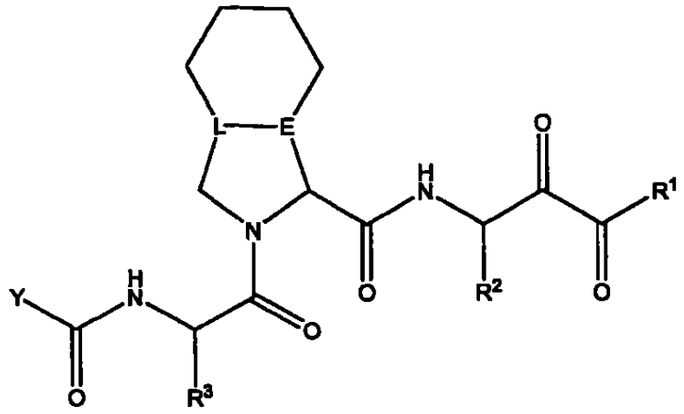
The above-noted statement "A and M are connected to each other such that the moiety:



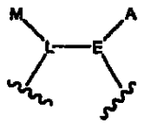
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl" can be illustrated in a non-limiting manner as follows. Thus, for example, in the case where A and M are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



(M-L-E-A taken together) 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 "alternately, (i) R^{15} and R^{16} 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 form a three to eight-membered cycloalkyl or heterocyclyl" means the following possibilities: (i) R^{15} and R^{16} are connected to form a cyclic structure while R^{17} and R^{18} are not; (ii) R^{17} and R^{18} are connected to form a cyclic structure while R^{15} and R^{16} are not; and (iii) R^{15} and R^{16} are connected to form a cyclic structure, *and* R^{17} and R^{18} are also

connected to form a cyclic structure. These possibilities can occur independent of one another.

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.

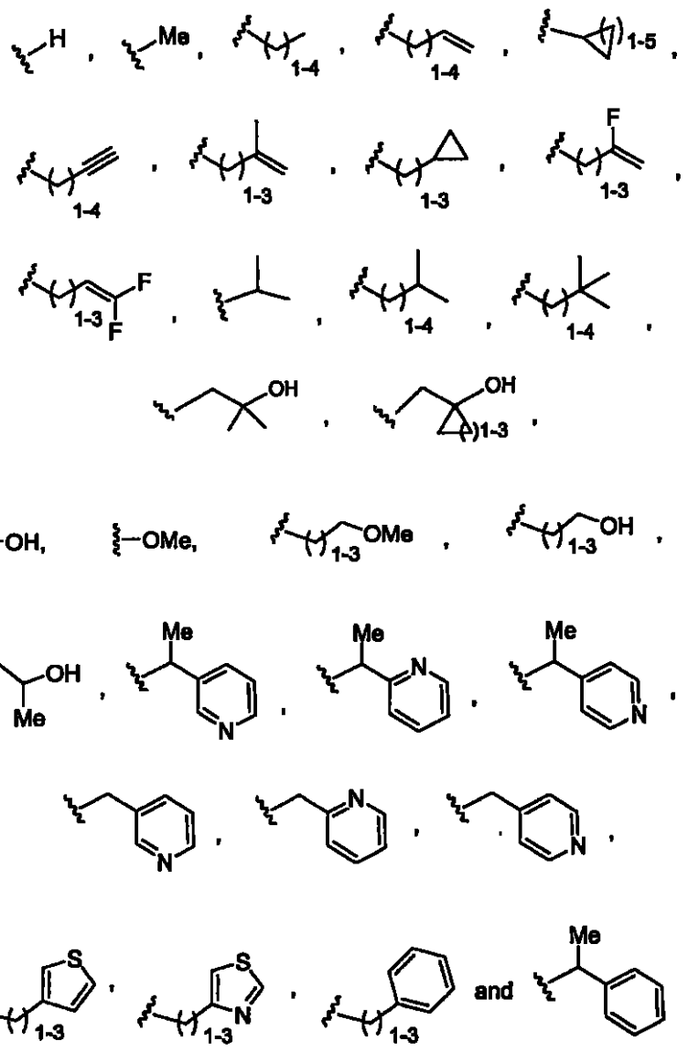
The compounds represented by Formula I, by themselves or in combination with one or more other suitable agents disclosed herein, can be useful for treating diseases such as, for example, HCV, HIV, (AIDS, Acquired Immune Deficiency Syndrome), and related disorders, as well as for modulating the activity 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.

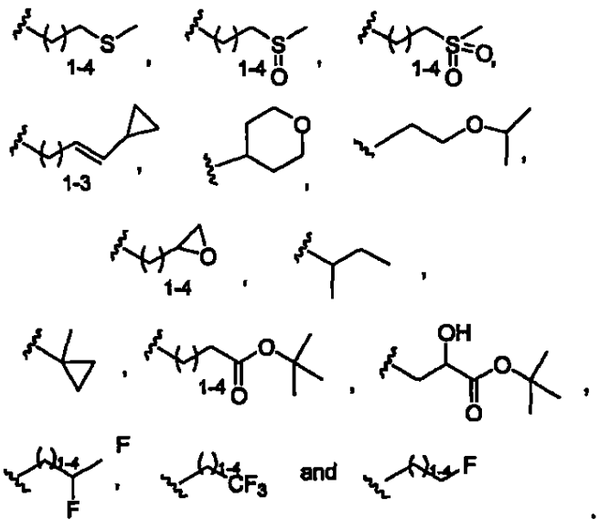
Detailed Description

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

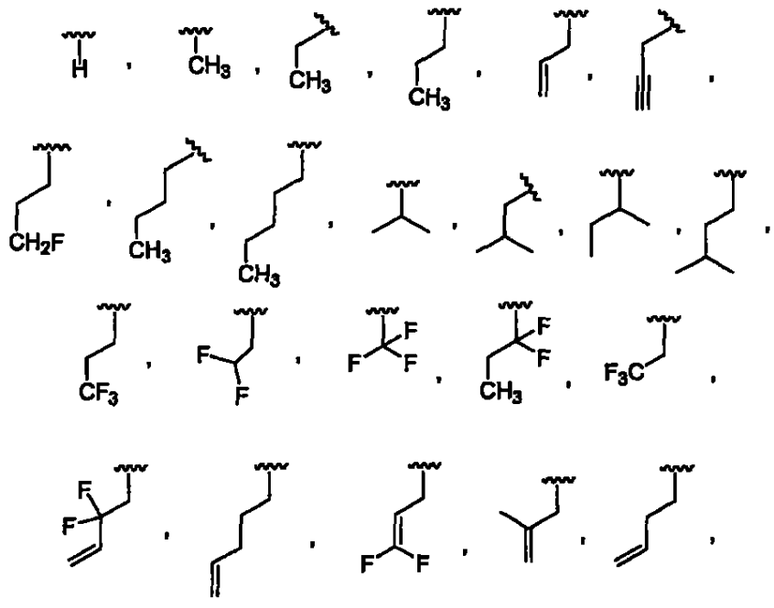
In another embodiment, R^1 is NR^9R^{10}, and R^9 is H, R^{10} is H, or R^{14} wherein R^{14} is H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl, alkenyl, alkynyl or heteroaryl-alkyl.

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

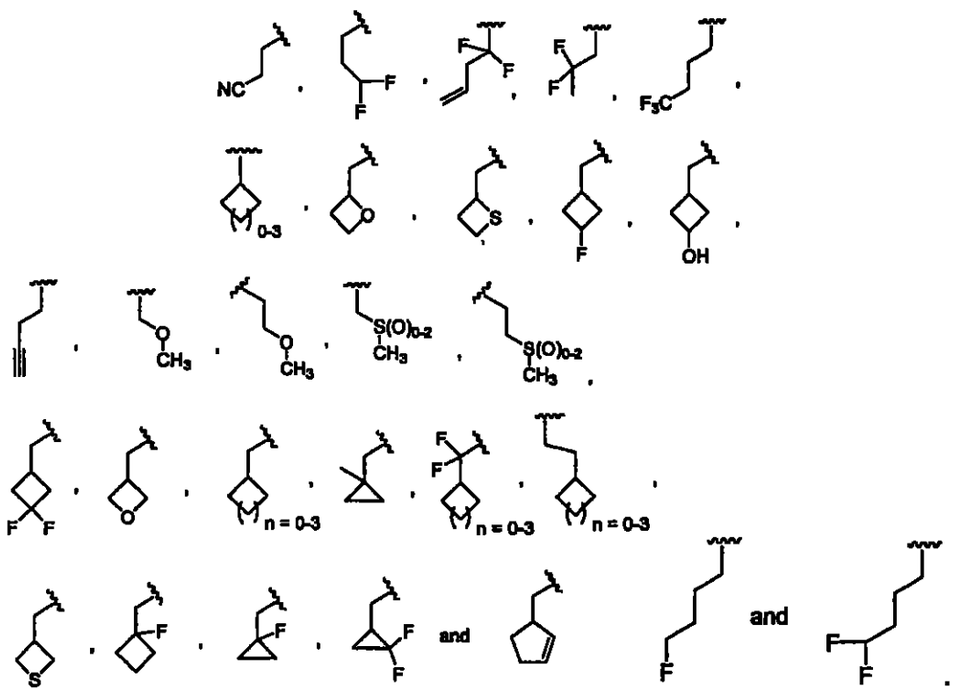

H
Me
1-4
1-4
1-5
1-4
1-3
1-3
F
1-3
F
F
1-3
1-4
1-4
OH
OH
1-3
OH,
OMe,
OMe
1-3
OH
1-3
OH
Me
Me
N
Me
N
Me
N
N
N
N
S
1-3
S
N
1-3
1-3
and
Me



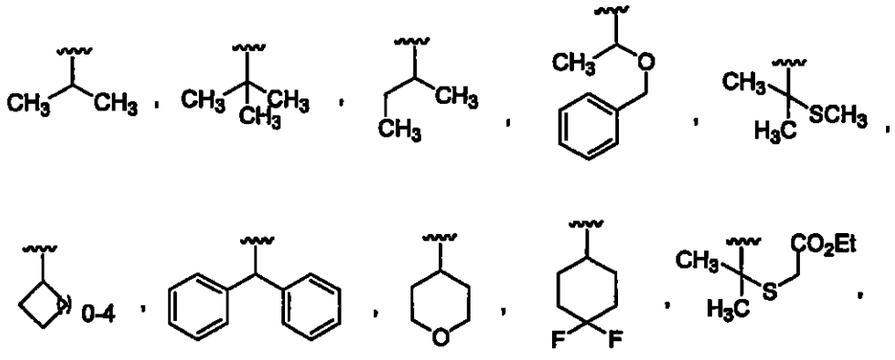
In another embodiment, R^2 is selected from the group consisting of the following moieties:

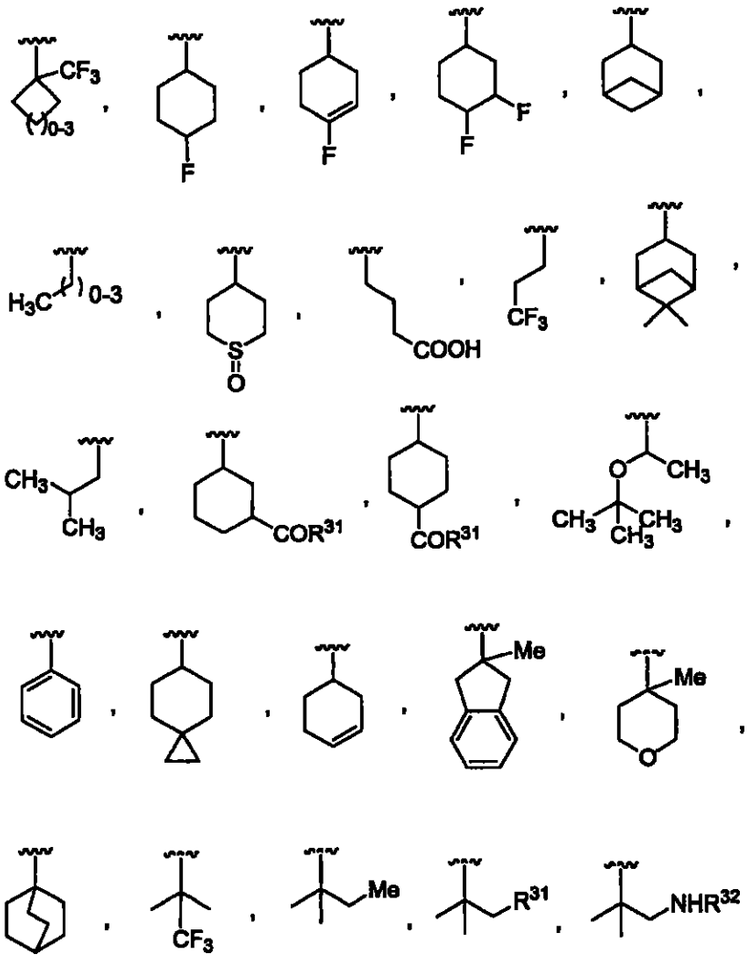


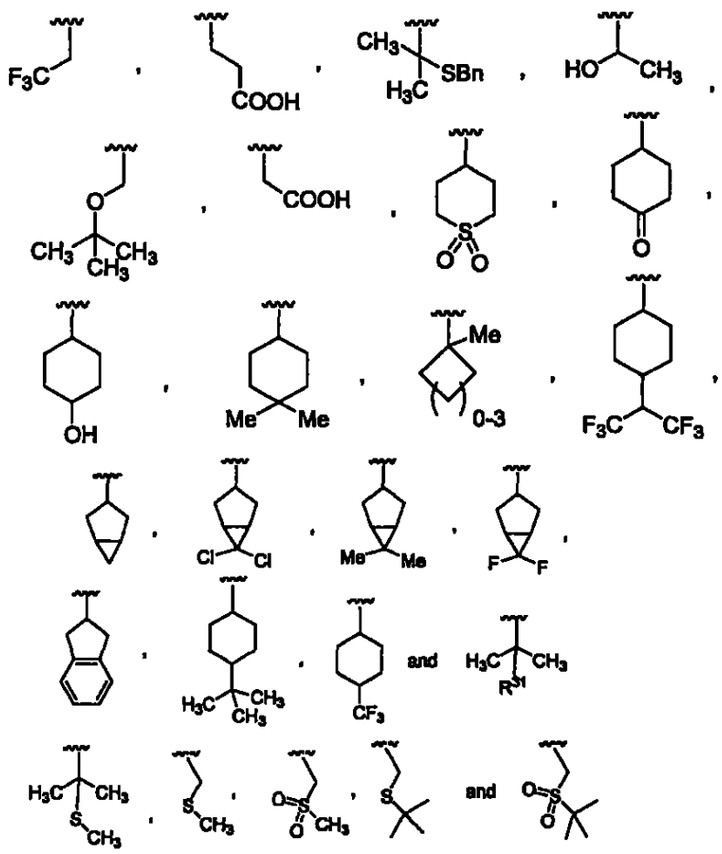
5



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



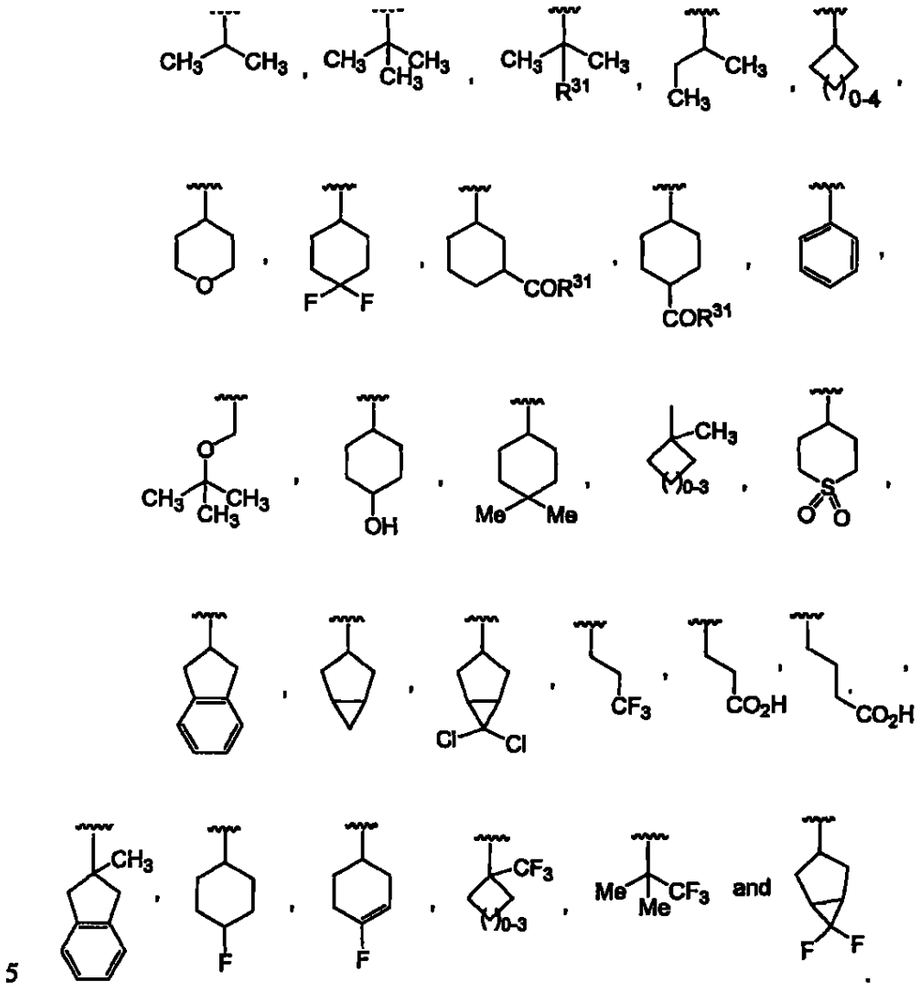

CF3
(CH2)0-3
F
F
F
F
H3C(CH2)0-3
S
O
COOH
CF3
CH3
CH3
COR31
COR31
O
CH3
CH3
CH3
CH3
Me
Me
O
CF3
Me
R31
NHR32



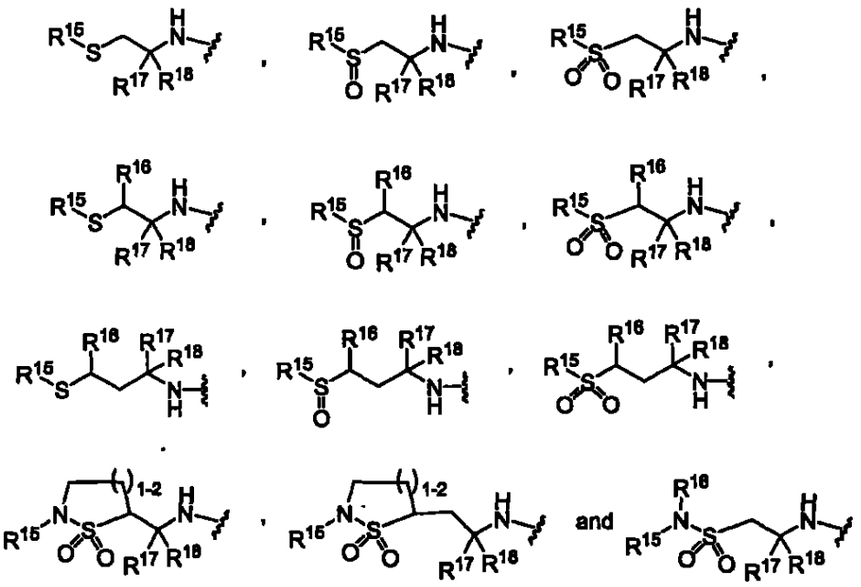
wherein R^{31} is OH or O-alkyl; and

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

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

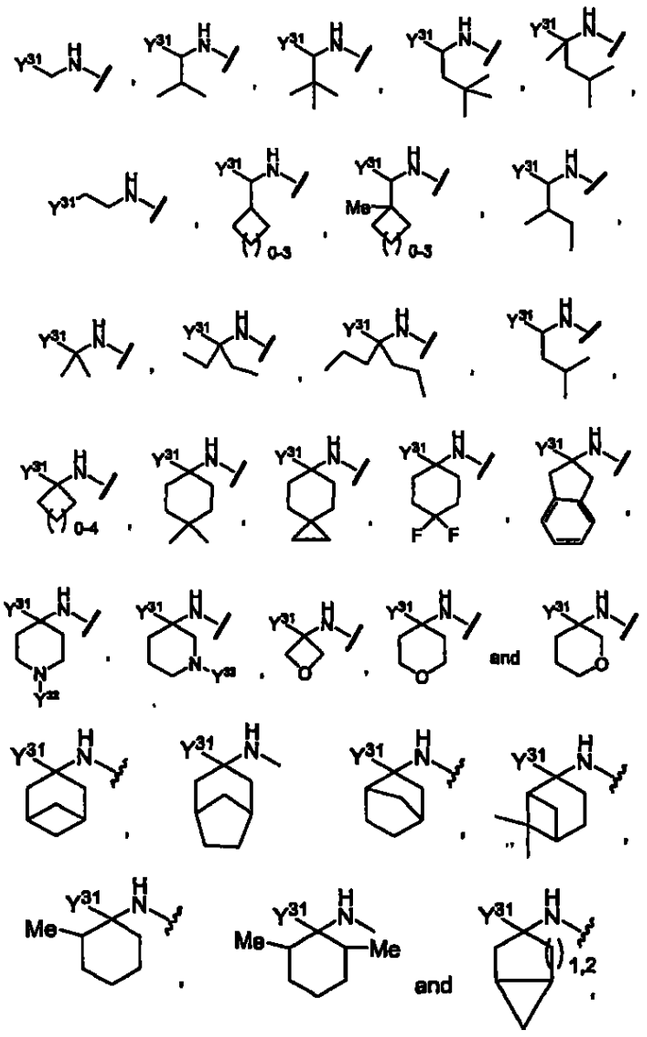


In another embodiment, Y is selected from the following moieties:

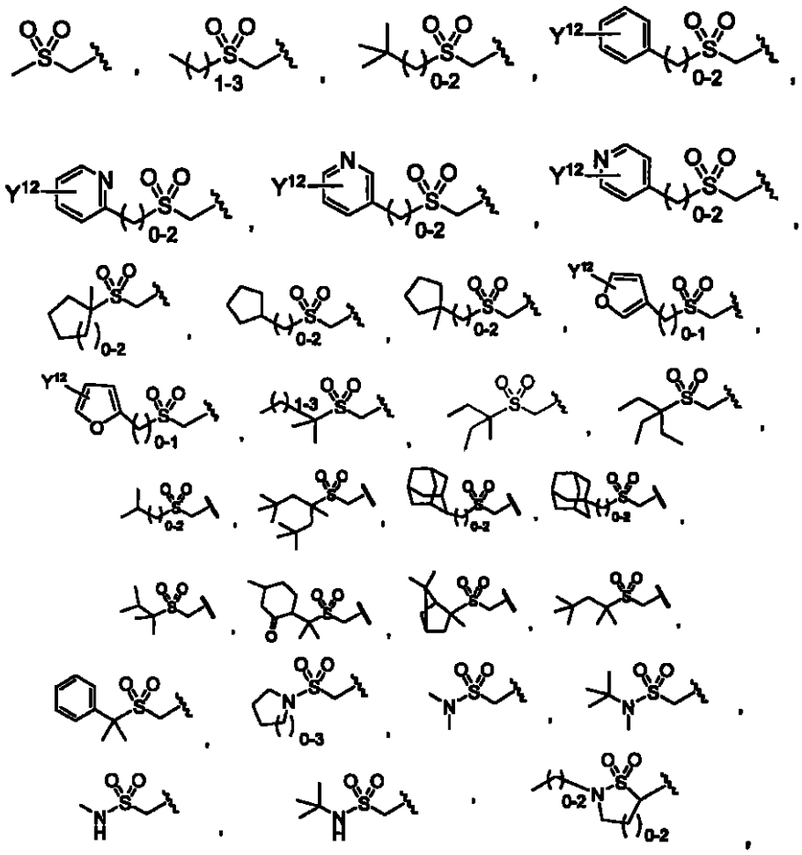


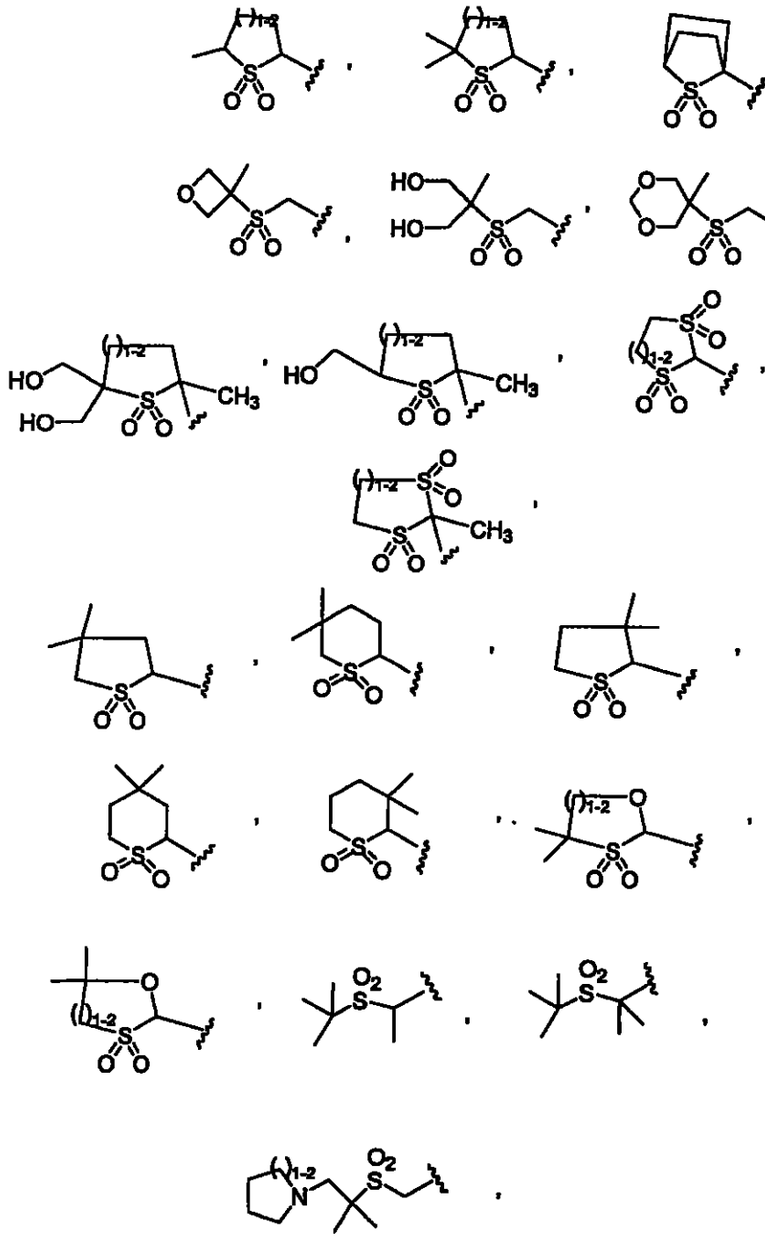
wherein R^{15}, R^{16}, R^{17} and R^{18} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, or alternately, R^{15} and R^{16} are connected to each other to form a four to eight-membered cycloalkyl or heterocyclic structure, and/or R^{17} and R^{18} are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl, wherein each of said 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, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

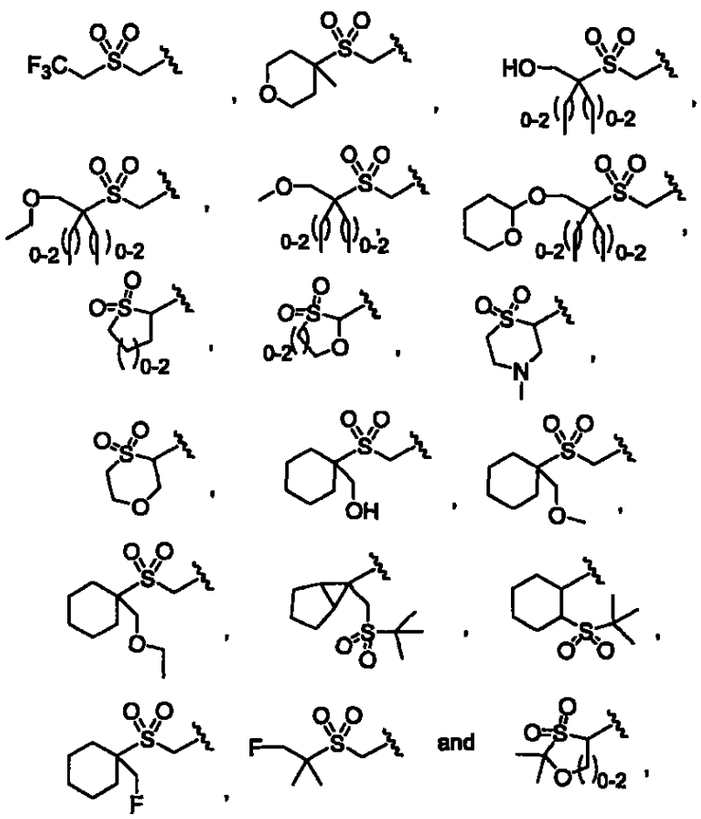
In an additional embodiment, Y is selected from the group consisting of:



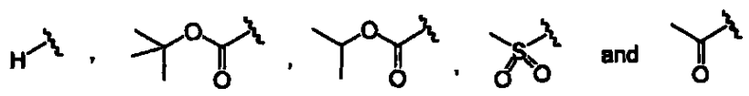
wherein Y^{31} is selected from the group consisting of:





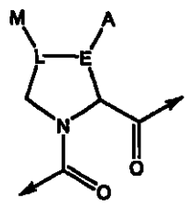


Y^{32} is selected from the group consisting of:

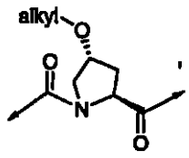
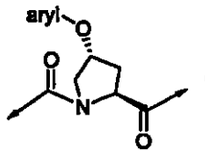
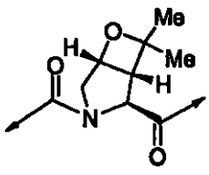
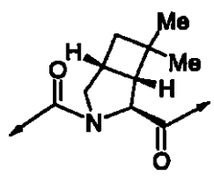
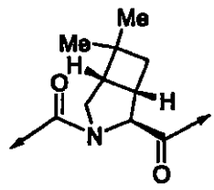
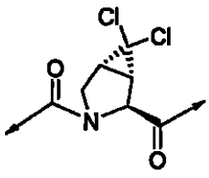
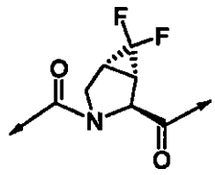
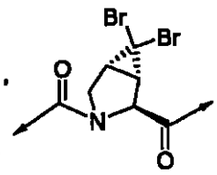
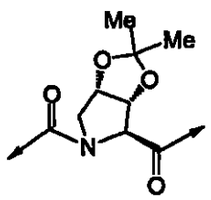


and Y^{12} is selected from the group consisting of H, CO_2H, CO_2Me, OMe, F, Cl, Br, NH_2, $N(H)S(O_2)CH_3$, $N(H)C(O)CH_3$, NO_2, $S(O_2)NH_2$, CF_3, Me, OH, OCF_3, and $C(O)NH_2$.

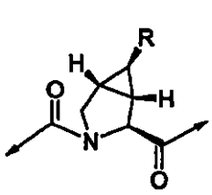
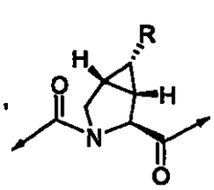
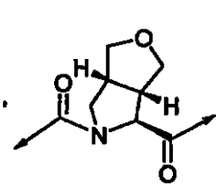
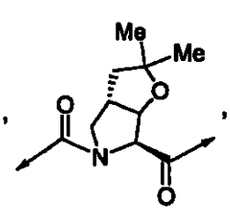
In another embodiment, the moiety:

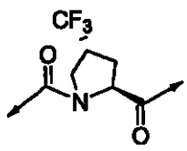


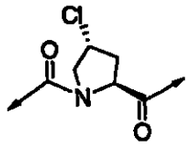
is selected from the following structures:

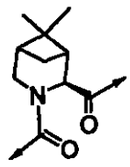










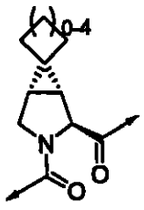
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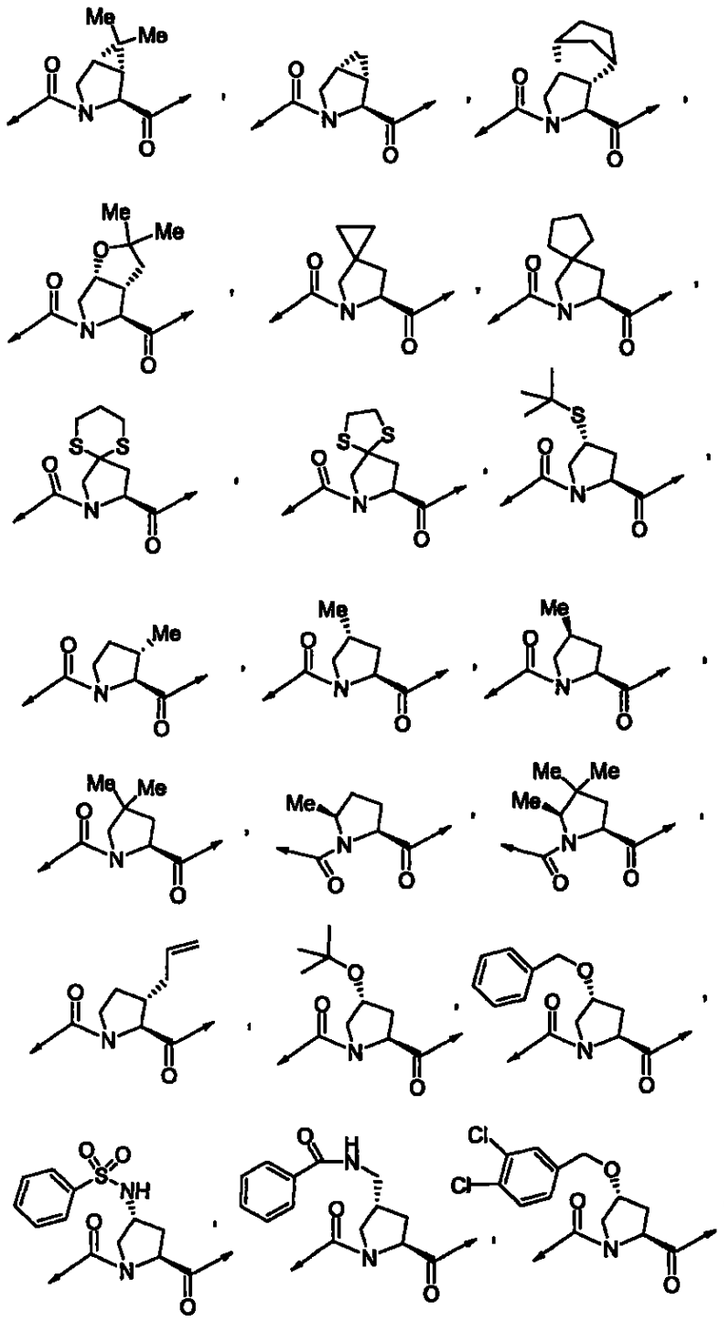





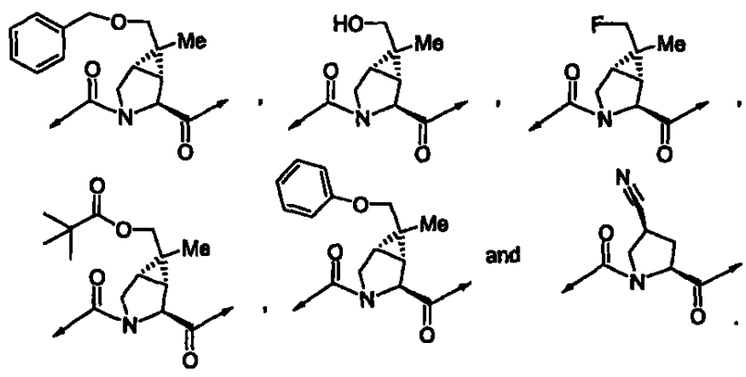

CF3
O
N
O


Cl
O
N
O

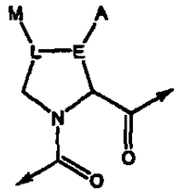

N
O
O


0-4
N
O
O

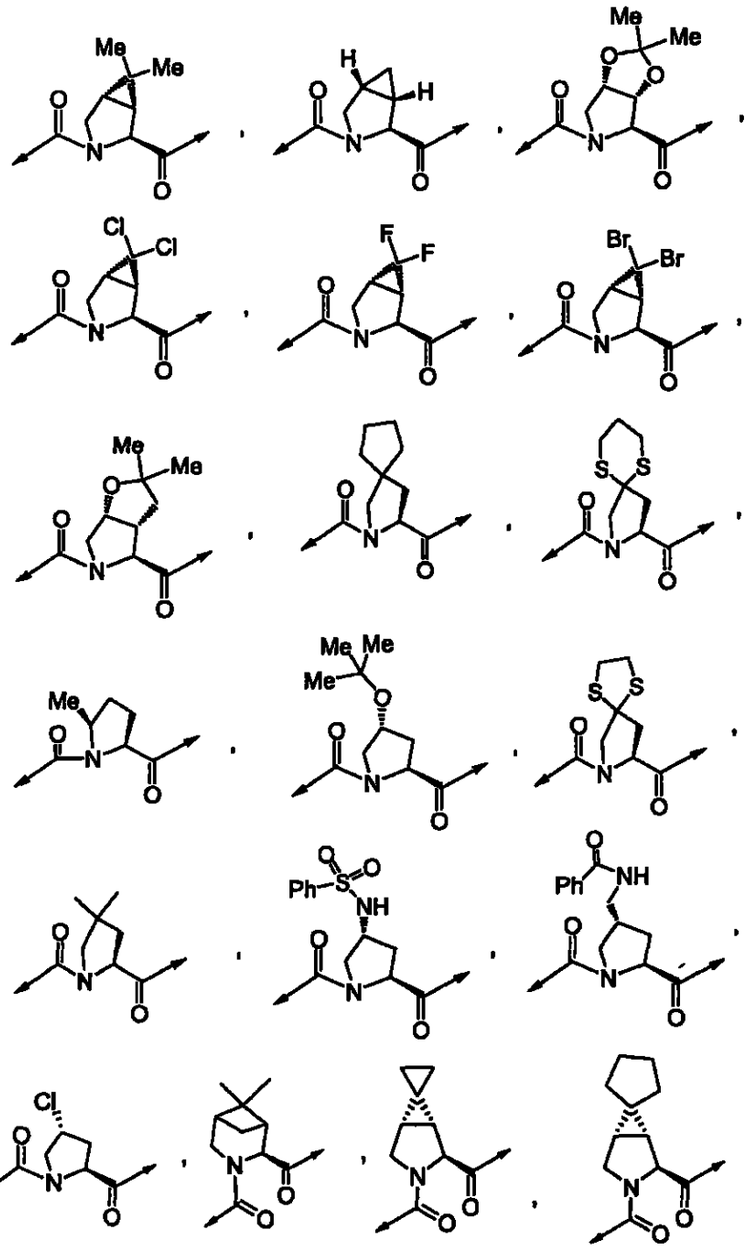


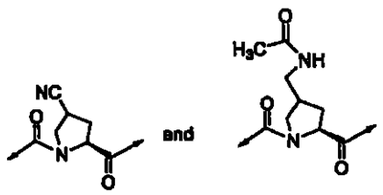


In an additional embodiment, the moiety:

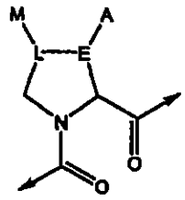


is selected from the following structures:

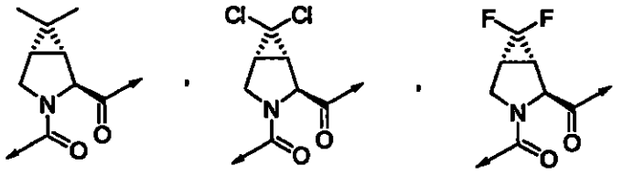

Me
Me
H
H
Me
Me
Cl
Cl
F
F
Br
Br
Me
Me
S
S
Me
Me
Me
S
S
Ph
S
NH
Ph
NH
Cl

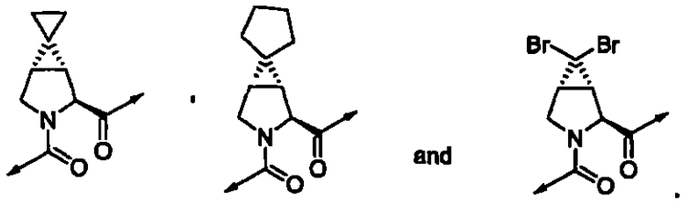


In an additional embodiment, the moiety:

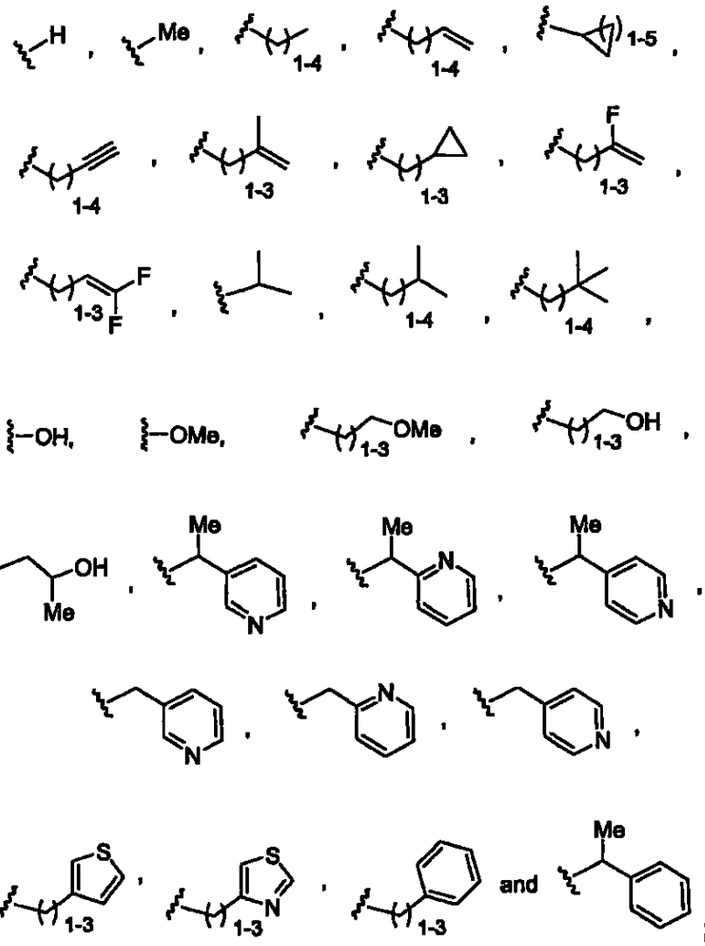


is selected from the following structures:

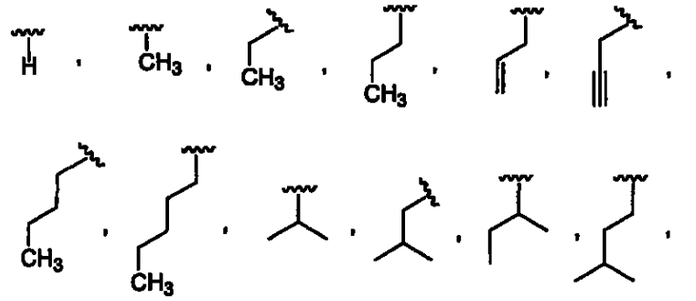


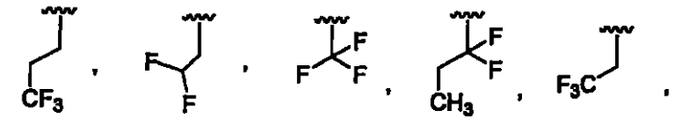


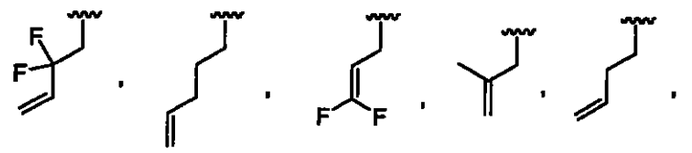
In a still additional embodiment, R^1 is NHR^{14}, where R^{14} is selected from the group consisting of:

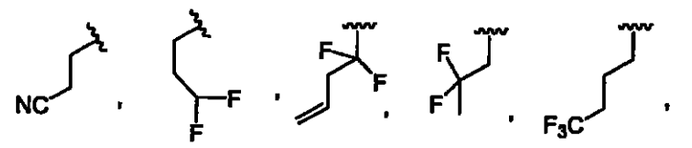


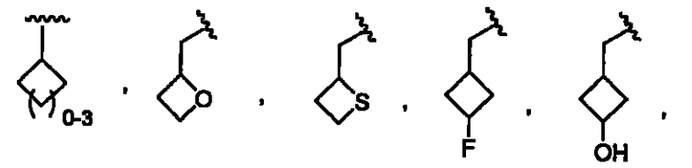
R^2 is selected from the group consisting of the following moieties:



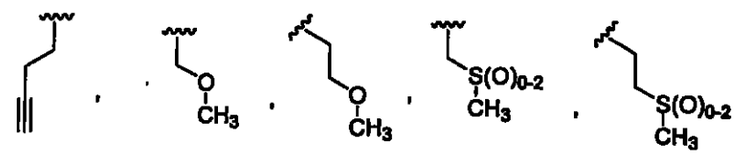

CF3
F
F
F
F
F
F
CH3
F3C

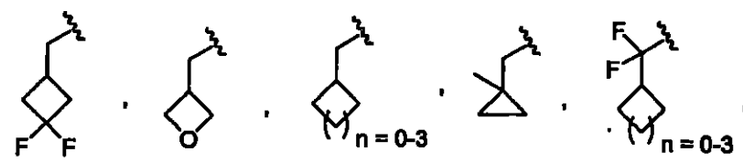

F
F
F
F

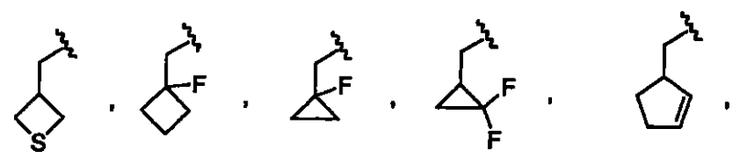

NC
F
F
F
F
F
F
F3C


0-3
O
S
F
OH

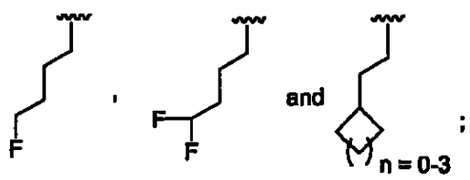
5


O
CH3
O
CH3
S(O)0-2
CH3
S(O)0-2
CH3

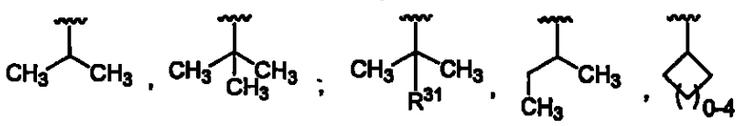

F
F
O
n = 0-3
F
F
n = 0-3

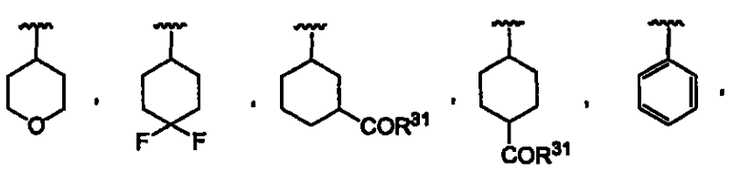

S
F
F
F
F

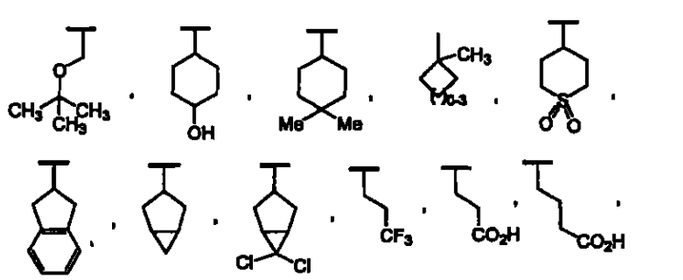
;

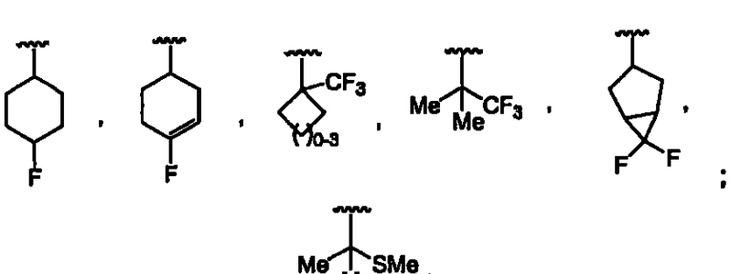


R^3 is selected from the group consisting of the following moieties:

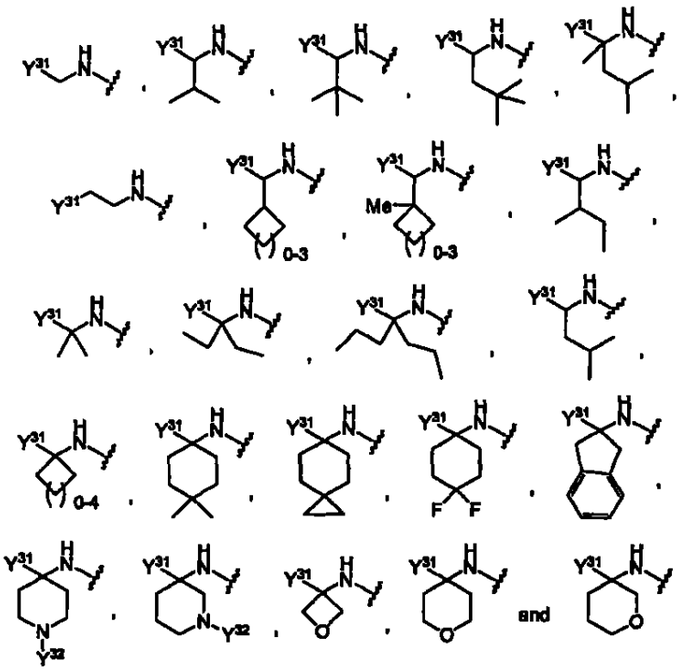




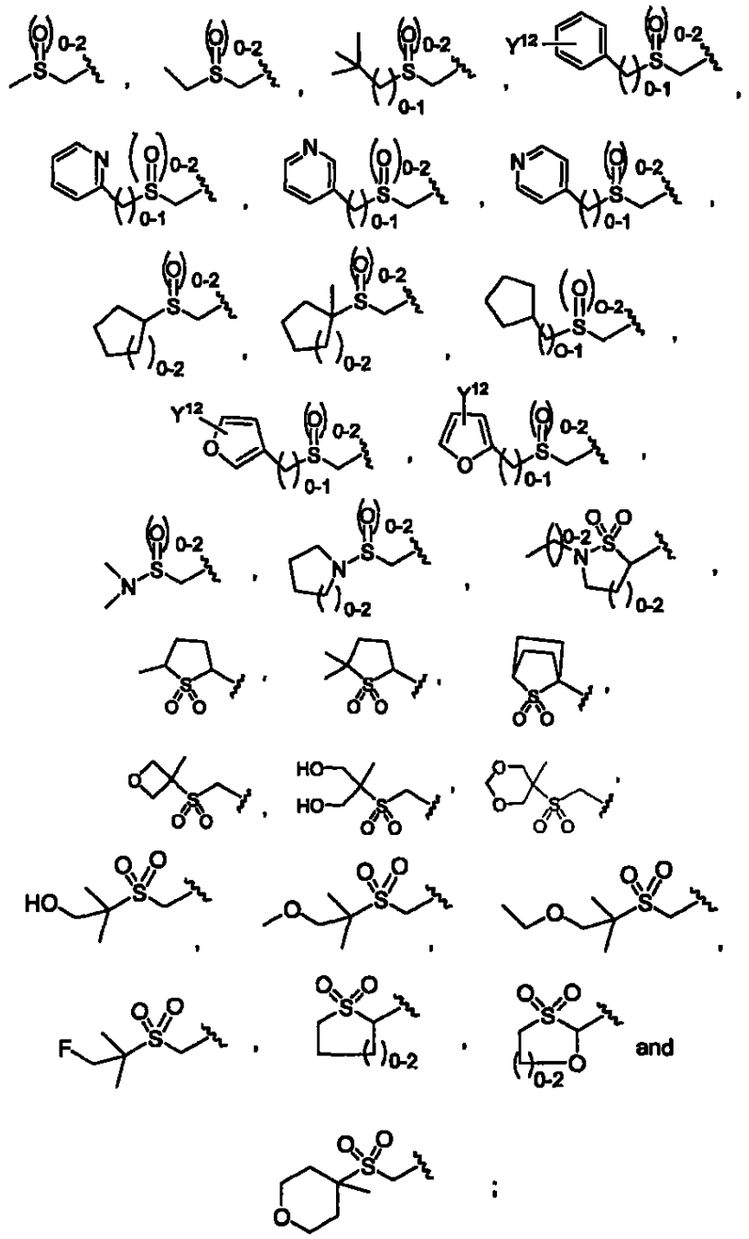




Y is selected from the group consisting of:



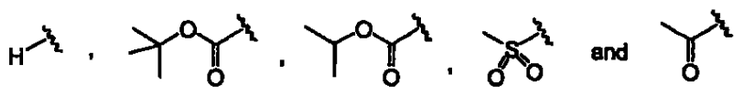
wherein Y^{31} is selected from the group consisting of:



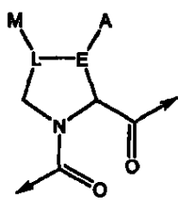
and

;

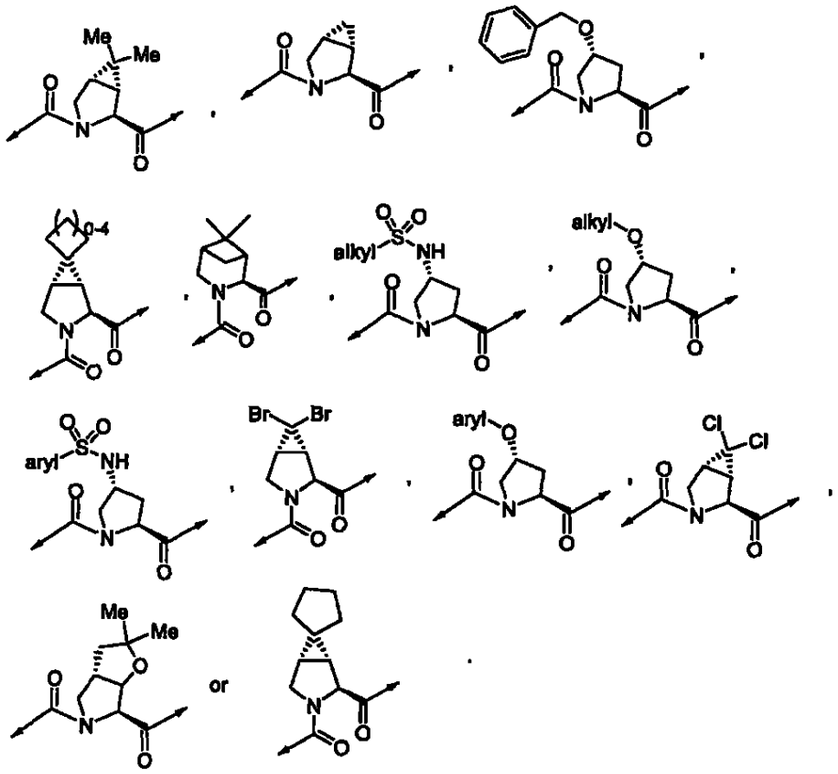
Y^{32} is selected from the group consisting of:



and Y^{12} is selected from the group consisting of H, CO_2H, CO_2Me, OMe, F, Cl, Br, NH_2, $N(H)S(O_2)CH_3$, $N(H)C(O)CH_3$, NO_2, $S(O_2)NH_2$, CF_3, Me, OH, OCF_3, and $C(O)NH_2$; and the moiety:

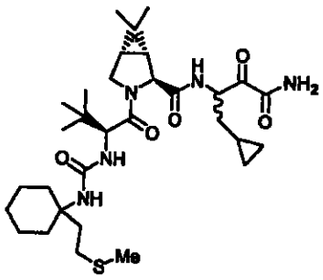


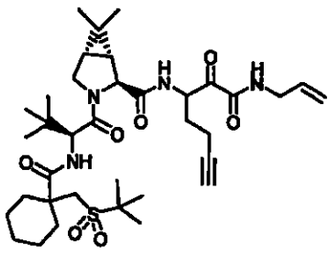
is:

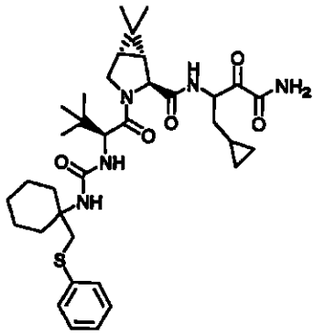


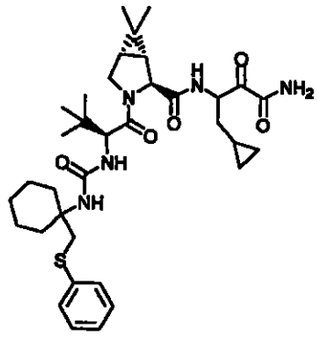
Yet another embodiment of the invention discloses compounds in **Table 1** below, as well as shown later in **Table 1, Table 3, Table 3A, Table 4, Table 4A** and **Table 5**:

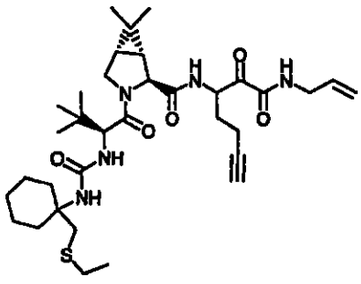
Table 1

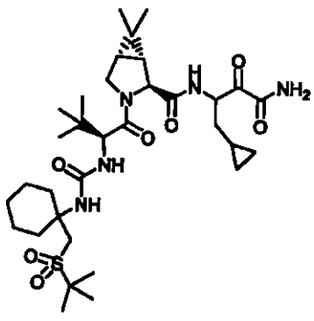


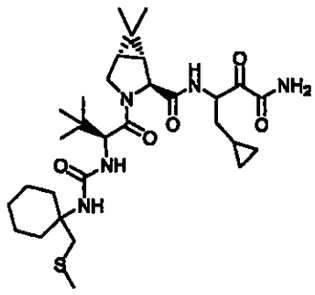


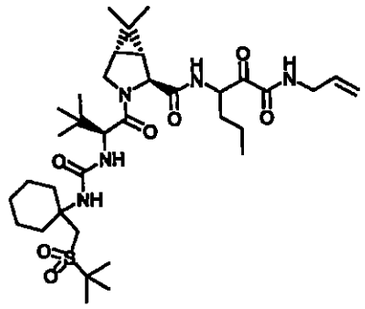


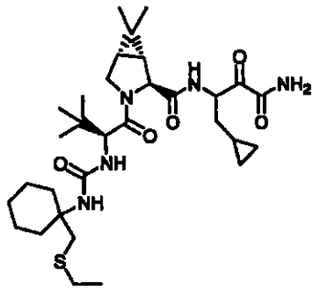


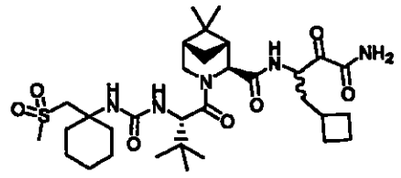


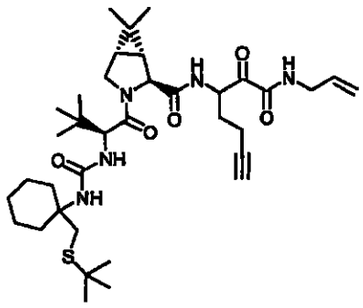


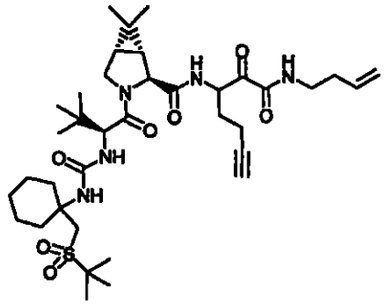


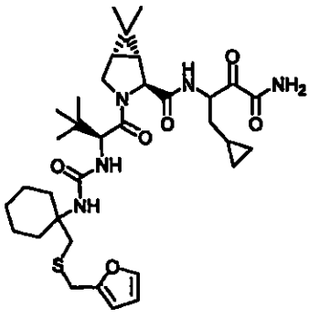


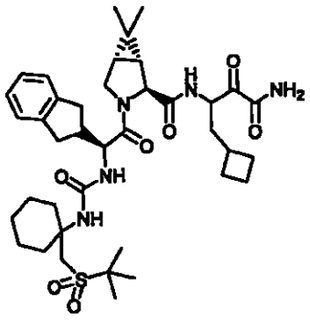


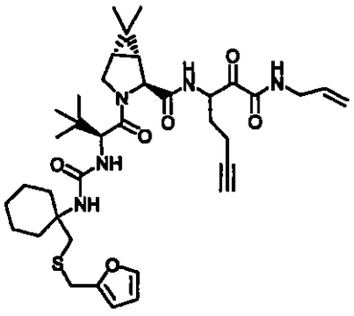


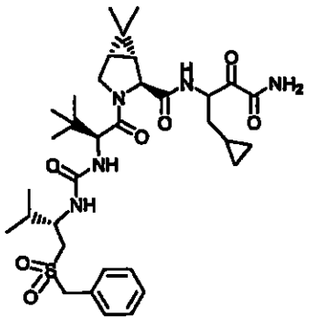


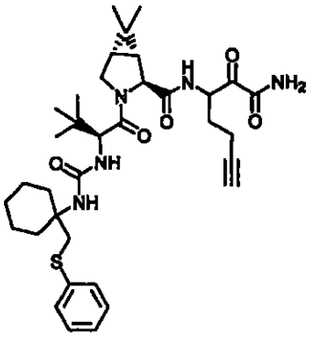


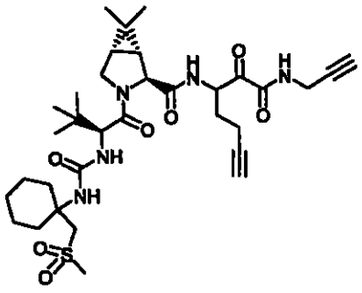


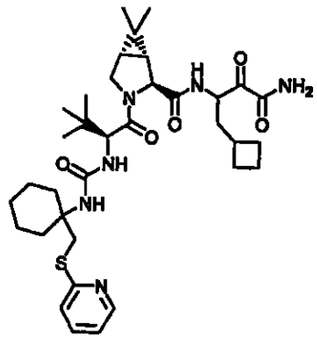


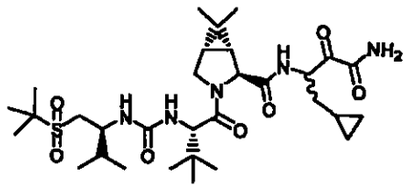


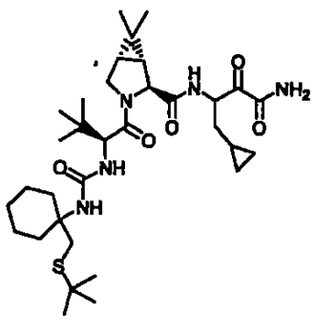


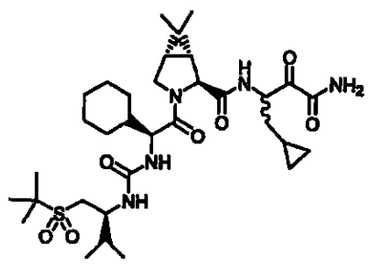


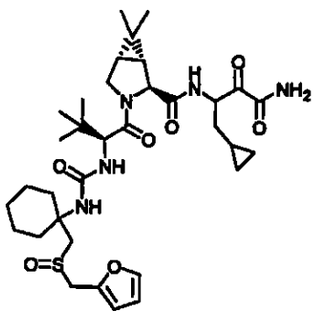


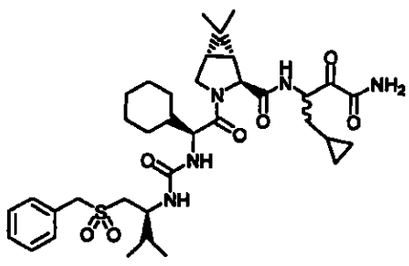


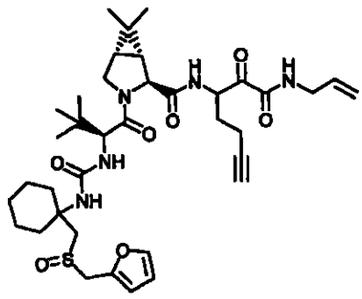


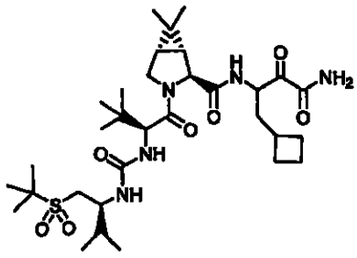


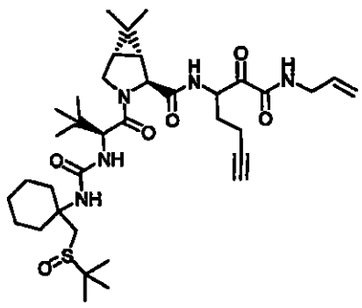


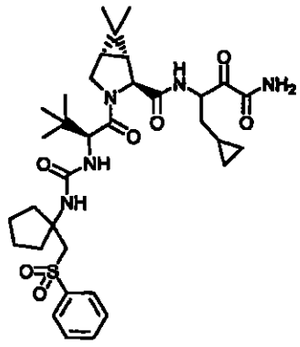


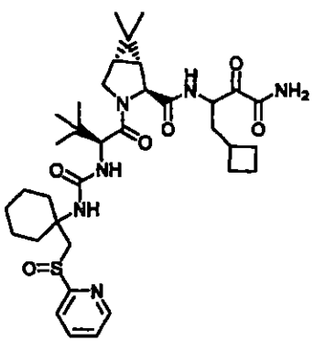


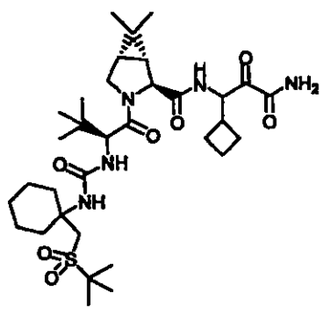


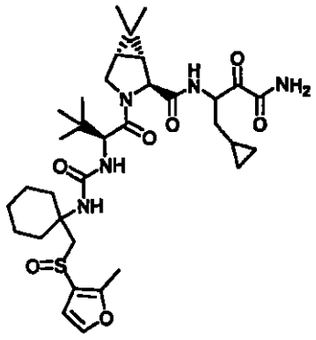


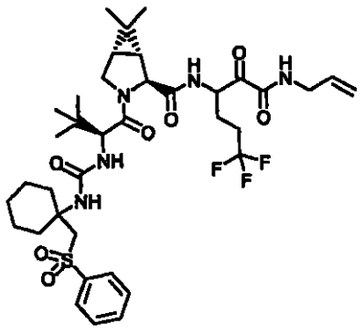


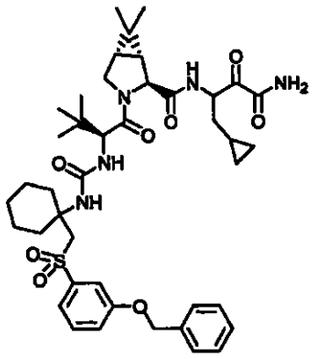


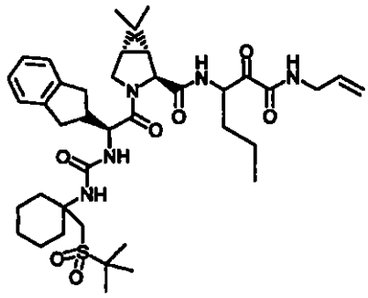


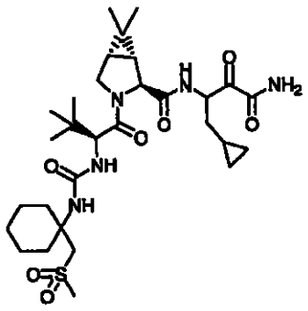


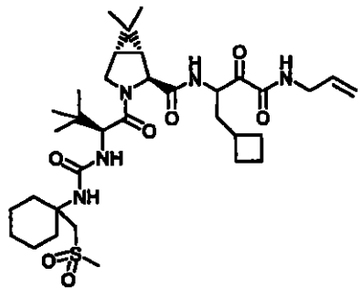


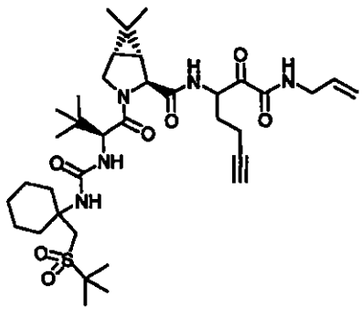


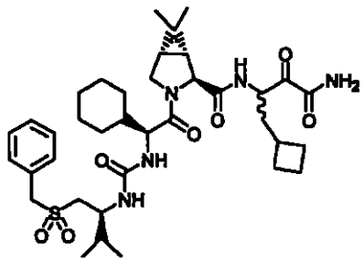


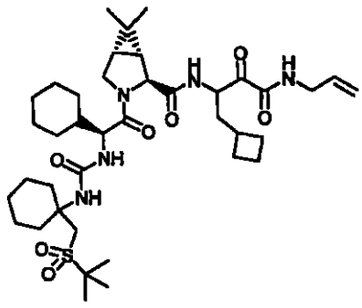


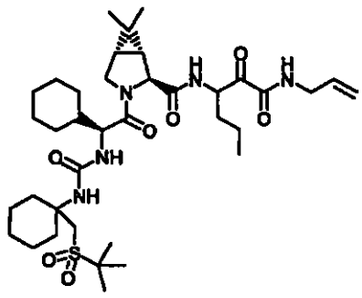


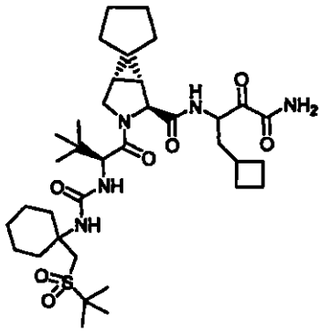


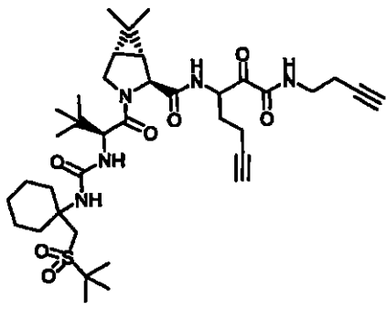


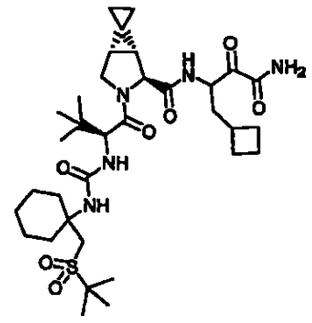


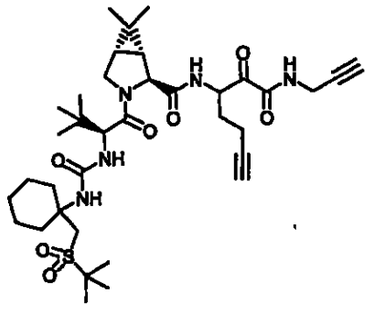


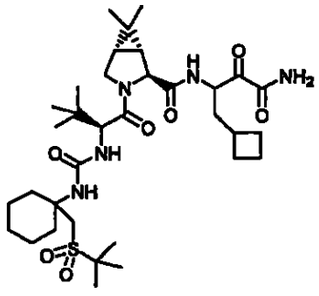


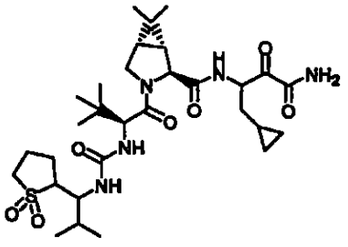


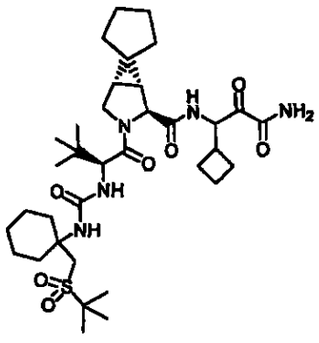


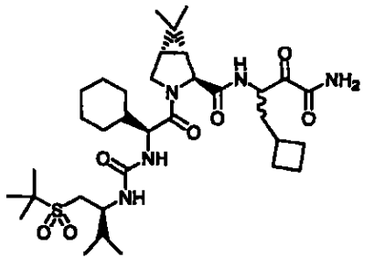


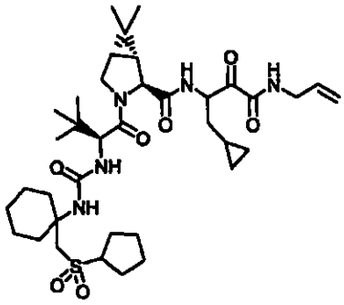


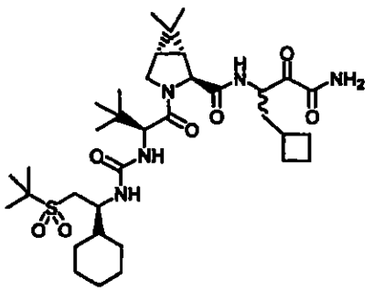


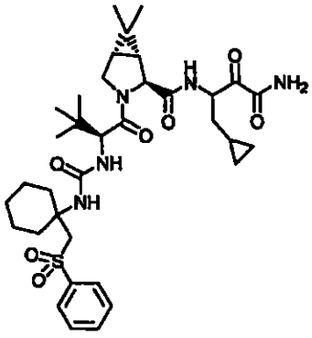


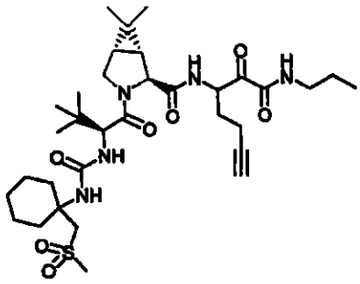


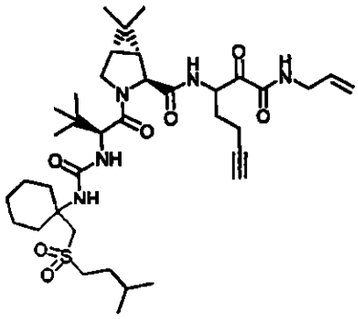


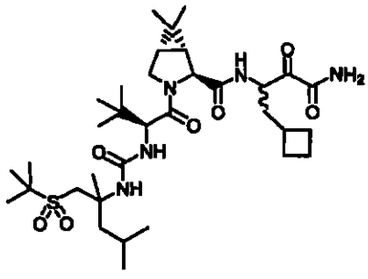


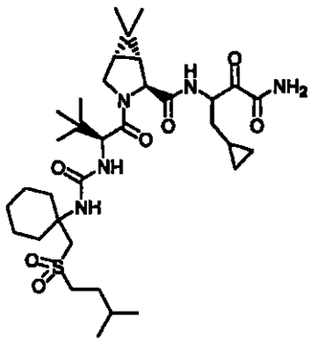


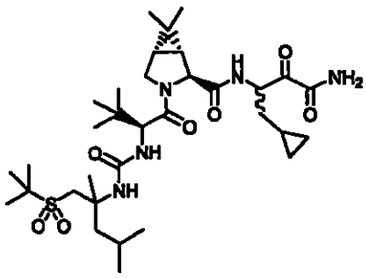


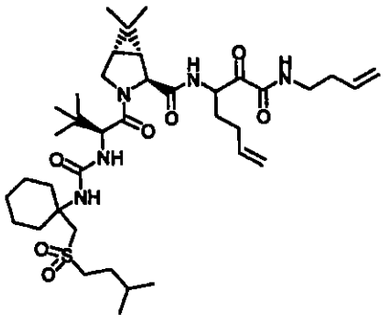


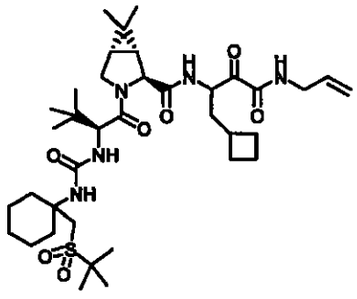


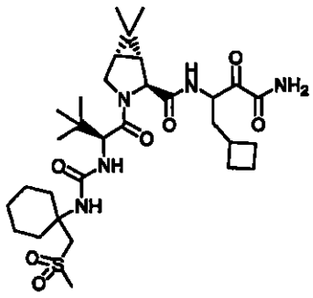


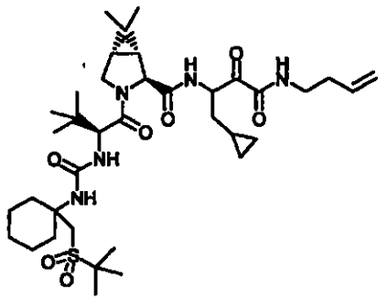


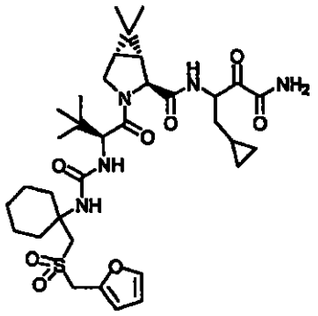


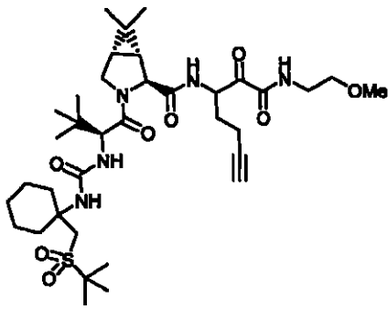


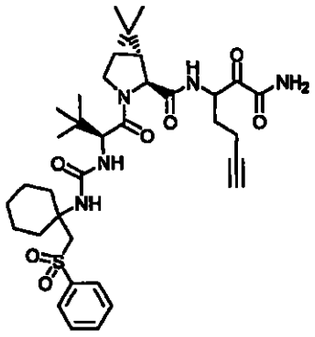


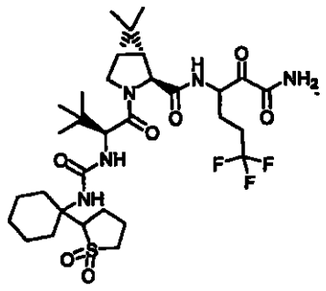


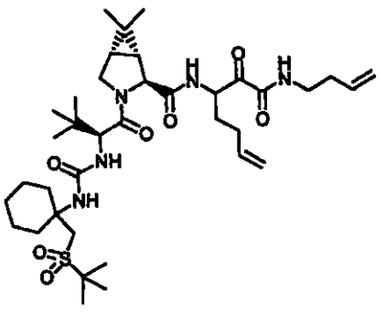


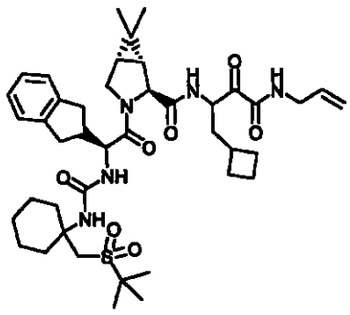


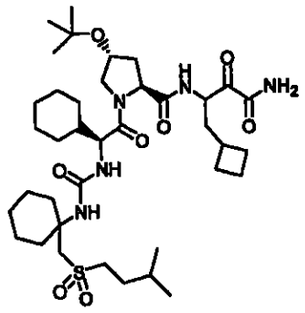


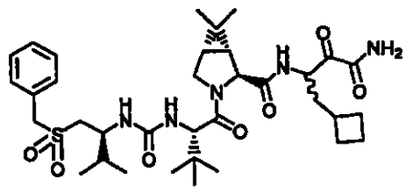


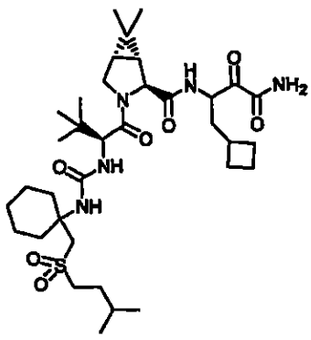


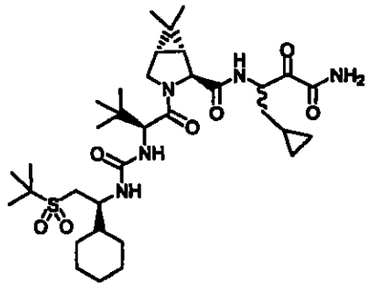


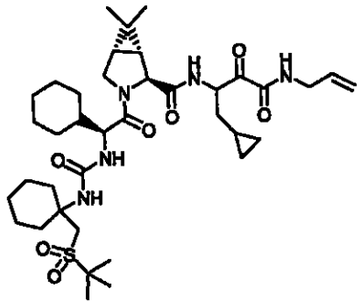


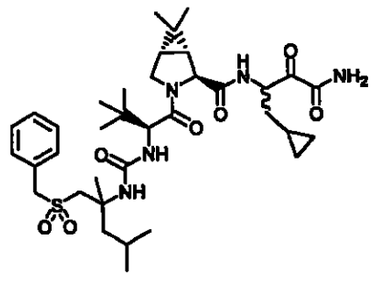


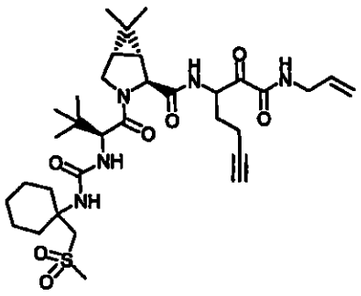


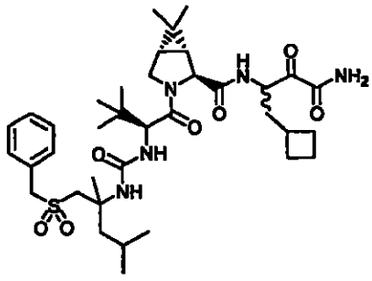


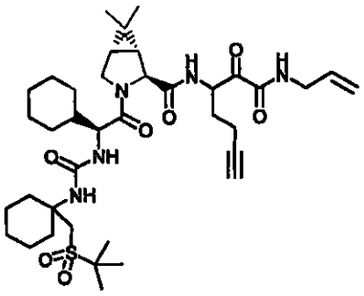


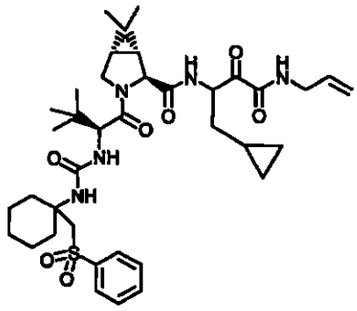


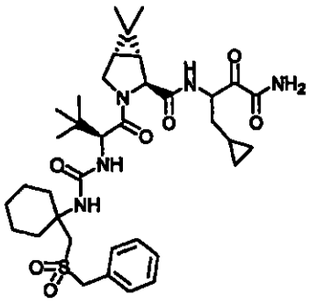


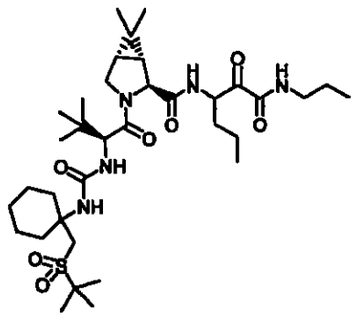


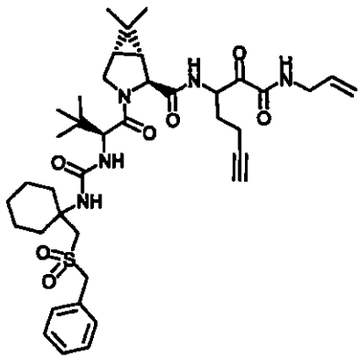


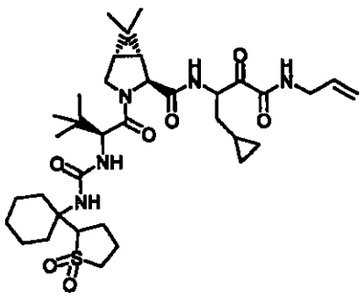


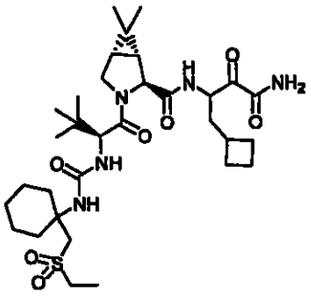


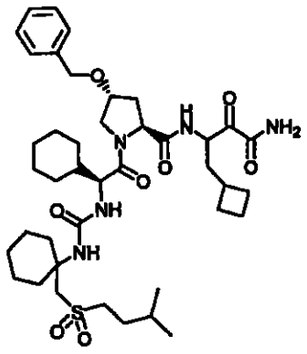


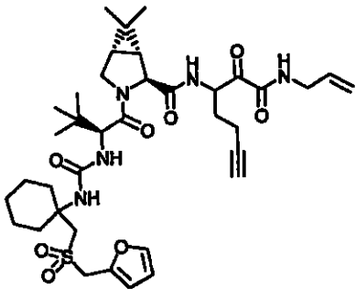


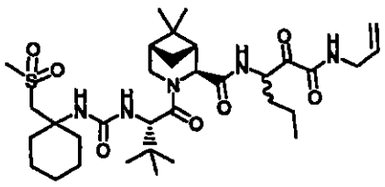


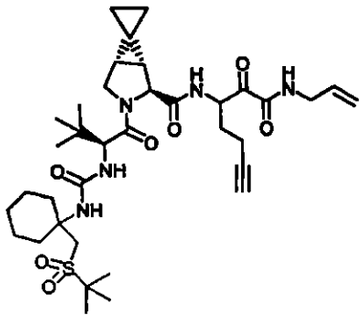


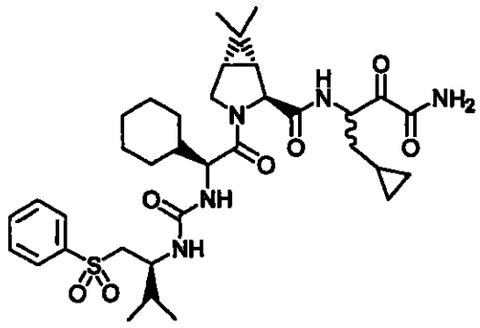


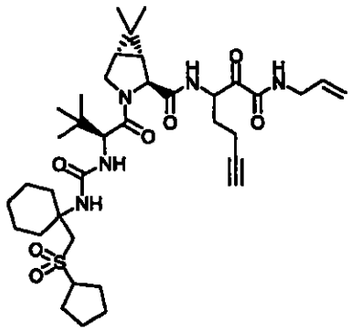


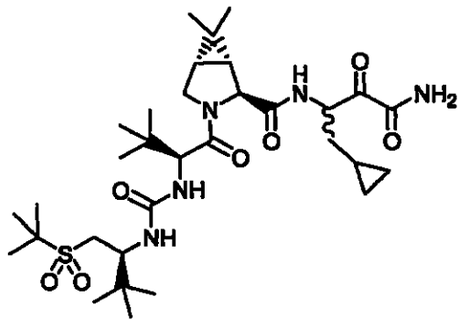


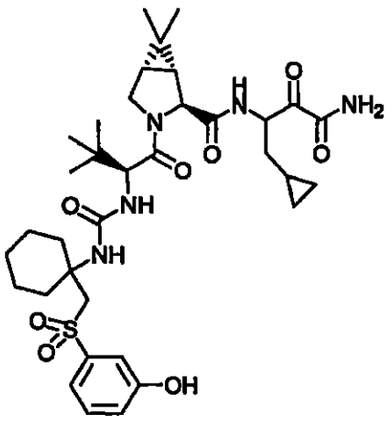


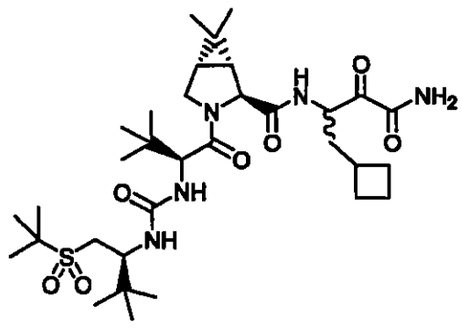


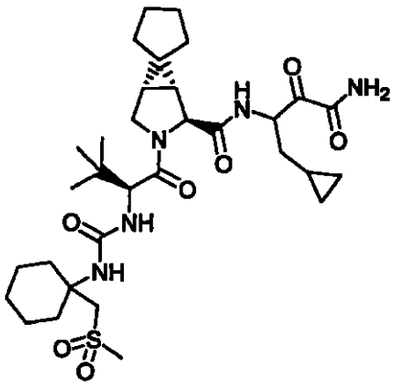


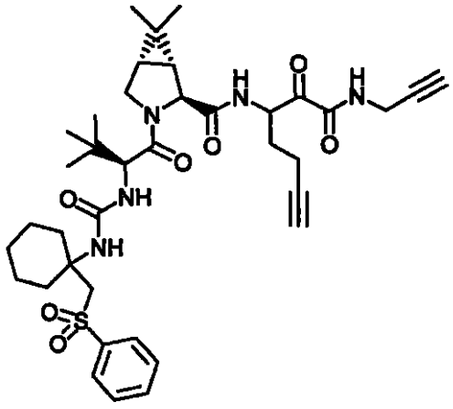


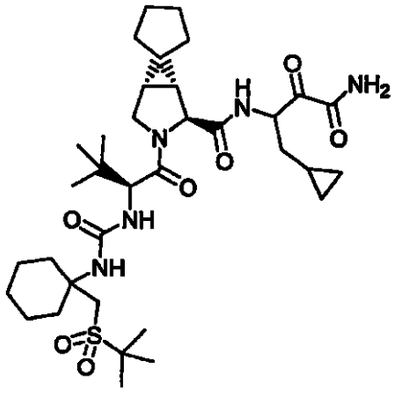


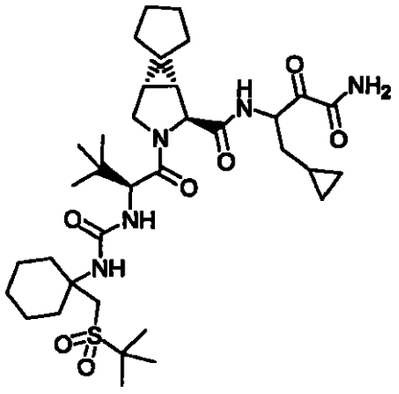


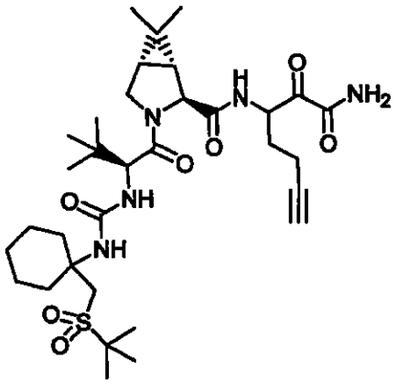


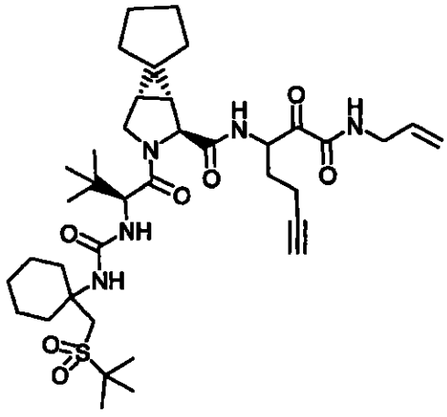


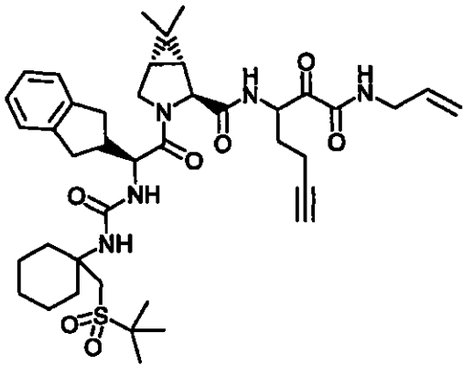


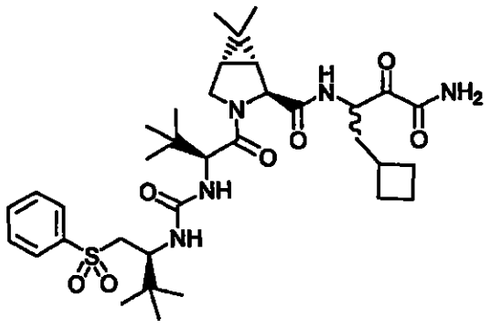


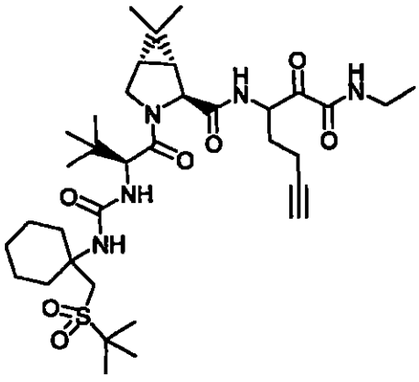


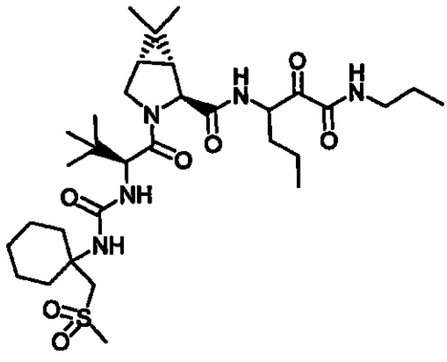


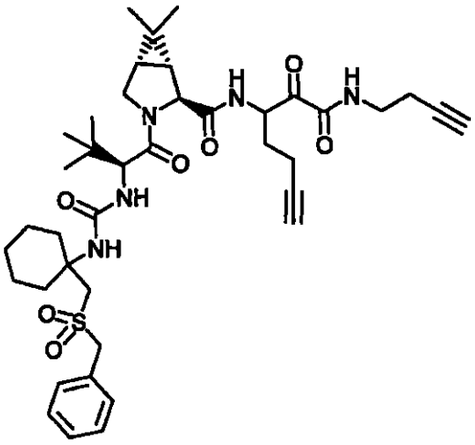


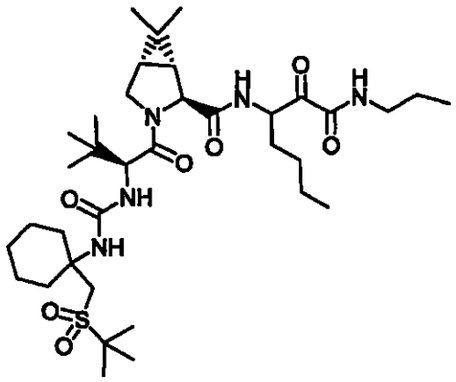


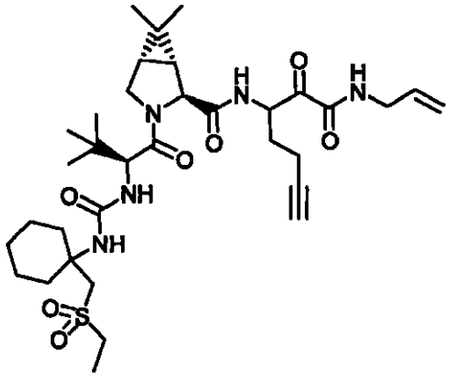


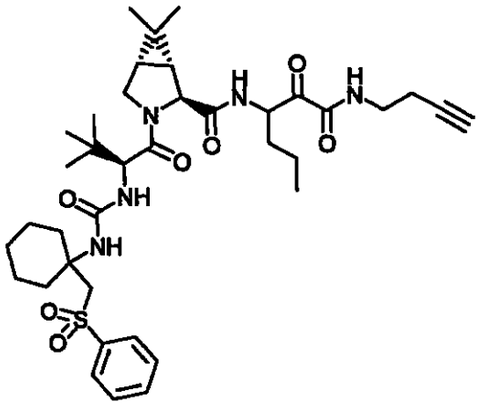


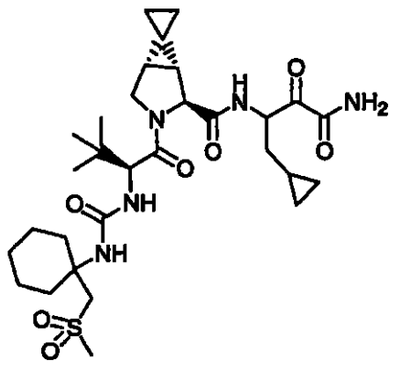


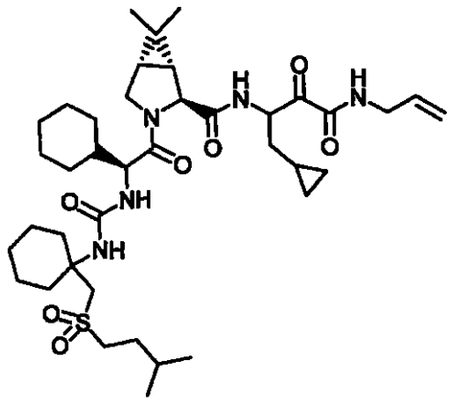


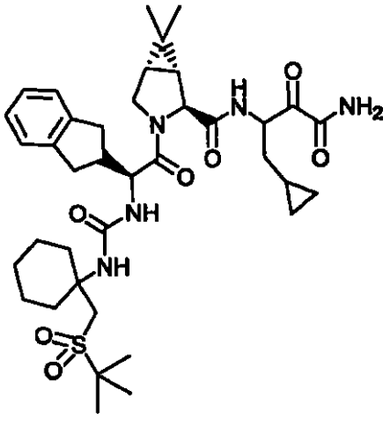


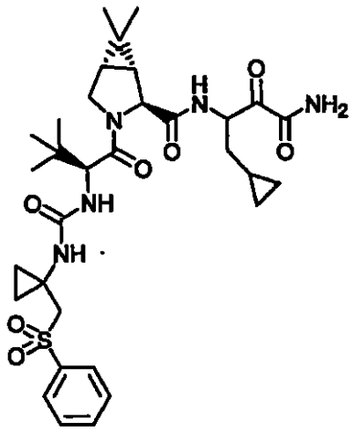


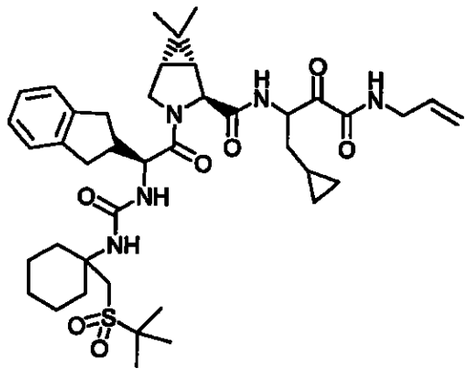


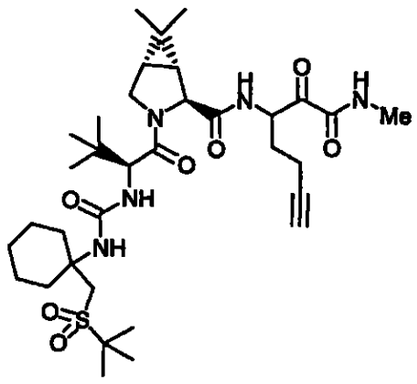


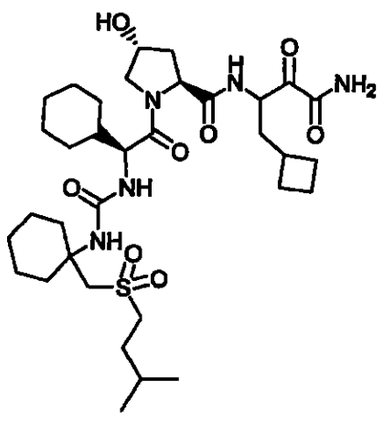


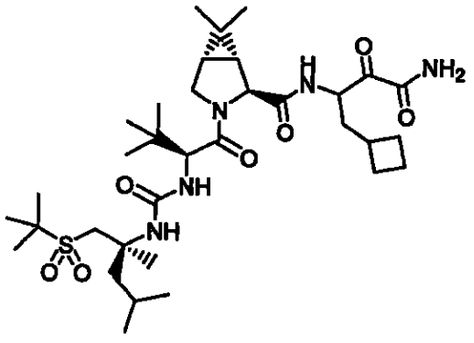


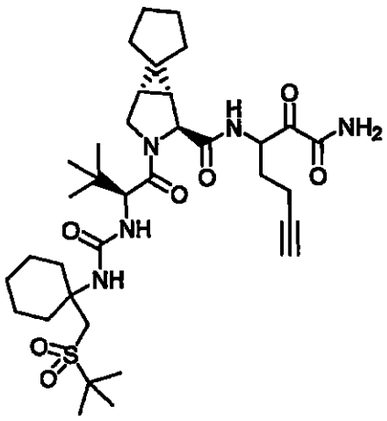


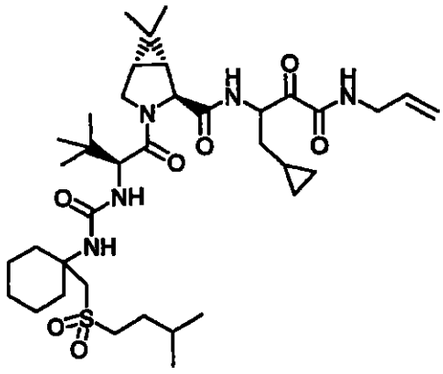


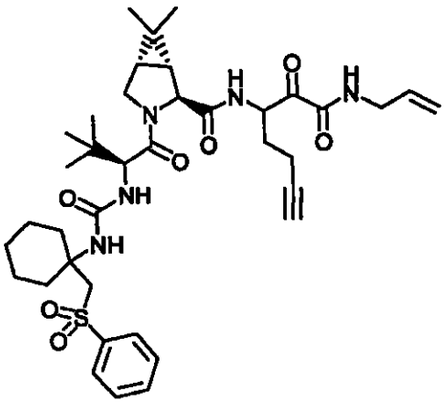


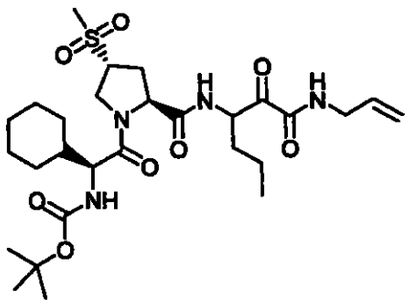


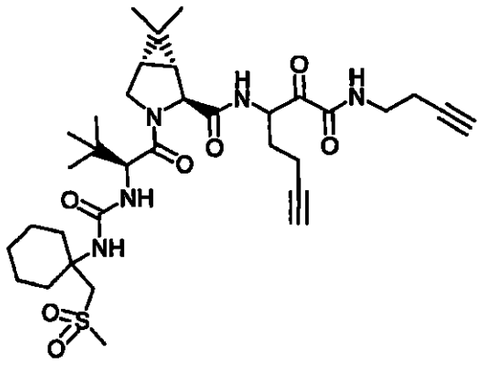


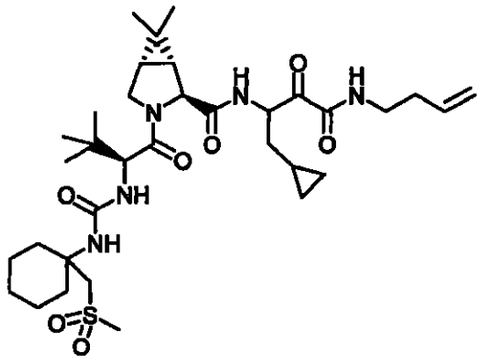


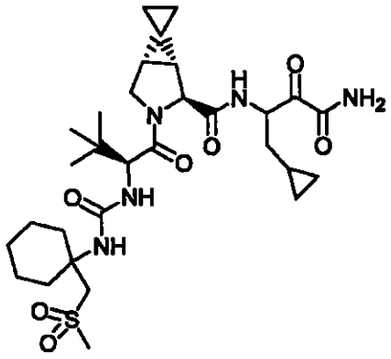


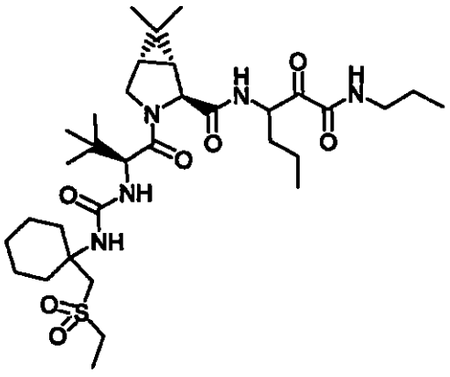


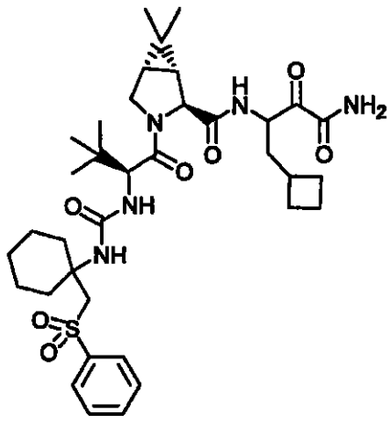


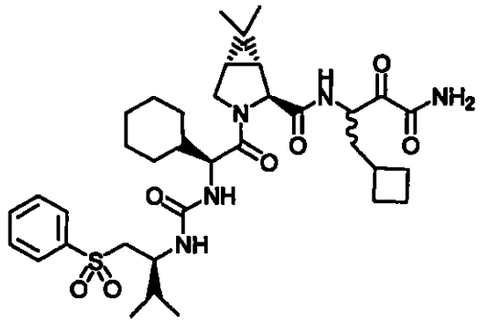


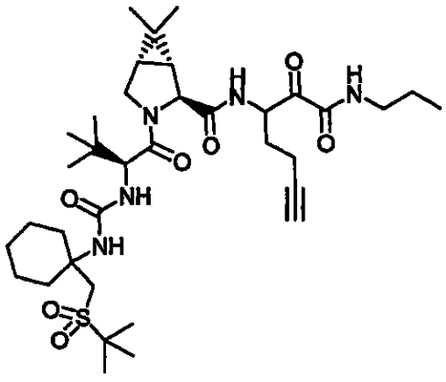


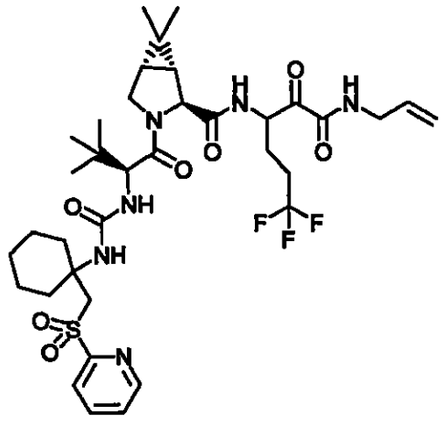


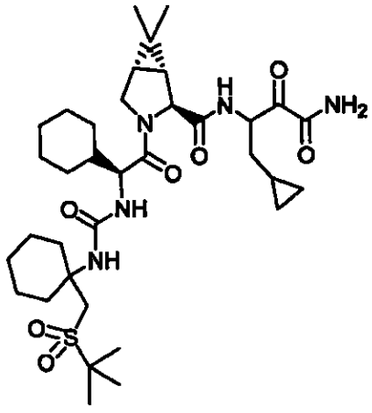


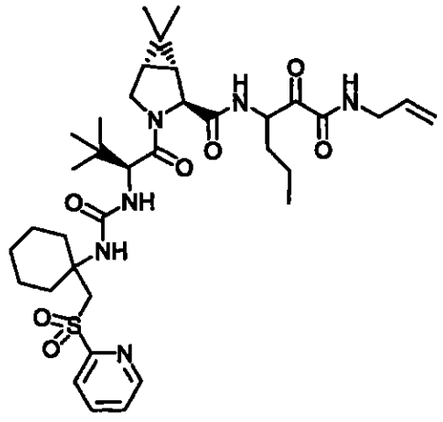


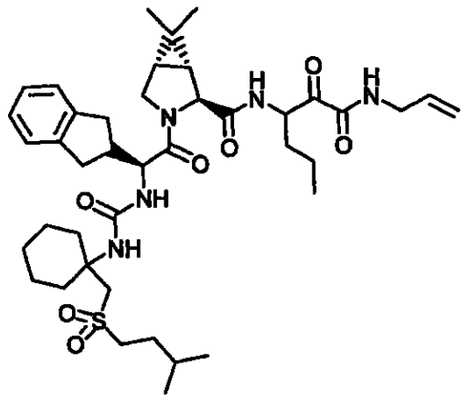


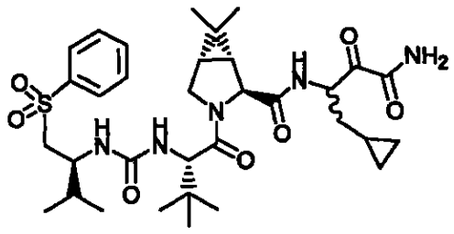


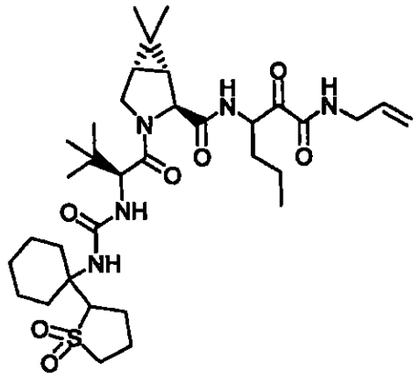


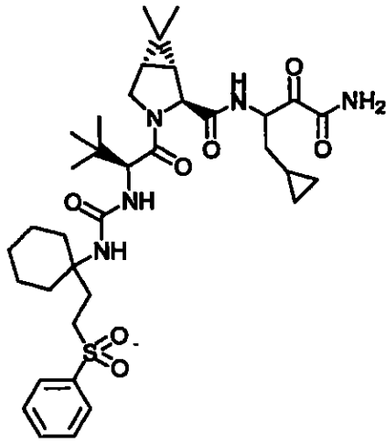


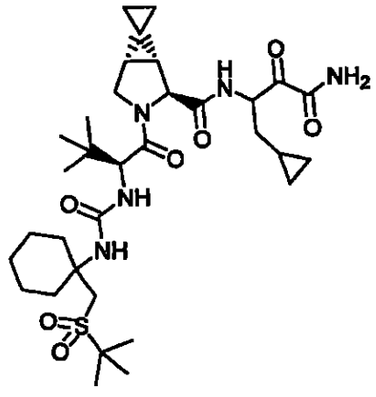


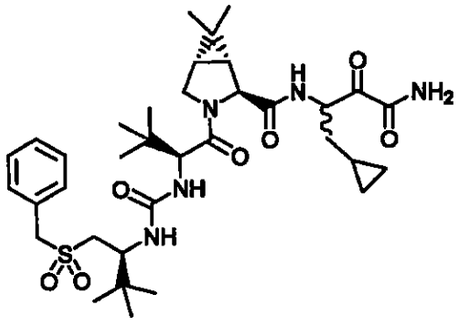


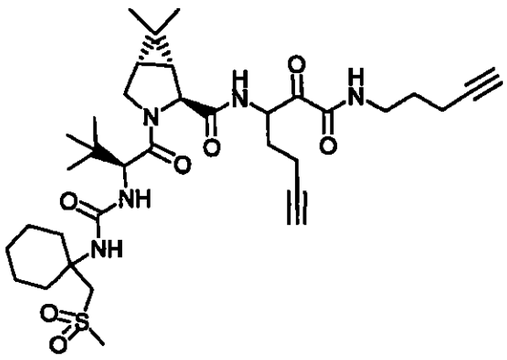


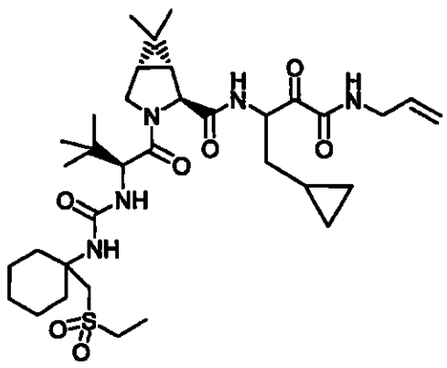


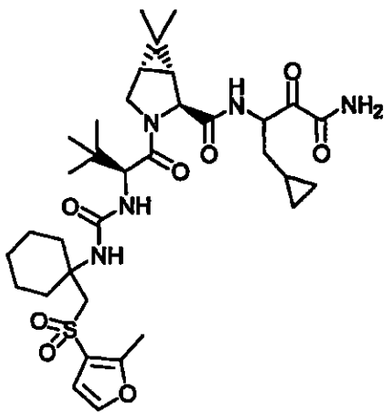


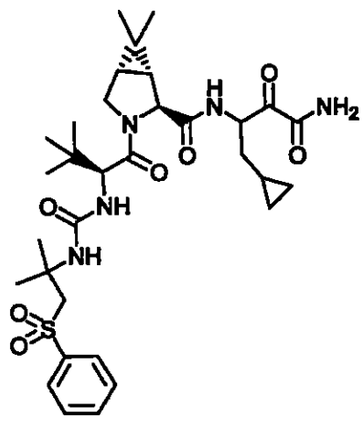


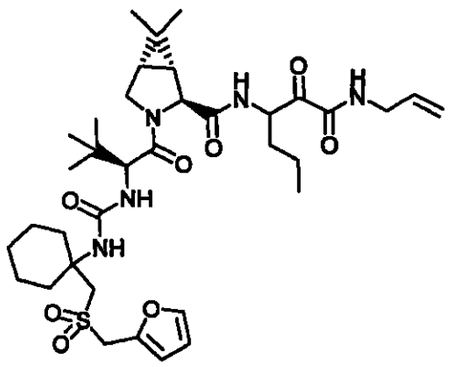


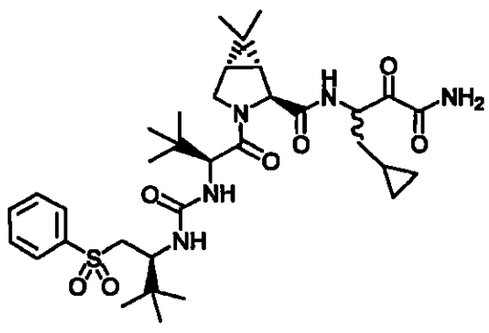


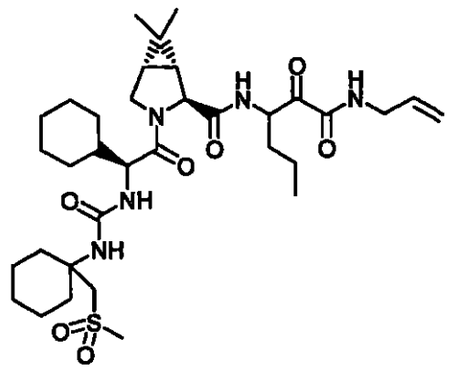


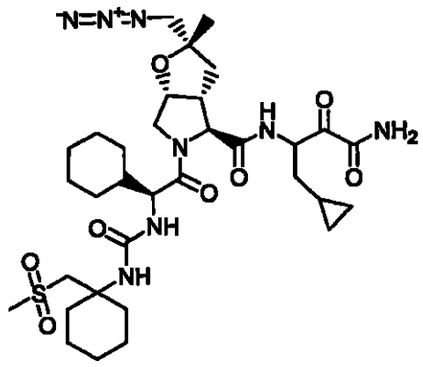


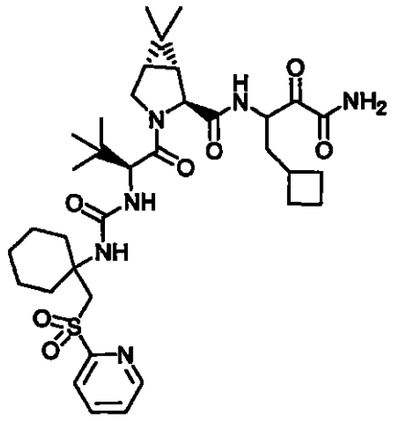


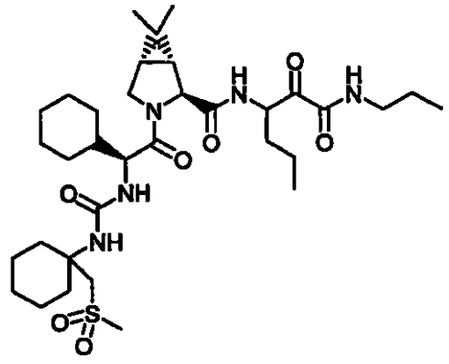


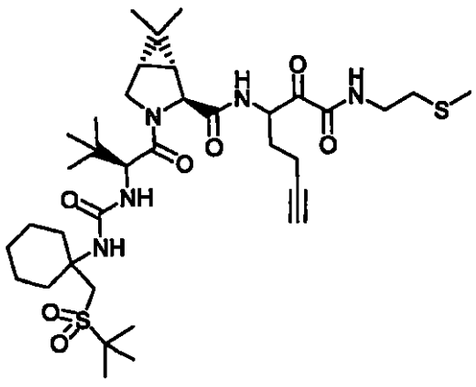


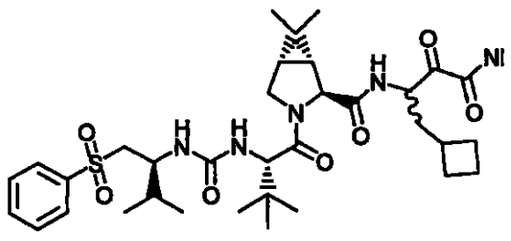


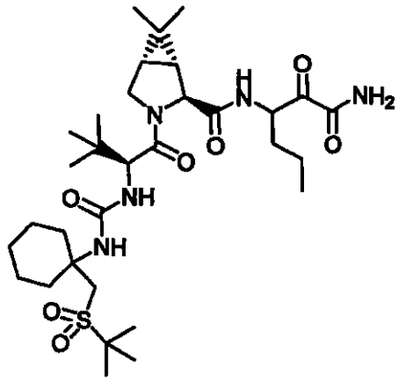


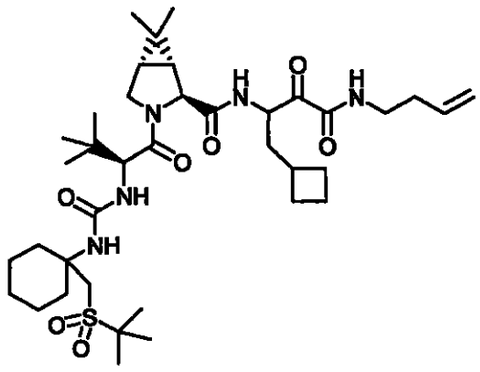


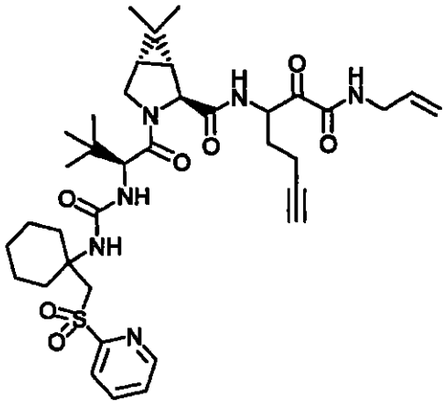


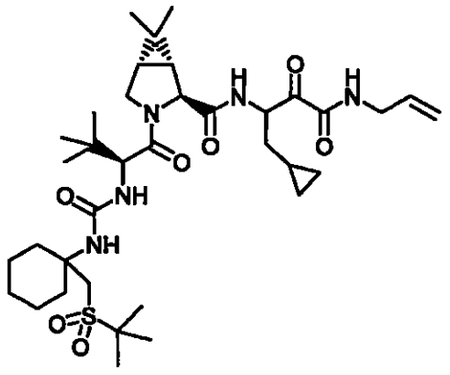


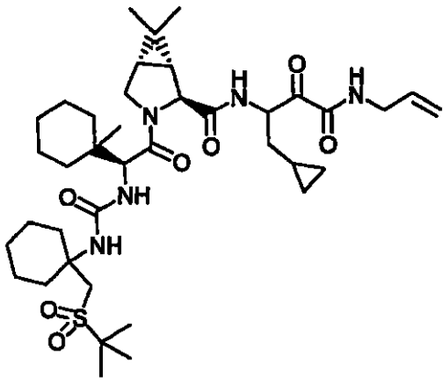


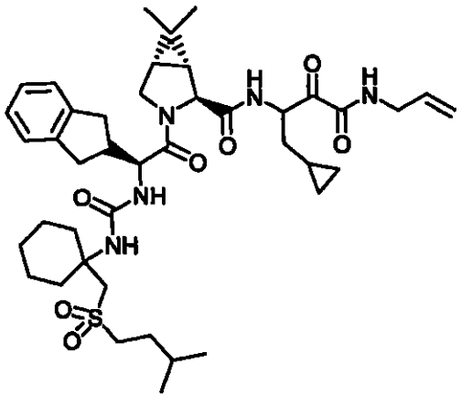


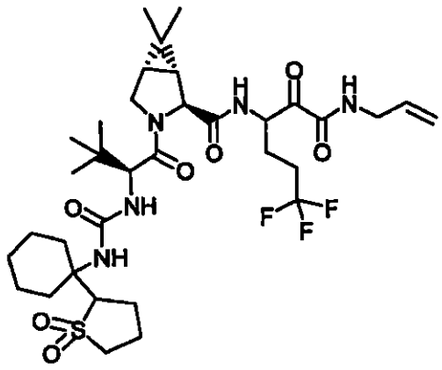


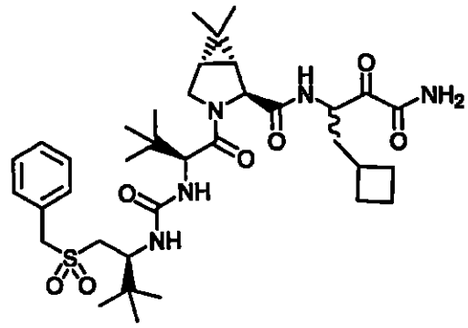


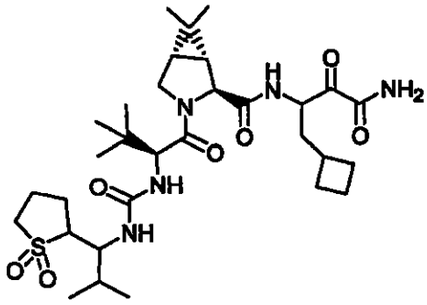


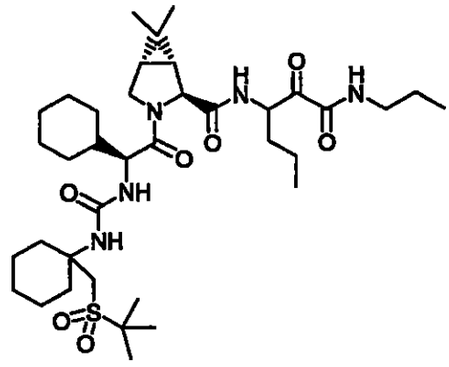


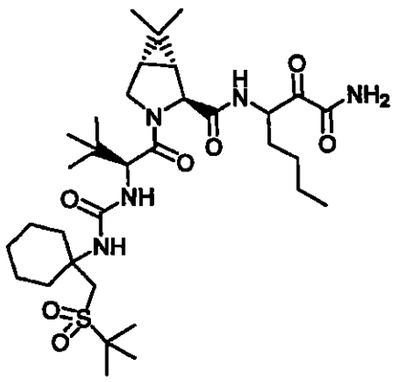


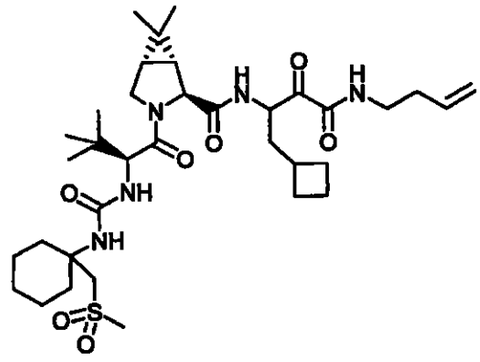


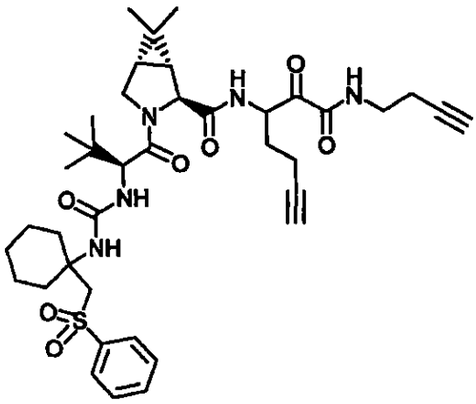


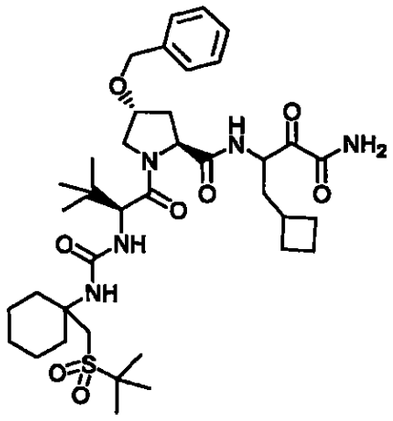


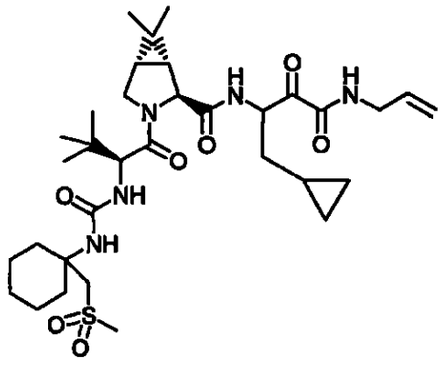


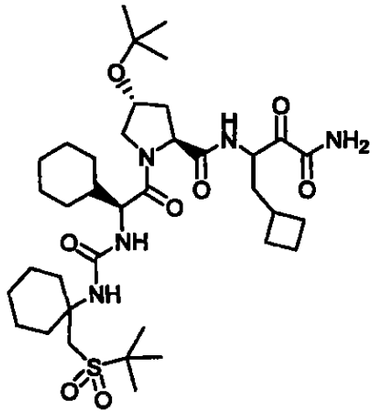


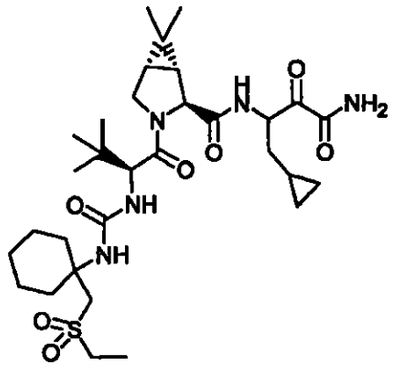


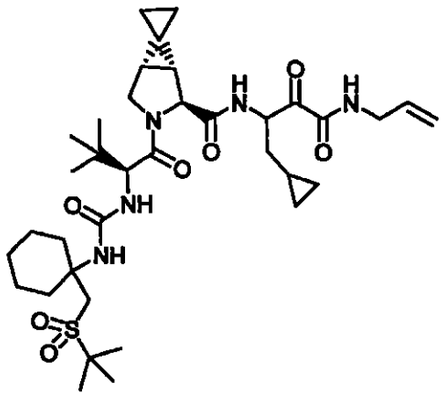


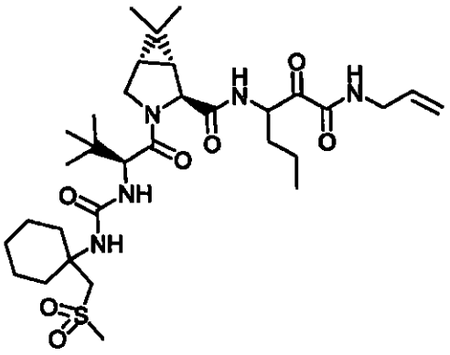


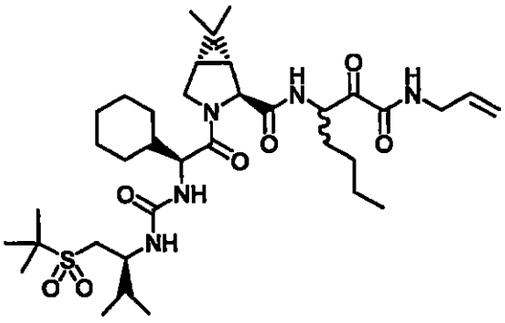


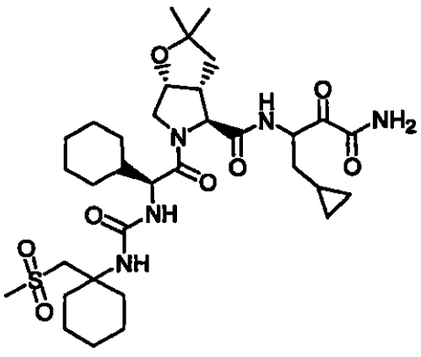


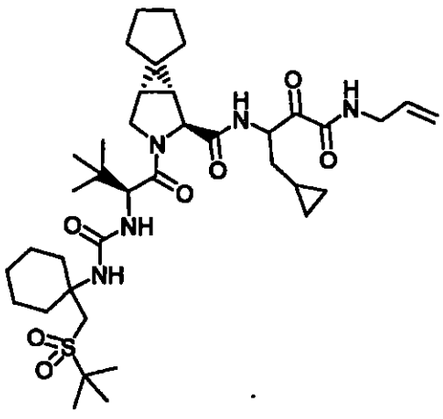


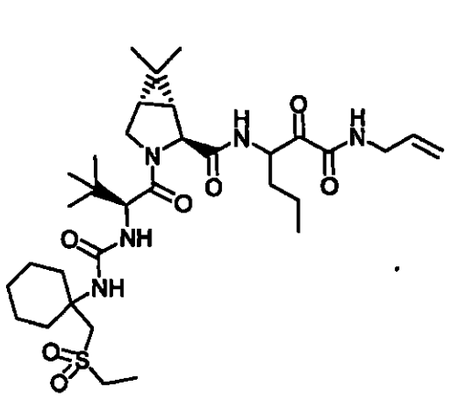


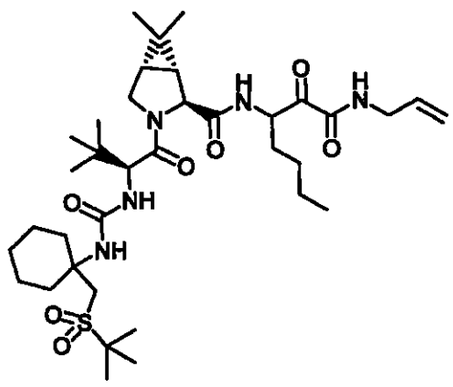






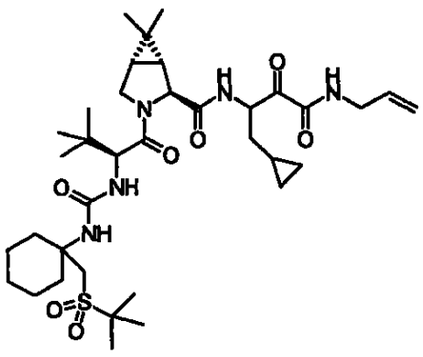


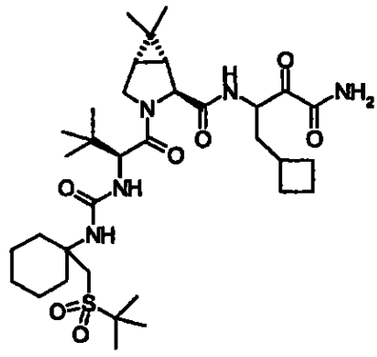


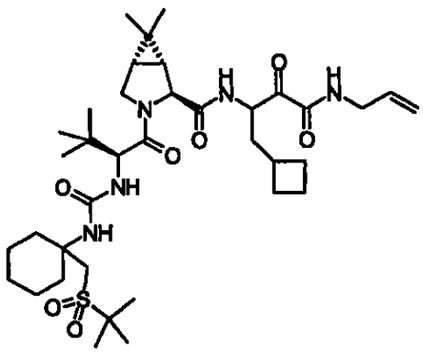


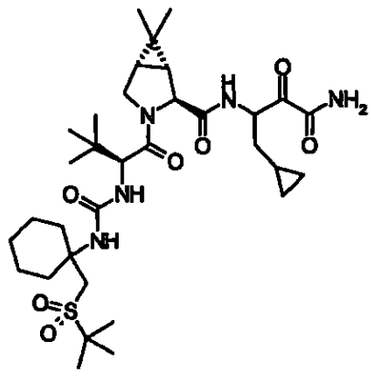
In an additional embodiment, this invention discloses the following compounds in **Table 2**:

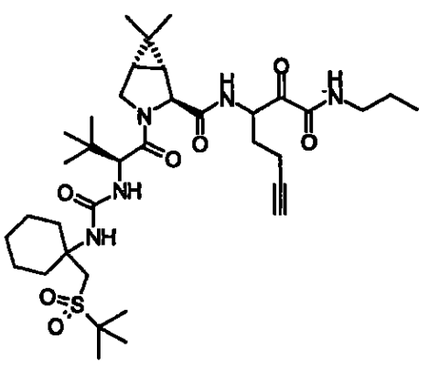
Table 2

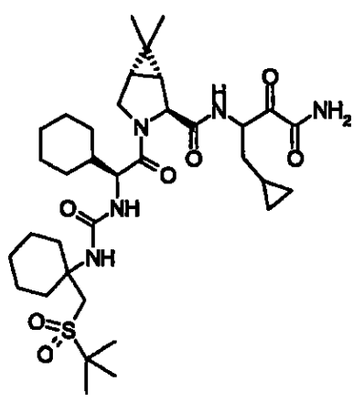


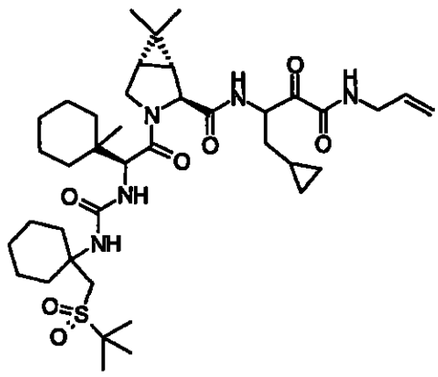


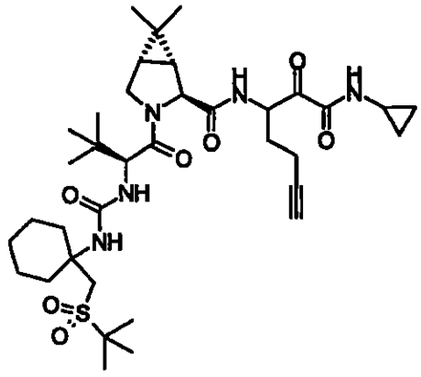


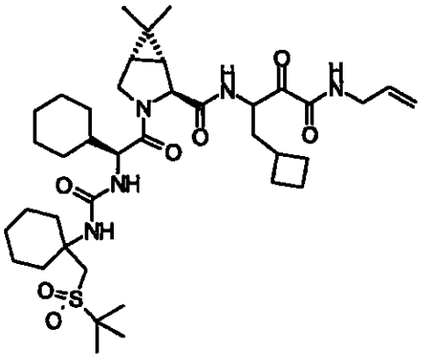


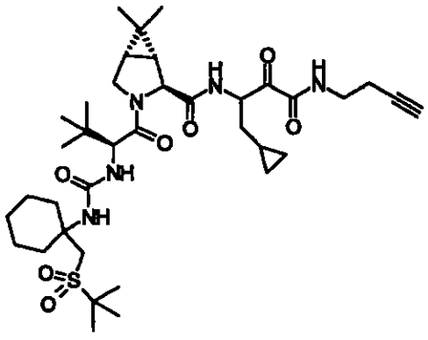


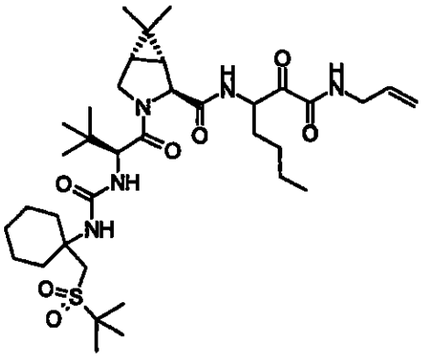


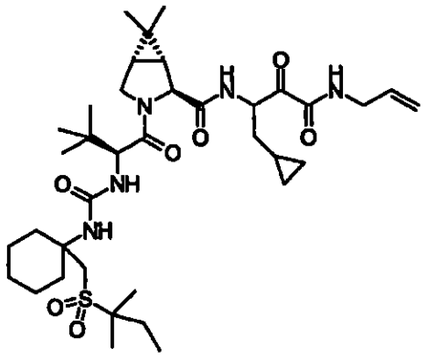


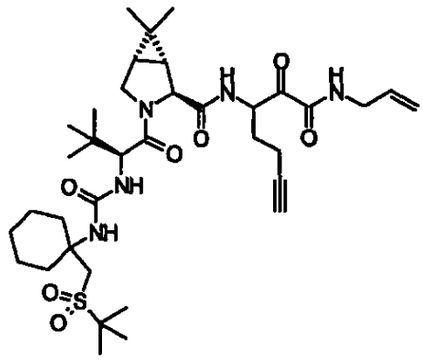


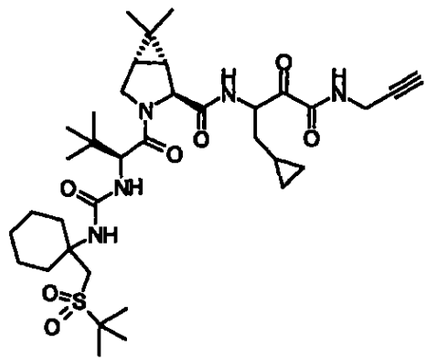


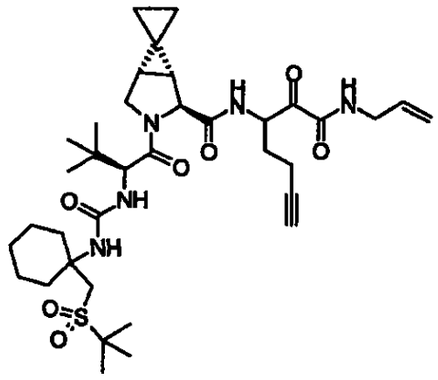












As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"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.

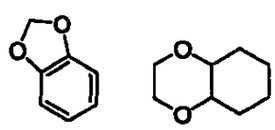
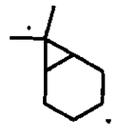
"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the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

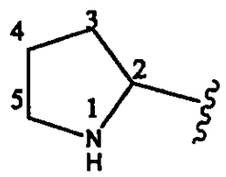
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, 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

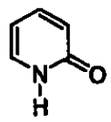
name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl 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:

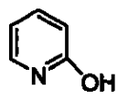


there is no -OH attached directly to carbons marked 2 and 5.

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 I, 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 I 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 I can form salts which are also within the scope of this invention. Reference to a compound of Formula I 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 I 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 I may be formed, for example, by reacting a compound of Formula I 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 I, 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, esters 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 I 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 I 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 I can be inhibitors of HCV protease, each compound by itself or one or more compounds of Formula I can be combined with one or more compounds selected from within Formula I. 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 I 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 I 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:

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

Et2O: 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

DMF-DMA: N,N-Dimethylformamide-dimethylacetal

iBoc: isobutoxycarbonyl

iPr: isopropyl

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

Boc: tert-Butyloxycarbonyl

Cbz: Benzyloxycarbonyl

Cp: Cylcopentyldienyl

Ts: p-toluenesulfonyl

Me: Methyl

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

DMAP: 4-N,N-Dimethylaminopyridine

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

PCC: Pyridiniumchlorochromate

KHMDS: Potassium Hexamethyldisilazide or Potassium bis(trimethylsilylamide)

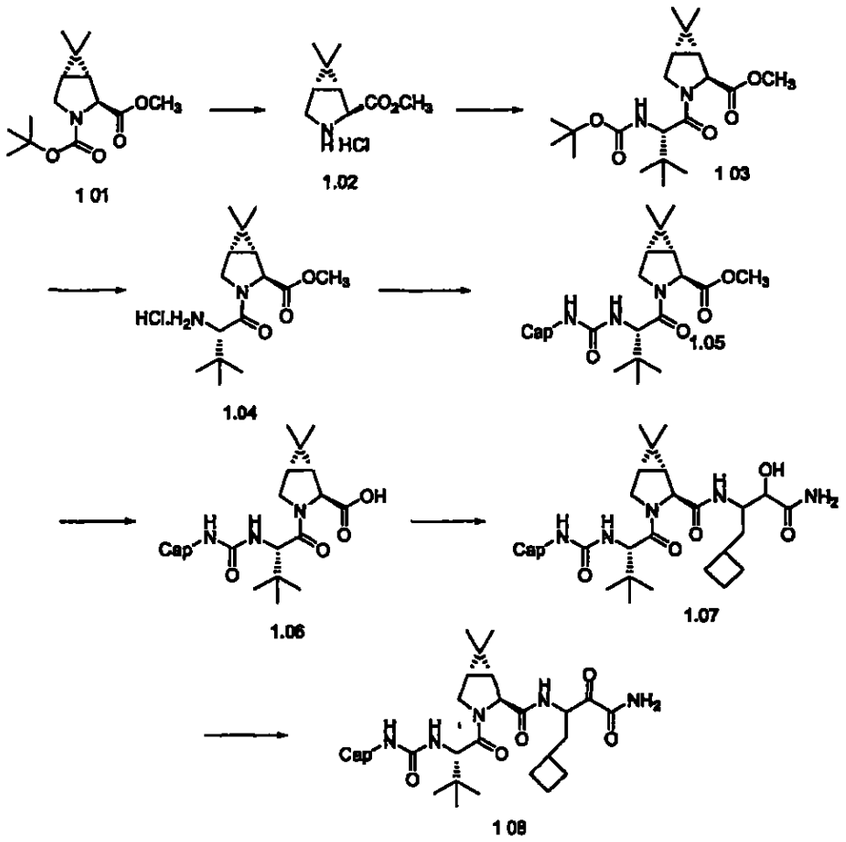
NaHMDS: Sodium Hexamethyldisilazide or Sodium bis(trimethylsilylamide)
LiHMDS: Lithium Hexamethyldisilazide or Lithium bis(trimethylsilylamide)
10% Pd/C: 10% Palladium on carbon (by weight).
TG: Thioglycerol

General Schemes for Preparation of Target Compounds

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

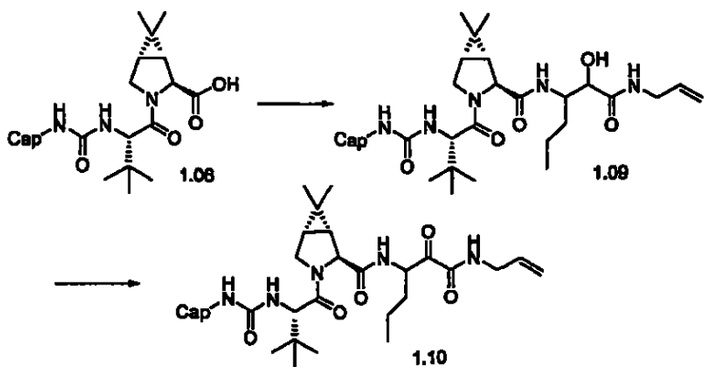
Method A

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 oxidation or related process – *see*, T. T. Tidwell, *Synthesis*, 1990, 857), or Dess-Martin Periodinane – *J. Org. Chem.*, (1983) 48, 4155) resulted in the target compound 1.08.



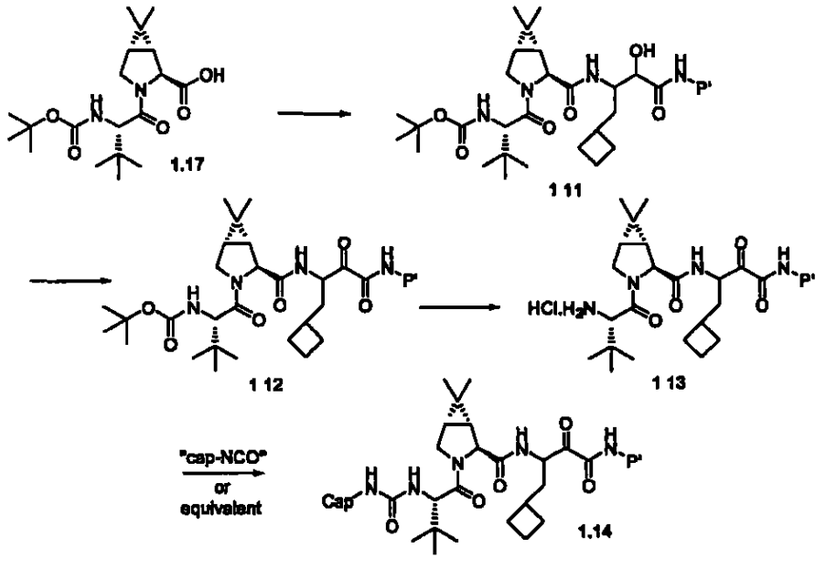
Method B

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.



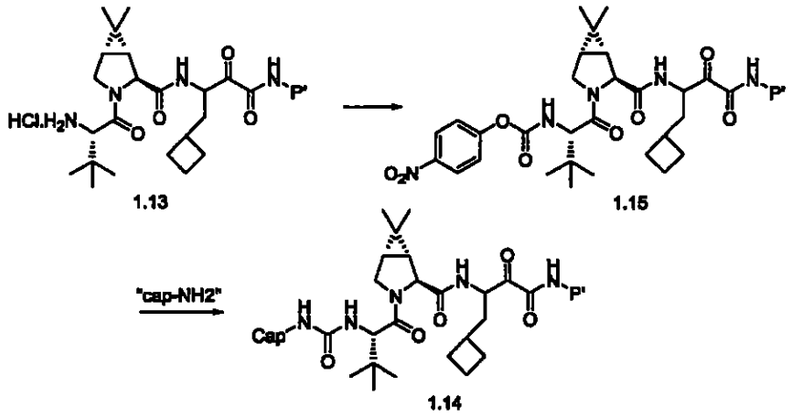
Method C

In another variation, peptide coupling of the N-Boc-P2-P_3-acid 1.17 with the appropriate P_1-P' amide moiety afforded the hydroxyl amide 1.11. Oxidation (Moffatt or Dess-Martin Periodinane) 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.



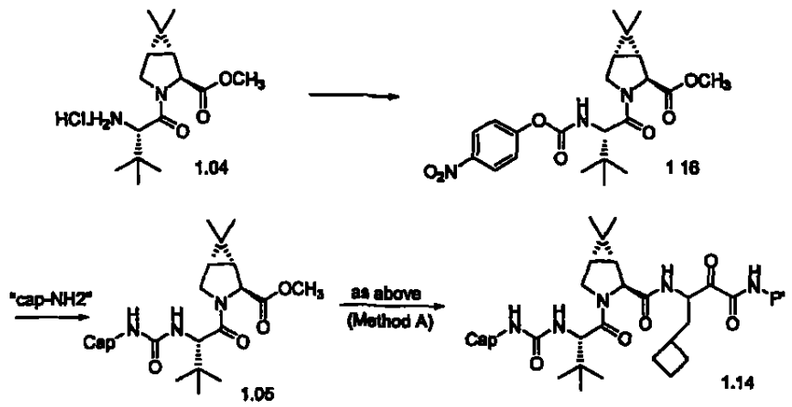
Method D

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 amine (or amine hydrochloride salt) of choice provided the target compound 1.14.



Method E

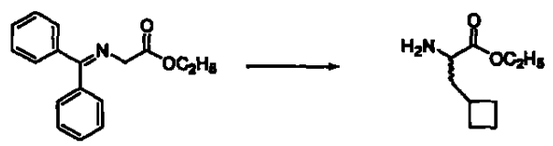
In yet another variation, the dipeptide hydrochloride salt 1.03 was converted to the 4-nitrophenyl carbamate as described above. Treatment with an amine (or amine hydrochloride salt) of choice provided the urea derivative 1.05. Hydrolysis and further elaboration as described in Methods A/B provided the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



Preparation of P1-P' moieties

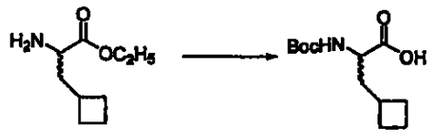
Preparation of Intermediates **10.11** and **10.12**

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.

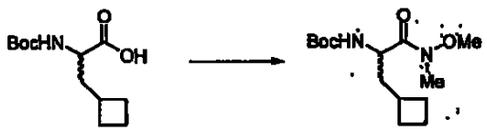
Step 2.



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.

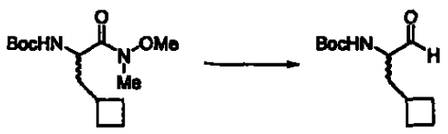
Step 3.



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.

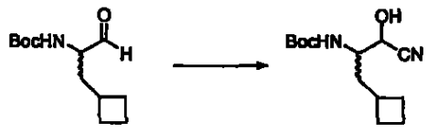
Step 4.



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).

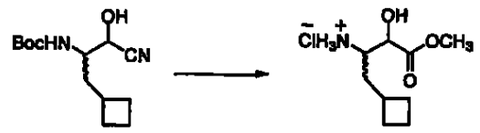
Step 5:



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.

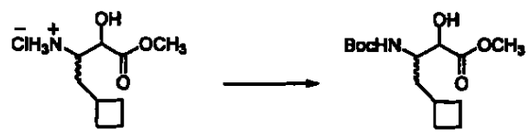


10.06 10.07

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.

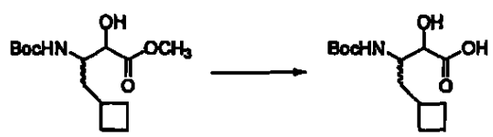
Step 7.



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 layers 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 $LiOH{\bullet}H_2O$ (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.

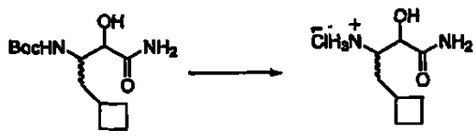
Step 9



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. saturated $NaHCO_3$, 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), $LiOH{\bullet}H_2O$ (820 mg, 20.8 mmol) at 0 °C in 50 mL of CH_3OH for 0.5 h.).

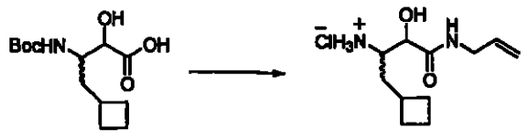
Step 10.



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.

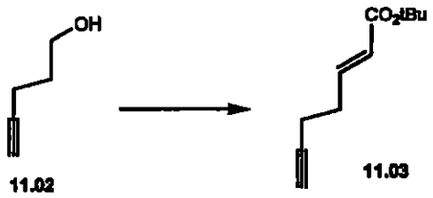


10.08 10.12

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**

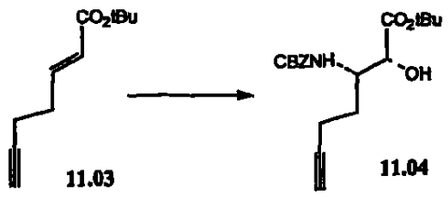
Step 1



11.02 11.03

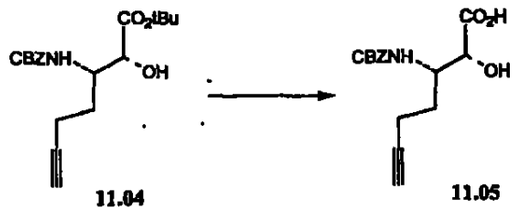
To a solution of 4-pentyn-1-ol, **11.02** (4.15g; Aldrich) was added Dess-Martin Periodinane (30.25g; Aldrich) and the resulting mixture was stirred for 45min. before the addition of (tert-Butoxycarbonylmethylene)triphenylphosphorane (26.75g; Aldrich). The resulting dark reaction was stirred overnight, 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



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



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



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.

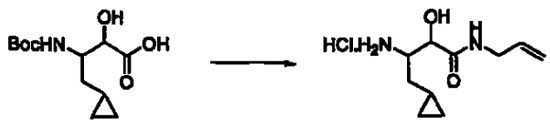
Step 2



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

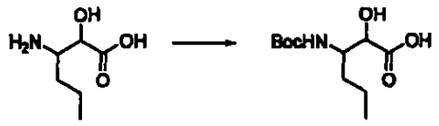


13.03 13.04

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%).

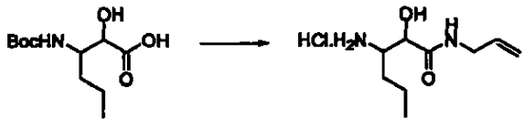
Step 3



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

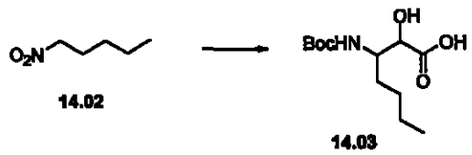


13.05 **13.01**

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**

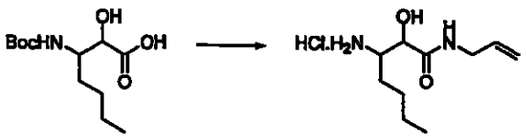
Step 1



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

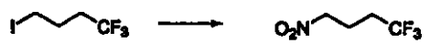


14.03 14.01

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**

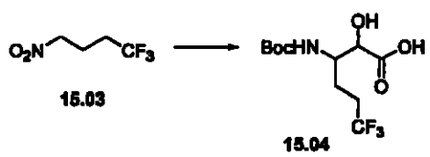
Step 1



15.02 15.03

To a suspension of silver nitrite (9 g, 58.5 mmol) in diethylether (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.

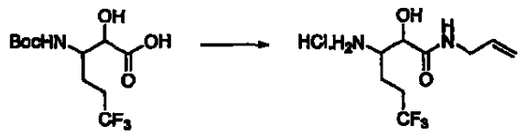
Step 2



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.

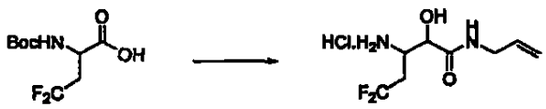
Step 3



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**

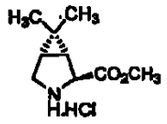


16.02 **16.01**

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 P2 / P3-P2 MOIETIES

Preparation of Intermediate **20.01**



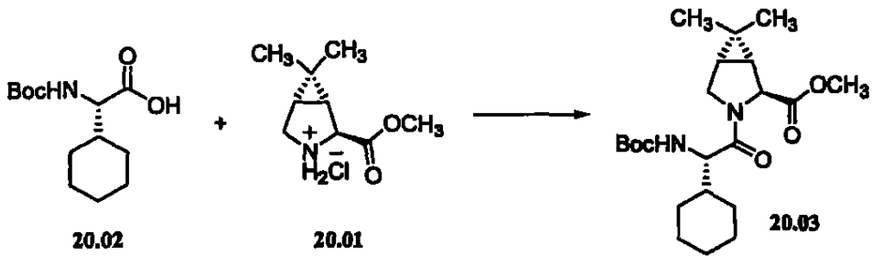
20.01

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.

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

Preparation of Intermediate **20.04**

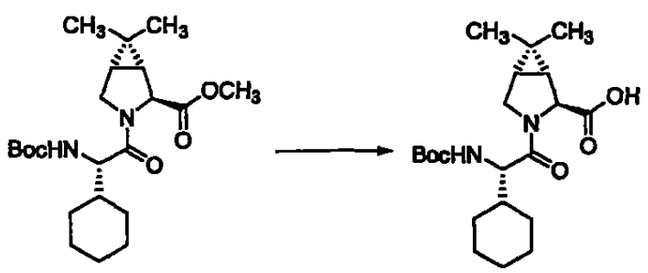
Step 1



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 saturated $NaHCO_3$ (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

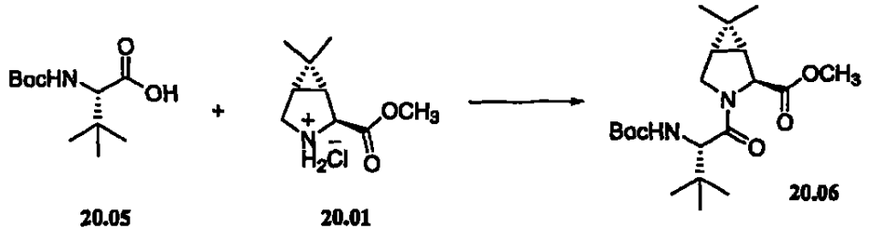


20.03 **20.04**

A solution of methyl ester **20.03** (4.0 g, 9.79 mmol) in THF/H_2O (1:1) was treated with LiOH•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 **20.07**

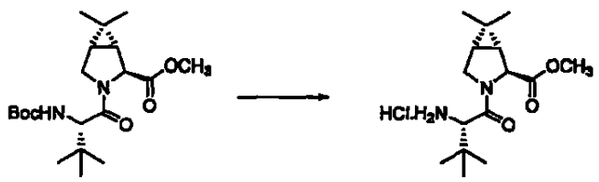
Step 1



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), saturated $NaHCO_3$, 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

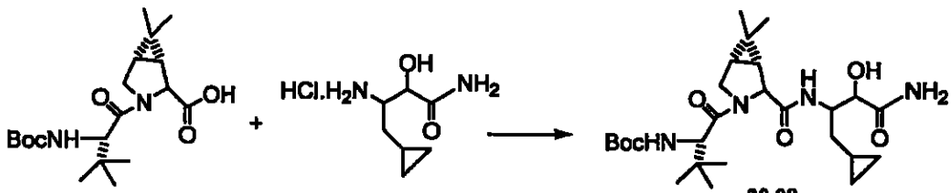


20.06 **20.07**

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.

Preparation of Intermediate **20.10**

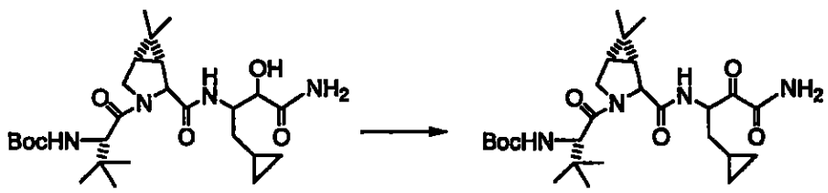
Step 1



1.17 **12.03** **20.08**

To a -20°C solution **1.17** (10.4 g, 28 mmol) 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 **20.08.**

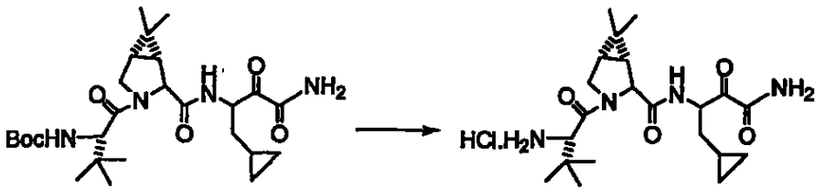
Step 2



20.08 **20.09**

The hydroxyamide **20.08** was oxidized to the required ketoamide **20.09** in a manner described for Example **198 (Step 8)**. LC-MS = 507 $(M+H)^+$.

Step 3



20.09 20.10

Deprotection of the t-Boc functionality of **20.09** to give the required material **20.10** was carried out as described for the transformation of **20.06** to **20.07**.

Preparation of Intermediate **21.01:**

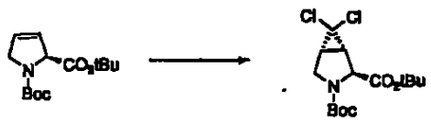
Step 1:



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%).

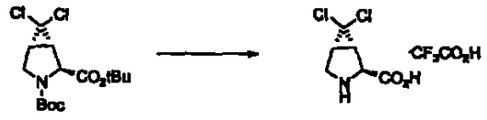
Step 2:



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

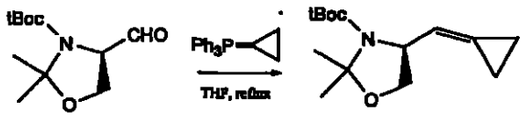


21.05 **21.01**

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**

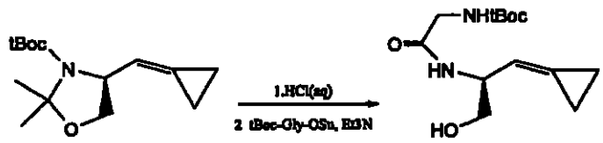
Step 1



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**

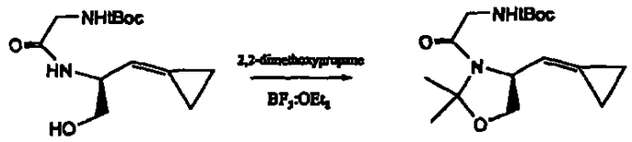
A solution of 1M HCl in MeOH/MeOAc was prepared by adding 14.2ml of acetyl chloride dropwise into cold methanol and diluting the resulting solution to 200ml at room temperature.

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).

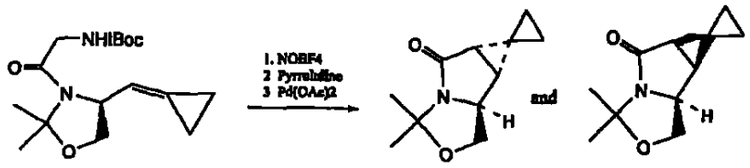
Step 3



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

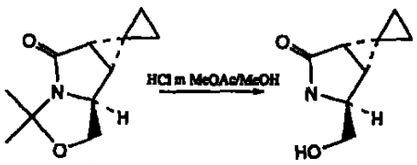


22.05 22.06 22.07

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).

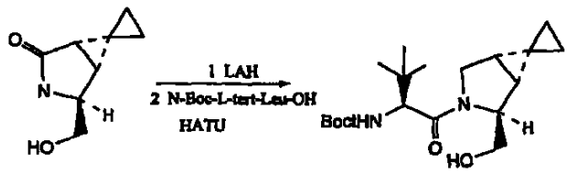
Step 5



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



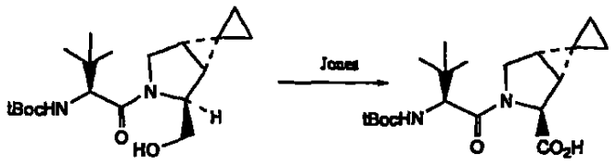
22.08 **22.09**

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

Step 7

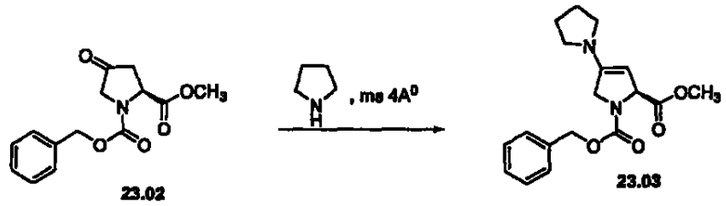


22.09 **22.01**

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 5°C 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:

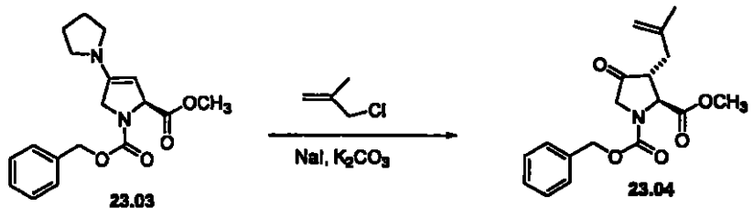


23.02 **23.03**

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:



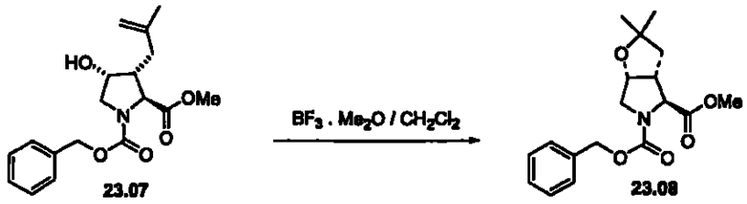
To a suspension of $NaBH(OAc)_3$ (3.93g, 18.5 mmoL) in CH_2Cl_2 (55 mL) was added a solution of product **23.05** from preceding step in anhydrous CH_2Cl_2 (20 mL) and acetic acid (2 mL). The slurry was stirred at ambient temperature for 20 h . Ice cold water (100 mL) was added to the slurry and stirred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

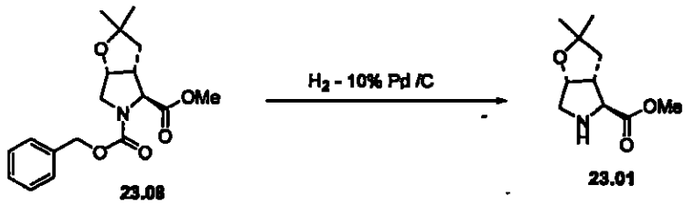
Step 6:



23.07 23.08

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 P3 MOIETIES

Preparation of Intermediate **50.01**

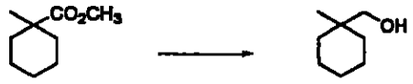
Step 1



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.

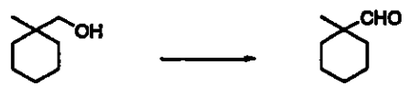
Step 2



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.

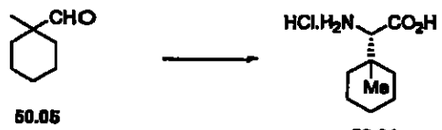
Step 3



50.04 50.05

The alcohol **50.04** from 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

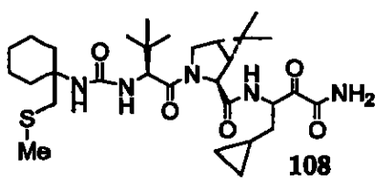


50.05 **50.01**

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).

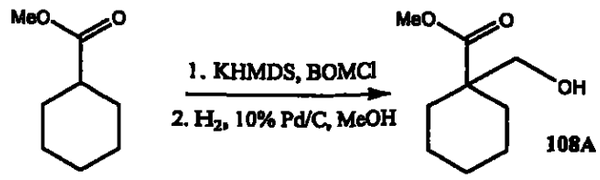
PREPARATION OF SPECIFIC EXAMPLES

Example 108:



108

Steps 1 and 2:



108A

Step1:

KHMDS (200ml of a 0.5M solution in toluene) was added, dropwise to a stirred solution of Methyl cyclohexanecarboxylate (11.1g; 78mmol) in anhydrous THF (200ml), at -78C under an atmosphere of nitrogen. When the addition was complete the reaction was maintained at this temperature for a further 0.5h. before the addition of Benzyl Chloromethyl Ether (18.6ml; 134mmol). The reaction was allowed to warm to room temperature overnight and water (100ml) was added. Aqueous work-up provided a residue which was purified by silica gel column chromatography using EtOAc; hexanes (1:10) as eluent to give the desired, impure, intermediate ether (14.98g) as a colorless oil.

Step2:

A black suspension of 10% Pd/C (0.5g) and the aforementioned crude ether (4.1g) in MeOH (80ml) was exposed to an atmosphere of nitrogen (balloon) at room temp., overnight. The reaction was filtered through a pad of celite and the solid was washed thoroughly with methanol. The combined filtrate was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography using EtOAc; hexanes (1:5) to give the primary alcohol (**108A**; 0.62g), a colorless oil.

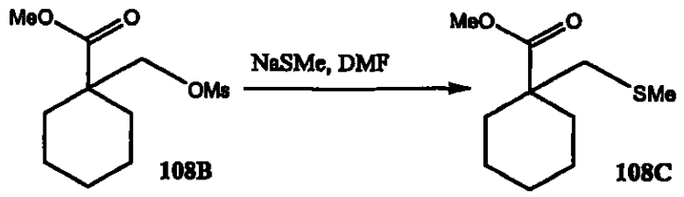
Step 3:



108A 108B

Methanesulfonyl Chloride (0.31ml) followed by triethylamine (0.75ml) were added to a stirred solution of the primary alcohol (**108A**; 0.62g) at 0C, under an atmosphere of nitrogen. The resulting mixture was stirred at this temperature for 0.5h. The reaction mixture was extracted into EtOAc and washed with aqueous 1M HCl, sat. aq. NaHCO3, water, dried (MgSO4) and concentrated. The residue (mesylate **108B**; 0.74g), was obtained as a yellow oil, which was used in subsequent steps without purification.

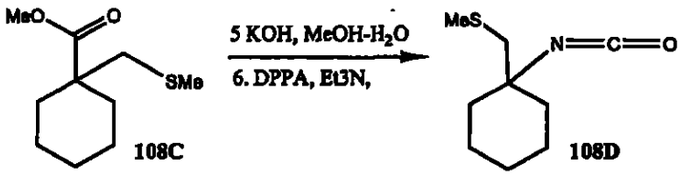
Step 4:



108B **108C**

Sodium Methanethiolate (0.236g; 2eq.) was added to a DMF (2ml) solution of the mesylate (**108B**; 0.42g) and the mixture was heated to 100C for 1h. Aqueous work-up and purification of the crude reaction product by silica gel column chromatography using EtOAc; hexanes (1:20) gave the sulfide (**108C**; 0.089g).

Steps 5 and 6:



108C **108D**

Step 5:

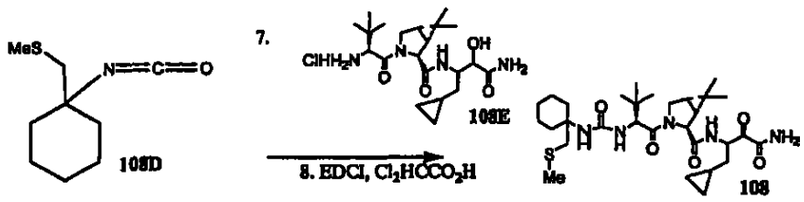
Potassium hydroxide (0.25g) was dissolved in a mixture of water (1ml) and ethanol (5ml) and added to the methyl ester (**108C**;0.089g) and the resulting mixture was heated to reflux, under an atmosphere of nitrogen over a week-end (approx. 72h.). After cooling, the reaction was partitioned between EtOAc and dilute aq. HCl. The organic phase was separated,

washed with brine, dried and concentrated to yield the crude intermediate carboxylic acid, used without purification.

Step 6:

Triethylamine (61ul) followed by DPPA (95ul) were added to a toluene solution of the carboxylic acid from the previous step and the reaction was heated to 100C overnight. After cooling, the reaction mixture was partitioned between EtOAc and sat. aq. sodium bicarbonate. The organic phase was separated, dried and concentrated to yield the isocyanate (**108D**; 50mgs), used without purification.

Steps 7 and 8:



Step 7:

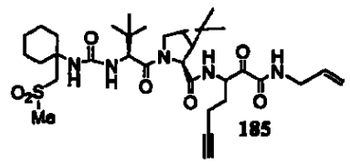
The isocyanate (**108D**; 50mg) in dichloromethane (1ml) was added to a mixture of the hydrochloride salt (**108E**; prepared from 20.08 in a manner described for the transformation of 20.06 to 20.07; 100mg) and triethylamine (111ul) in dichloromethane (2ml) and the resulting mixture was stirred at room temperature for 4 hours. 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) and concentrated to yield a residue which was used in step 8 without purification.

Step 8:

The residue in the aforementioned step was dissolved in a mixture of toluene (3ml) and dimethylsulfoxide (3ml) and EDCI (647 mg) followed by dichloroacetic acid (140ul) were added and the resulting reaction mixture was

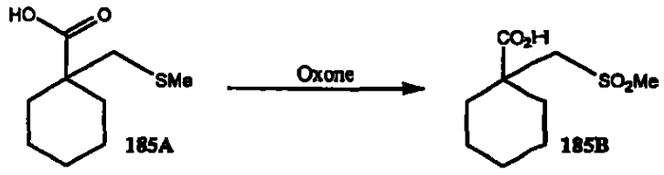
stirred at room temperature for a period of 4h. The reaction mixture was partitioned between EtOAc and 5% aq. sodium sulfite. The organic phase was separated, washed with 10% aq. HCl, sat. aq. sodium bicarbonate, water, dried (magnesium sulfate) and concentrated to yield a residue which was purified by silica gel column chromatography using acetone: hexanes (40:60) as eluent to provide the desired keto-amide (**108**; 11.5mgs). MS: MH+, 592.1.

Example 185:



185

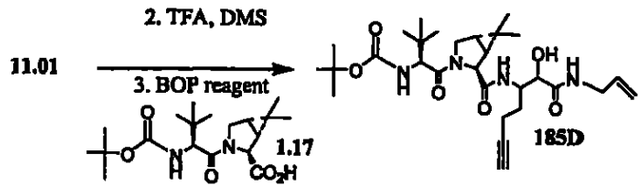
Step 1:



185A **185B**

Oxone (5.68g) was dissolved in water (5ml) and added to the carboxylic acid **185A** (1.25g) in methanol (5ml) while cooled in an ice bath. The reaction mixture was allowed to warm to room temp., overnight. The volatiles were removed under reduced pressure and the residue was partitioned between methylene chloride and water. The aqueous phase was separated and extracted with methylene chloride (X2). The combined organic phases were dried and concentrated to yield the sulfone (**185B**; 1.10g) as a white solid, used in subsequent procedures without purification.

Steps 2 and 3:



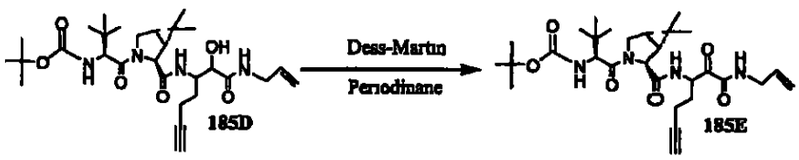
Step 2:

The benzyl carbamate (**11.01**;0.16g) was dissolved in TFA (7ml) and dimethyl sulfide (1.78ml) was added and the resulting mixture was allowed to stand at room temperature for a period of 3h., before removing the volatiles under reduced pressure. This gave a residue which was used in step 3 below.

Step3:

Triethylamine (111ul) was added to a mixture of the residue from step 2, the carboxylic acid (**1.17**; 0.180g) and BOP reagent (0.236g) in dichloromethane (5ml) and the reaction mixture was stirred at room temperature overnight. The reaction was partitioned between ethyl acetate and aq. 10% HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried (magnesium sulfate) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc: Hexanes (70:30) as eluent to give the desired hydroxy-amide (**185D**; 0.165g) as a white solid.

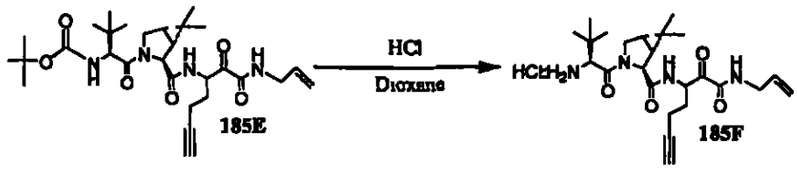
Step 4:



The periodinane (0.236g) was added to a stirred solution of the alcohol (**185D**; 0.152g) in dichloromethane (5ml) and the resulting white suspension was stirred for a period of 2h. before being added to a mixture of EtOAc and 5% aq. sodium sulfite. The organic phase was separated washed with sat. aq.

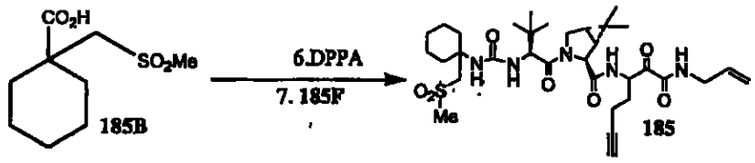
sodium bicarbonate, water, dried and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc: Hexanes (40:60) as eluent to give the desired keto-amide (**185E**; 0.147g) as a white solid. MS: MH+, 545.5.

Step 5;



A solution of HCl in dioxane (4M; 5ml; Aldrich) was added to the carbamate (**185E**; 0.14g) and allowed to stand at room temperature for a period of 3h. The volatiles were removed under reduced pressure to provide the hydrochloride salt (**185F**; 0.126g: contains a small quantity of dioxane).

Steps 6 and 7:



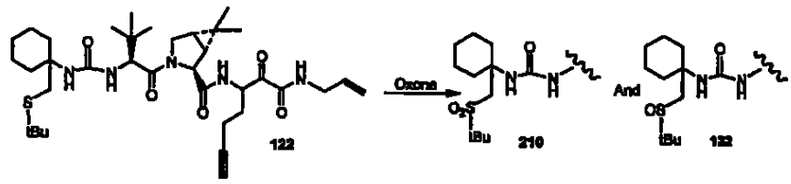
Step 6:

DPPA (19ul) was added to a mixture of the carboxylic acid (**185B**; 20mgs) and triethylamine (13ul) in toluene (1ml) and the resulting reaction mixture was heated to reflux for a period of 1h. After cooling, the reaction was partitioned between EtOAc and sat. aq. sodium bicarbonate. The organic phase was separated, dried and the volatiles removed under reduced pressure. Gave the crude intermediate isocyanate which was used in step **7**, below without purification.

Step 7:

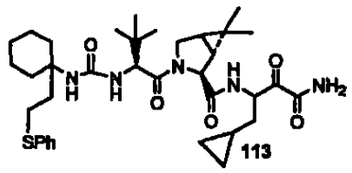
The product from step 6 was dissolved in dichloromethane (1mL) and added to a mixture of the hydrochloride salt (**185F**; 20mgs) and triethylamine (60ul) in dichloromethane (1ml) and the resulting mixture was stirred at room temperature for a period of 1h. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried and the volatiles were removed under reduced pressure. The resulting residue was purified by silica gel plate chromatography using EtOAc: Hexanes (1:1) as eluent to provide the keto-amide (**185**; 16.3mgs) as a white solid. MS: MH+, 662.5.

Preparation of Compounds of Formulas **132** and **210** Directly From a Compound of Formula **122**

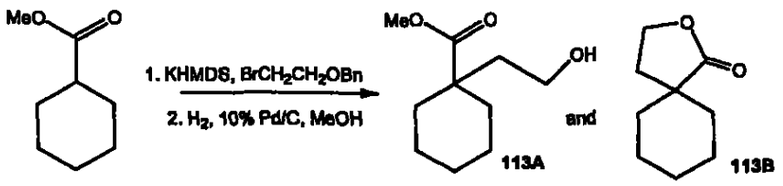


Using the sulfide **122** (prepared in a similar manner as 108 using methyl ester 210A rather than 108C; 20mg), oxone (27mg; 1.5eq.), water (1ml), methanol (1ml) and the procedure set forth previously (**185A** to **185B**) gave a crude reaction product which was purified by silica gel plate chromatography using EtOAc as eluent. Gave the sulfone (**210**; MH+= 704.4; 5.6mg) as a white solid followed by a mixture of sulfoxides (**132**; MH+ = 688.5; 6.3mg), also a white solid.

Preparation of Compound **113**



Steps 1 and 2:



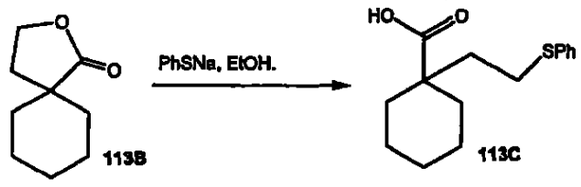
Step 1:

Using Methyl cyclohexanecarboxylate (5.55g), KHMDS (100ml of a 0.5M solution in toluene), anhydrous THF (100ml) and benzyl 2-bromoethyl ether (10.09g) and the procedure set forth previously(Example **108**, Step1), the desired intermediate benzyl ether (6.83g) was obtained after silica gel column chromatography (EtOAc:Hexanes:15:85).

Step 2:

Using the aforementioned benzyl ether (5.00g), 10% Pd/C (1.00g), methanol (20ml) and the procedure set forth previously (Example **108**; Step2) the lactone (**113B**; 0.87g), followed by the alcohol (113A; 2.01g) were obtained following column chromatography on silica gel (EtOAc; Hexanes; 1:10).

Step 3:



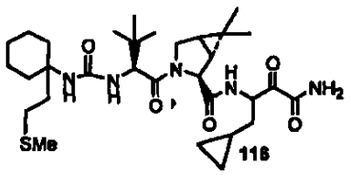
Step 3:

Sodium thiophenoxide (0.68g) was added to a solution of the lactone (**113B**; 0.84g) in ethanol (15ml) and the resulting mixture was heated to reflux, under an atmosphere of nitrogen overnight. After cooling, aqueous work-up and purification of the crude reaction product by silica gel column

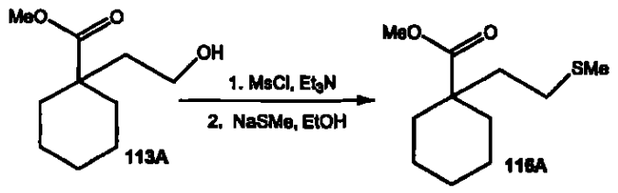
chromatography (EtOAc-Hexanes; 30:70) gave the carboxylic acid (**113C**; 0.32g), as a yellow solid.

Using previously described chemistry for the conversion of **108C** to **108**, **113C** was converted to **113** in a similar manner. MS, MH+, 668.3.

Preparation of Compound **116**:



Steps 1 and 2



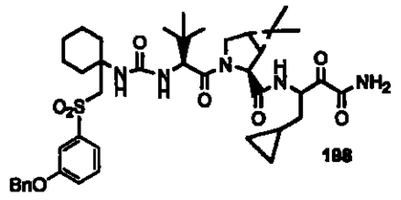
Step 1:

Using the alcohol (**113A**; 1.00g), methane sulfonylchloride (1.12g), triethylamine (0.82g), methylene chloride (10ml) and the procedure set forth previously (**108A** to **108B**), the desired, intermediate mesylate was obtained and was used in the next step, without purification.

Step 2:

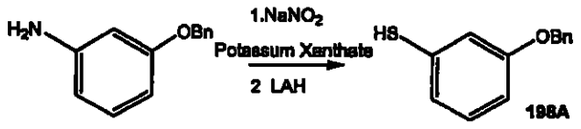
Using the aforementioned mesylate, sodium methanethiolate (0.75g), ethanol (10ml) and the procedure set forth previously (**108B** to **108C**) at room temperature, the desired sulfide (**116A**; 0.78g) was obtained after silica gel column chromatography (EtOAc-Hexanes; 1:10). Using the procedures set forth previously (**108C** to **108D**) and (**108D** to **108**), intermediate **116A** was transformed into **116**. MS; MH+, 606.1.

Preparation of Compound **198**



198

Steps 1 and 2"



198A

Steps 1 and 2:

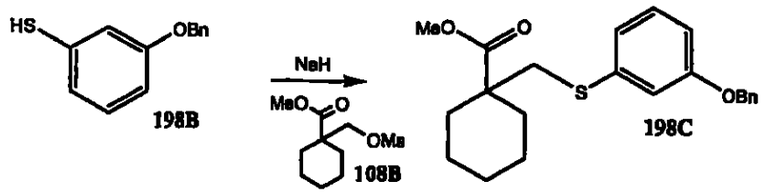
Step 1:

3-Benzyloxyaniline (5.00g; Aldrich) was dissolved in a mixture of conc. HCl (10ml) and ice (10.00g) was added. Sodium nitrite (1.85g) in water (10ml) was added while cooled in an ice bath. When the addition was complete, Potassium O-Ethylxanthate was added and stirred at this temperature until the evolution of nitrogen gas ceased, then heated at 40-45C for a period of 1.5h. After cooling, aqueous work-up and purification by silica gel column chromatography (2-5% EtOAc in hexanes) to give the intermediate xanthate (3.60g).

Step 2:

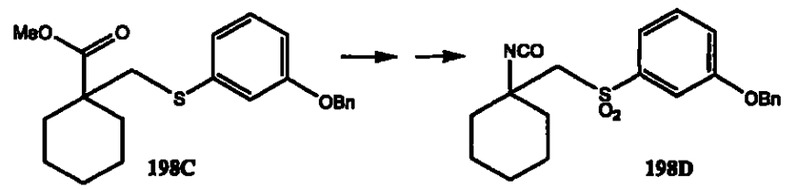
Lithium Aluminum Hydride (6.4ml of a 1M solution in THF) was added dropwise to a stirred solution of the aforementioned xanthate (1.49g) in THF (10ml) and stirred at R.T. for a period of 0.5h. The reaction was quenched with excess acetone and partitioned between EtOAc and aq. 1M HCl. The organic phase was separated, dried and concentrated. The crude reaction product was purified by silica gel column chromatography (1-2% EtOAc in hexanes) to give the thiophenol (**198A**; 0.84g), a white solid.

Step 3:



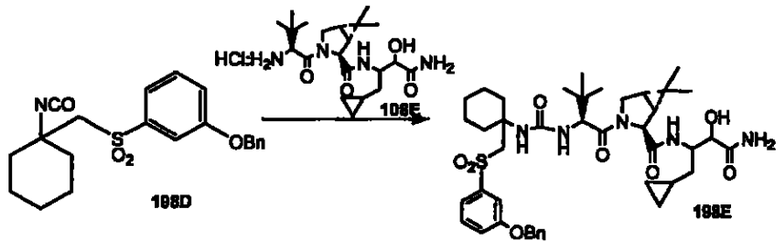
The mercaptan (**198B**; 0.72g) was added to a suspension of NaH (0.08g of a 60% dispersion in mineral oil) in anhydrous DMF, while cooled in an ice bath under an atmosphere of nitrogen. The resulting mixture was stirred for 1h. and the mesylate (**108B**; 0.417g) was added and the reaction was allowed to warm to R.T., overnight. Aqueous work-up and purification of the crude reaction product by silica gel column chromatography (3% EtOAc in hexanes) gave the sulfide (**198C**; 0.313g).

Steps 4-6:



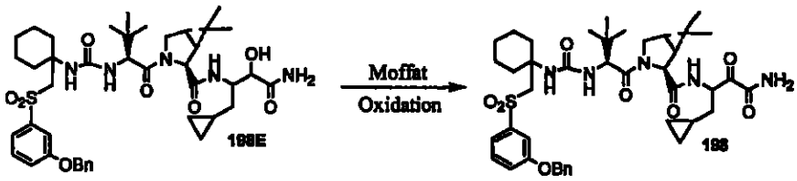
Using the sulfide (**198C**) generated in the previous step, the isocyanate (**198D**) is produced using procedures set forth in (**108C** to **108D**) and **185A** to **185D**). The isocyanate (**198D**) is used in subsequent procedures without purification.

Step 7:



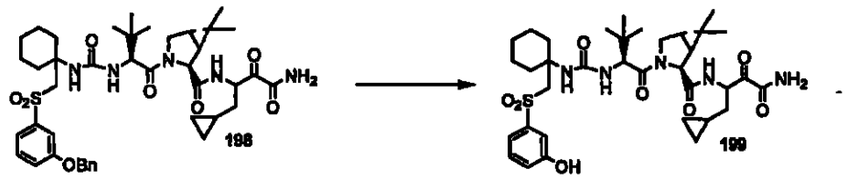
The isocyanate (**198D**; 0.139g) in a minimal amount of dichloromethane (approx. 1ml) was added to a mixture of the hydrochloride salt (**108E**; 0.080g) and triethylamine (0.126ml) and the resulting mixture was stirred at room temperature for a period of 4 hours. The reaction mixture was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried and concentrated. The crude reaction product (**198E**) was used crude in the next step.

Step 8:



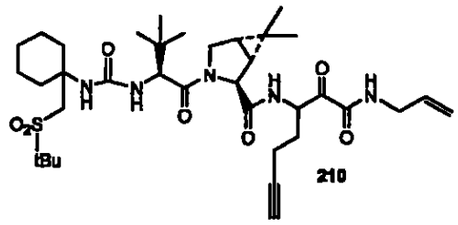
The crude product from the previous step (**198E**) was dissolved in DMSO (3ml) and toluene (3ml) and EDCI (0.346g) followed by dichloroacetic acid (0.074ml) was added and the resulting mixture was stirred at room temperature for a period of 4 hours. The reaction was partitioned between EtOAc and 5% aq. sodium sulfite. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried and concentrated. The crude reaction product was purified by silica gel column chromatography using acetone:hexane (30:70) as eluent to give the keto-amide (**198**; MH+ = 792.2; 55mgs).

Preparation of the Phenol **199** from Benzyl Ether **198**:



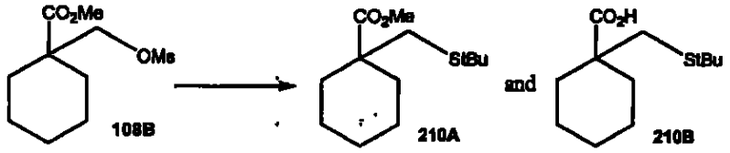
10% Pd-C (25mg) followed by formic acid (0.125ml) were added to a solution of the benzyl ether (**198**; 50mg) in ethanol (4ml) and the resulting black suspension was refluxed for a period of 1hour. After cooling, the reaction was filtered through a pad of celite and the solid was washed with methanol. The combined filtrate was concentrated under reduced pressure to give the desired phenol (**199**; MH+= 702.2; 23mg).

Alternative Preparation of Compound of Formula **210:**



210

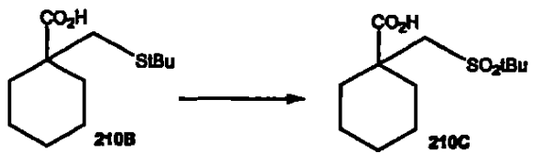
Step1:



Dimethylformamide (20ml; anhydrous; Aldrich) was added to sodium hydride (0.56g; Aldrich) and tert-butyl mercaptan was added to the suspension while cooled in an ice bath under an atmosphere of nitrogen. Once the addition was complete the mesylate (**108B**; prepared as above from 2.00g of alcohol; **108A**) was added and the resulting mixture was stirred overnight at room temperature. The reaction was partitioned between EtOAc and water and the organic phase was separated, dried (MgSO4). column chromatography on silica gel using EtOAc-Hexanes (2:98) to provide the methyl ester-sulfide (**210A**; 1.75g).

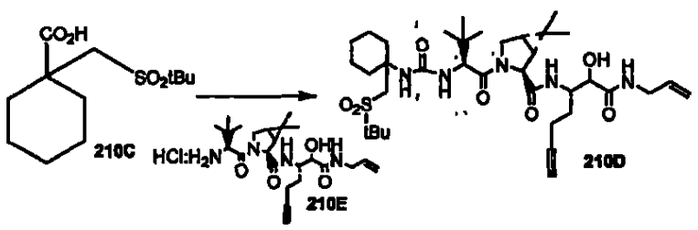
EtOAc was added to the aqueous phase and 10% aq. HCl was added until the water layer pH=1. The organic layer was separated, washed with water, dried and concentrated under reduced pressure to give the sulfide-carboxylic acid (**210B**; 0.747g) as a white solid.

Step 2:



To the sulfide (**210B**; 2.287g) in methanol (75ml) was added a solution of oxone (18.00g; Aldrich) and the resulting white suspension was stirred overnight at room temperature. The volatiles were removed under reduced pressure and the white solid partitioned between EtOAc and water. The organic phase was separated, dried and concentrated to provide the sulfone (**210C**; 2.52g; contains some solvent).

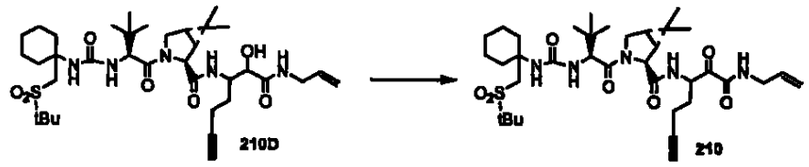
Step 3:



Triethylamine (0.173ml), followed by DPPA (0.268ml) were added to a solution of the carboxylic acid (**210E**; 0.325g) in toluene (3ml) and the resulting mixture was heated to 110C (oil bath) for a period of 1 hour. After cooling the reaction mixture was partitioned between EtOAc and sat. aq. sodium bicarbonate. The organic phase was separated, dried and concentrated. The residue was dissolved in dichloromethane (1ml) and added to a mixture of the hydrochloride salt (**185F**; 0.300g) and triethylamine

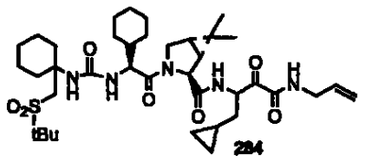
(0.044ml) in dichloromethane (3ml) and the resulting reaction mixture was stirred at room temperature overnight. The reaction was partitioned between EtOAc and 10% aq. HCl, The organic phase was separated, washed with saturated aq. sodium bicarbonate, water, dried and concentrated to yield a crude product which was used in the next step without purification.

Step 4:

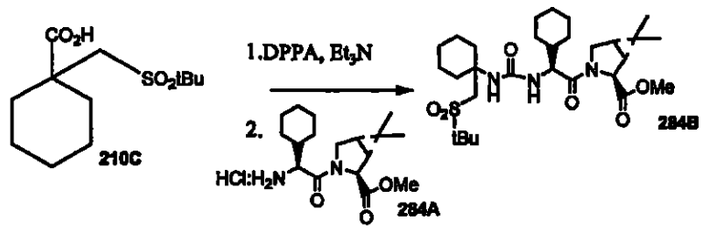


The residue from the previous step (**210D**) was dissolved in dichloromethane (5ml) and Dess-Martin periodinane (0.527g) was added and the reaction mixture was stirred at room temperature for 3 hours. The reaction was partitioned between EtOAc and 5% aq. sodium sulfite. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-Hexanes (70:30) as eluent to give the desired keto-amide (**210**; 0.310g).

Preparation of Compound of Formula **284:**



Steps 1 and 2:



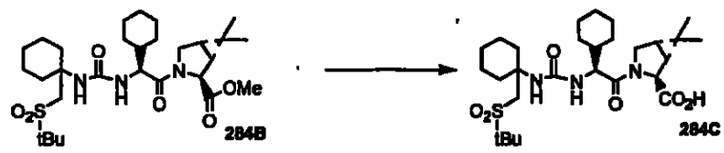
Step1:

Using the carboxylic acid (**210C**; 2.52g), DPPA (2.07ml), triethylamine (1.34ml) in toluene (10ml) and the procedure set above the crude Isocyanate was formed.

Step 2:

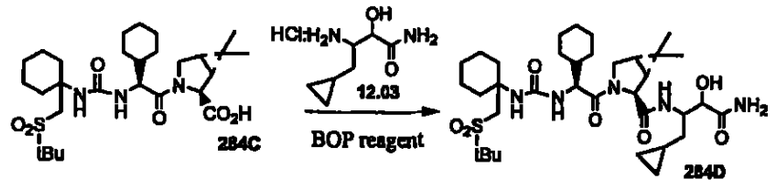
The intermediate isocyanate was dissolved in dichloromethane (2ml) and added to a mixture of the hydrochloride salt **284A** (prepared from 20.04 using the transformation described for 20.06 to 20.07; 1.66g) and triethylamine (3.4ml) and the mixture stirred at room temperature overnight. Aqueous work-up and purification of the residue on silica gel using EtOAc-Hexanes (3:97) gave the desired urea (**284B**) .

Step 3:



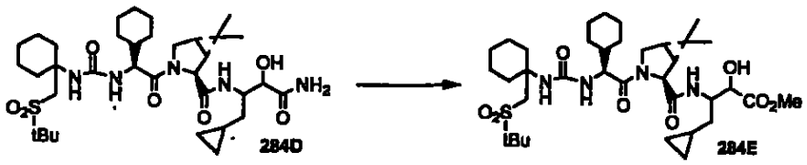
The methyl Ester (**284B**) was dissolved in a mixture of dioxane (90ml) and water (30ml) and lithium hydroxide: monohydrate (0.402g; 2eq) was added and the reaction was allowed to stir at room temperature for 3 hours. The reaction mixture was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, dried and concentrated to yield the carboxylic acid (**284C**; 2.65g).

Step 4:



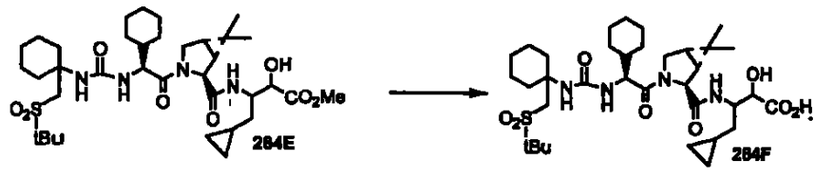
BOP reagent (2.54g) followed by triethylamine (2.4ml) were added to a solution of the carboxylic acid (**284C**; 2.65g) and the hydrochloride salt (**12.03**; 0.933g) in dichloromethane (20ml) and stirred at room temperature overnight. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried and concentrated. The residue was purified by silica gel column chromatography using 2-10% MeOH in dichloromethane as eluent to give the desired amide (**284D**; 2.92g).

Step 5:



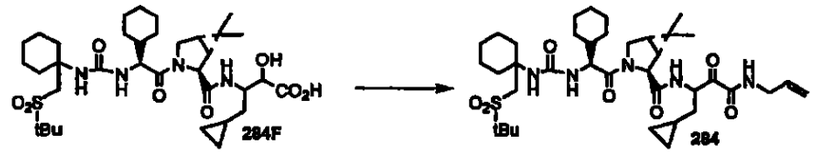
To a solution of the carboxamide (**284D**; 2.92g) in methanol (30ml) was added DMF-DMA (1.12ml) and the resulting mixture was stirred at room temperature for 3 hours and then refluxed for 1.5 hours until T.L.C. indicated that no starting material was left. After cooling, the reaction was partitioned between diethyl ether and 1N aq. HCl. The organic phase was separated, dried and concentrated. Silica gel column chromatography of the residue gave the methyl ester (**284E**), which was treated as shown in Step 6, below.

Step 6:



The methyl ester (**284E**) was dissolved in a mixture of dioxane (30ml) and water (10ml) and lithium hydroxide: monohydrate (0.354g) was added and the resulting mixture was stirred for 3 hours. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, dried and concentrated to provide the carboxylic acid (**284F**; 2.80g).

Steps 7 and 8:



Step 7:

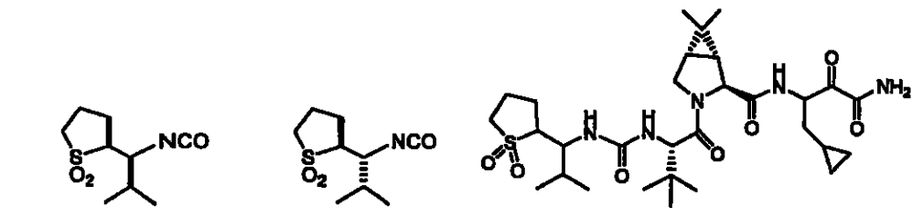
Allyl amine (0.045ml), BOP reagent (0.266g) and triethylamine (0.25ml) were added to a mixture of a solution of the hydroxy-acid (**284F**; 0.348g) in dichloromethane (5ml) and the resulting mixture was stirred at room temperature overnight. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried and concentrated to provide a residue, used without purification in Step 8, below..

Step 8:

The residue was dissolved in dichloromethane (5ml) and Dess-Martin periodinane (0.424g) was added and the reaction mixture was stirred at room temperature for 3 hours. The reaction was partitioned between EtOAc and 5% aq. sodium sulfite. The organic phase was separated, washed with sat. aq, sodium bicarbonate, water, dried and concentrated. The crude reaction

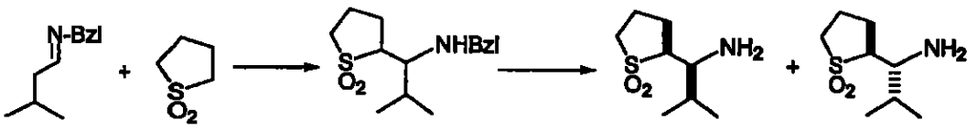
product was purified by silica gel column chromatography to yield the desired keto-amide (**284**; 0.296g). MH+, 732.2.

Preparative Example **331**. Preparation of Intermediates of Formulas **331D** and **331E** for the Compound of Formula **331**:



rac-**331D** rac-**331E** **331**

Step 1. Preparation of Compounds of Formulas **331B** and **331C**:

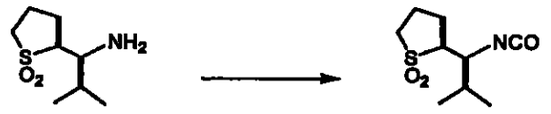


331A **331B** **331C**

N-benzyl-4-methylbutanimine (prepared as described: *Synthesis*, **1985**, 679) and tetrahydrothiophene 1,1-dioxide were reacted in the manner described in Example 336, except at -78° C, to afford compound **331A**, which was hydrogenolyzed in the manner described in Example 336, except at a pressure of 1 atm. The crude product was chromatographed on silica gel, eluting with a gradient of EtOAc to 1:1 acetone-EtOAc to obtain first one racemic diastereomer: H^1-NMR ($CDCl_3$) δ 3.2 (m, 1H), 3.1-2.9 (m, 3H), 2.3-2.1 (m, 2H), 2.1-1.9 (m, 1H), 1.9-1.7 (m, 2H), 1.02 (d, 3H), 0.85 (d, 3H).

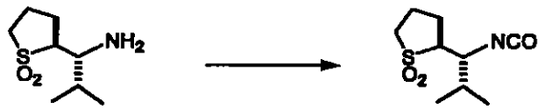
Further elution afforded the other racemic diastereomer: H^1-NMR ($CDCl_3$) δ 3.2 (m, 1H), 3.2-2.9 (m, 4H), 2.3-2.1 (m, 3H), 2.1-2.0 (m, 1H), 1.78 (sex., 1H), 0.96 (m, 6H).

Step 2. Preparation of Compounds of Formulas **331D** and **331E**.



and

331B **331D**



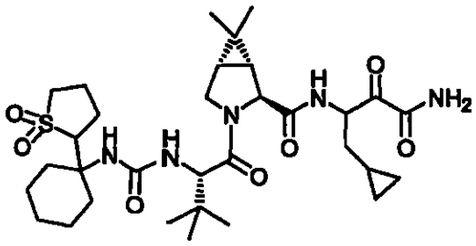
331C **331E**

Compounds **331B** and **331C** were separately reacted with phosgene in the manner described in Example 336 to afford two diastereomeric isocyanates:

the one, from the higher R_f amine: H^1 -NMR ($CDCl_3$)) δ 3.79 (dd, J_1 = 9.9 Hz, J_2 = 3.0 Hz, 1H), 3.25 (m, 1H), 3.1-3.0 (m, 2H), 2.25 (m, 2H), 2.2-2.0 (m, 1H), 2.0-1.7 (m, 2H), 1.09 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H).

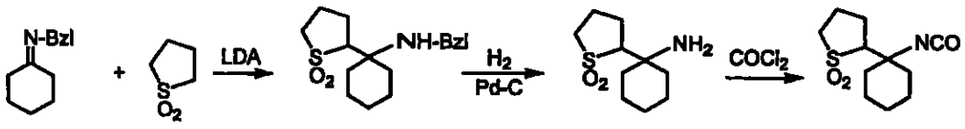
the other, from the lower R_f amine: H^1 –NMR ($CDCl_3$)) δ 3.92 (dd, J_1 = 6.6 Hz, J_2 = 4.8 Hz, 1H), 3.3-2.9 (m, 3H), 2.4 (m, 1H), 2.3 (m, 1H), 2.2-2.0 (m, 3H), 1.03 (t, Δv= 6.3, 6H).

Preparative Example 336. Preparation of Compound of Formula 336.



336

SCHEME 336-1



336A **336B** **336C**

Step 1. Preparation of Compound of Formula **336A**.

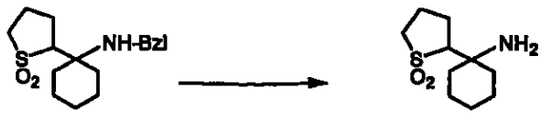


336A

A solution of 20 mL of 2N LDA in hexane-THF was added to 60 mL THF and the solution was cooled to -30° C. Then 4.80 g of tetrahydrothiophene 1,1-dioxide (Aldrich Chemical Co.) was added slowly between -30° C and -10° C, and the stirred at -10° C for an additional 10 min. At -10° C, 7.5 g of N-benzylcyclohexylimine (prepared as described: *Synthesis*, 1998, 1609.) was added at once. After 0.5 h at ambient temperature the mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The extracts are dried over anhydrous Mg_2SO_4, filtered, and the filtrate evaporated. The residue was chromatographed on silica gel, eluting with EtOAc-hexane (3:7) to afford 1.3 g of compound **336A**:

H^1-NMR ($CDCl_3$): δ 7.5-7.2 (m, 5H), 3.76 (ABq, Δv = 230 Hz, J = 12, 2H), 3.41 (m, 1H), 3.13 (m, 1H), 2.94 (m, 1H), 2.4-1.3 (m, 14H).

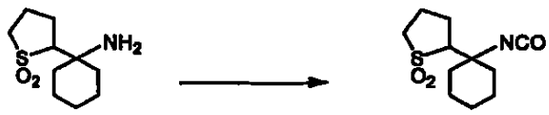
Step 2. Preparation of Compound of Formula **336B**.



336A **336B**

A solution of 1.3 g of compound **336A**, 30 mL EtOH, 1.2 mL of 4n HCl/dioxane solution, and 0.35 g of 10% Pd-C was hydrogenated at 3 atm for 1.5 h. The mixture was filtered, and the filtrate evaporated. The residue was treated with 2 n NaOH and extracted with CH_2Cl_2, the extract was dried and evaporated to leave 0.51 g of compound **336B**, which solidified on standing: H^1-NMR ($CDCl_3\delta$ 3.2-2.9 (m, 3H), 2.4-1.8 (m, 6H), 1.7-1.2 (m, 8H).

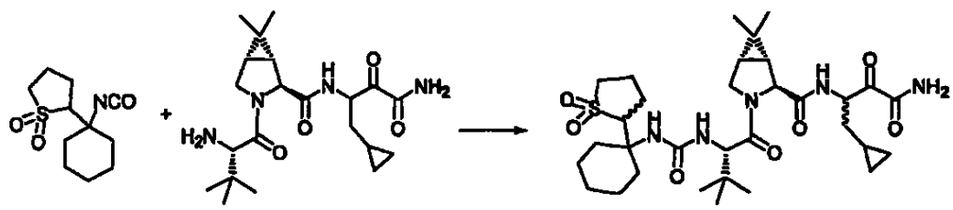
Step 3. Preparation of Compound of Formula **336C**



336B **336C**

To a solution of 0.75 g phosgene in 30 mL toluene at 0° C was slowly a solution of 0.5 g of compound **336B** and 0.80 mL diisopropylethylamine in 10 mL CH_2Cl_2. The mixture was stirred at room temperature for 5 h, concentrated to 15 mL, filtered, then diluted with fresh toluene to 18 mL to produce a 0.12 M solution of compound **336C**, which was used for subsequent reactions. .

Step 4. Preparation of Compound of Formula **336**

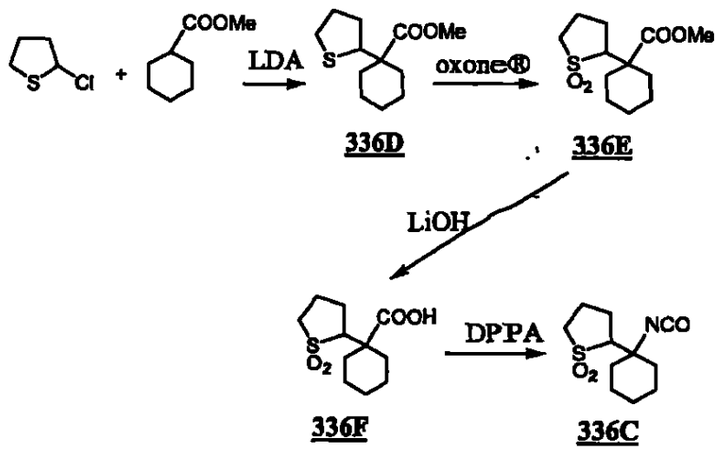


336C **20.10** **336**

Compound **336C** was reacted with compound **20.10** in the manner described in preparative example 108 to produce compound **336** as a mixture of diastereomers H^1-NMR (DMSO-d_6) δ 8.40(m), 8.33 (m), 8.00 (d), 7.75 (s), 6.25 (m), 6.10 (s), 6.01 (s), 4.18 (m), 3.92(m), 3.83 (m), 3.78 (m), 3.13 (m), 2.90 (m) 2.47 (m), 2.1-0.8 (m; Me_A: 1.01; Me_B: 0.82; Bu^t: 0.91), 0.40 (m), 0.19 (m).

Example **336C**. Alternate synthesis of compound **336C**.

SCHEME 336-2



336D **336E** **336F** **336C**

Step 1. Preparation of Compound of Formula **336E**.



336E

2-Chlorotetrahydrothiophene (prepared as described: *Chem. Pharm. Bull.*, ***1986***, *34*(9), 3644) was reacted with α-lithiocyclohexanecarboxylic acid in the manner described in preceding examples to afford sulfide ester compound **336D** in 39% yield. Compound **336D** was oxidized with oxone® in the manner described in preceding examples to afford sulfone ester compound **336E**: H^1 NMR($CDCl_3$) δ 3.73 (s, 3H) 3.3-3.0 (m, 2H), 3.0-2.9 (m, 1H), 2.6-2.4 (m, 1H), 2.4-1.3 (m, 13H).

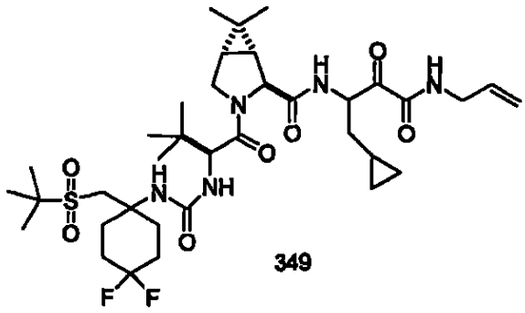
Step 2. Preparation of Compound of Formula **336C**.



336E **336C**

Compound **336E** was hydrolyzed with LiOH in water-dioxane at 100° C in the manner described in preceding examples to afford sulfone carboxylic acid compound **336F**: H^1 NMR($CDCl_3$) δ 3.4-3.2(m, 1H), 3.2-3.1 (m, 1H), 3.1-2.9 (m, 1H), 2.3-2.1 (m, 3H), 2.1-1.8 (m, 3H), 1.8-1.3 (m, 7H). Compound **336F** was reacted with diphenylphosphorylazide in the manner described in preceding examples to afford compound **336C** as a colorless solid: H^1 NMR($CDCl_3$) δ 3.2 (m, 1H), 3.1-2.9 (m, 2H), 2.45 (d, 1H), 2.4-1.9 (m, 4H), 1.85-1.5 (m, 7H), 1.5-1.2 (m, 2H).

Synthesis of Compound 349:

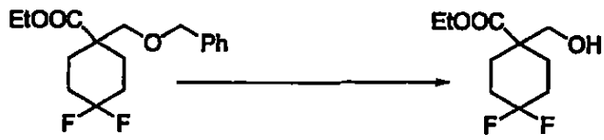


349



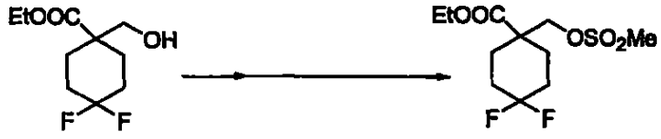
349A 349B

To a solution of the ethyl ester (**349A**; 10 g; 0.052 mol.) in diethyl ether (50 ml) at -78^0 C (bath temp.) was added KHMDS (0.5 M in toluene; 156.087 ml; 1.5 equiv.). The resulting solution was stirred for 30 minutes, then benzyl chloromethyl ether (11.89 ml; density 1.13; 1.65 equiv.) was added. The reaction mixture was stirred at -78^0 C to R.T. for 24 h. Reaction was stopped by addition of saturated aq. NH_4Cl. It was then diluted with ethyl acetate and the combined organic phase was washed with brine, dried over Na_2SO_4 and evaporated to dryness *in vacuo* to provide a light brown oil (24.2 g). It was chromatographed over silica gel (300 g). The column was eluted with 1% - 4% ethyl acetate in n-hexane providing in some of the fractions pure **349B** (6.54 g).



349B 349C

A solution of the benzyl ether (**239B**; 2.8316 g; 0.0091 mol.) in $CHCl_3$ (49.5 ml) was treated with methane sulfonic acid (22.65 ml) and the reaction mixture stirred at room temperature for ~70 minutes. Ice was added to the reaction mixture and it was diluted with ethyl acetate. The organic phase was washed with saturated $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness *in vacuo* to provide yellowish oil (2.86 g). It was chromatographed over SiO_2 (65 g). The column was eluted with 15% - 25% ethyl acetate in n-hexane providing in some of the fractions pure **349C** (1.5913 g).



349C **349D**

A stirred solution of the alcohol (**349C**; 1.14 g; 0.0051 mol.) in methylene chloride (6.4 ml) was cooled in ice bath and treated with Et_3N (0.7857 ml; density 0.726; 1.1 equiv.) and methanesulfonyl chloride (0.4168 ml; density 1.48; 1.05 equiv.). After ~2 hrs the reaction mixture was diluted with methylene chloride and it was washed with 6N HCl followed by saturated $NaHCO_3$. The organic phase was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to provide the mesylate **349D** (1.5447 g) as a light yellow oil.



349D **349E**

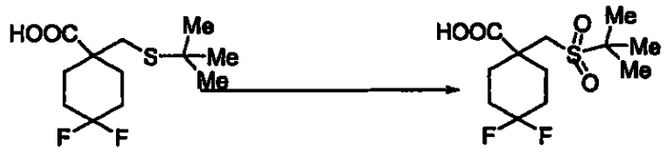
A stirred suspension of NaH (0.4114 g; 60% dispersion in mineral oil; 2 equiv.) in dry DMF was treated with tert.-butyl thiol (1.16 ml; density 0.8; 2 equiv.) with ice bath cooling. The reaction mixture was stirred for 30 minutes after which the mesylate (**349D**; 1.5447 g; 1 equiv.) was added in dry DMF (8+2 ml). Ice bath was removed and the reaction mixture was stirred at room

temperature overnight. The reaction mixture was acidified with 6N HCl and extracted with ethyl acetate. The ethyl acetate extract was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to provide crude 349D (2.87 g) which was chromatographed over SiO_2 (60 g). The column was eluted with 3% ethyl acetate providing in some of the fractions pure **349E** (1.38 g) as a colorless oil.



349E 349F

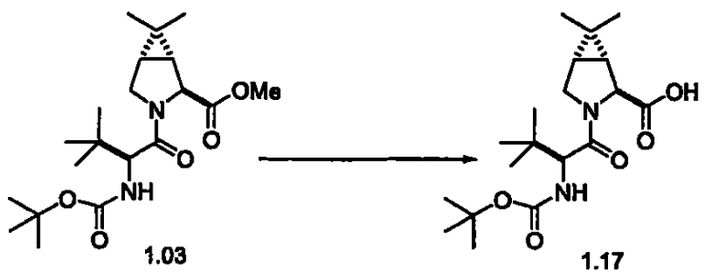
A solution of the ethyl ester (**349E**; 1.38 g; 0.00468 mol.) in ethanol (16 ml) and water (4.13 ml) was treated with KOH pellets (2.63 g; 10 equiv.). The resulting solution was refluxed for 7 h and then allowed to cool to room temperature overnight. Ethanol was evaporated *in vacuo* and the residue partitioned between CH_2Cl_2/water, acidified with 6N HCl to pH 1. The organic phase was separated and the aqueous phase extracted three times with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to provide **349F** (1.19 g) as a off white solid, m.p. 93-95^0 C.



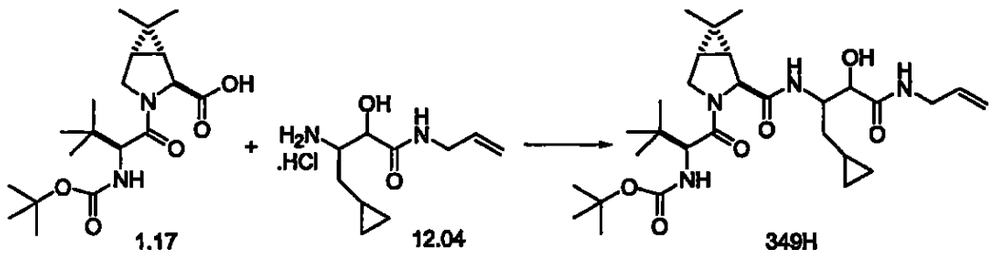
349F 349G

The oxone (8.24 g; 3 equiv.) dissolved in water (31 ml) was added to a stirred solution of the sulfide (**349F**; 1.19 g; 1 equiv.) in methanol (31 ml) at 0^0 C (bath temp). The reaction was stirred at 0^0 C to R.T. over the weekend. Solvents were evaporated in-vacuo and the residue partitioned between

CH_2Cl_2/water. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to provide **349G** (1.29 g) as a crystalline solid, m.p. 212^0 C.

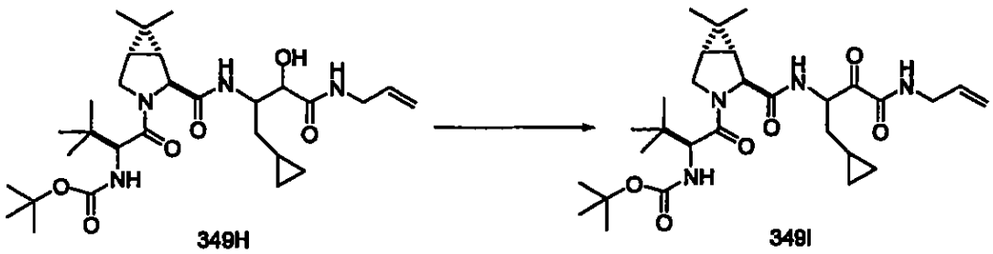


To a cooled (ice bath) solution of the ester (**1.03**; 4.56 g; 0.0119 mol.) in dioxane (18.23 ml) was added with stirring 1.0 N LiOH (18.23 ml). The reaction mixture was stirred for 2 hrs. TLC indicated some starting material still remaining, so added 2+1 ml 1.0 N LiOH and stirred overnight. Reaction complete by TLC. 6N HCl was added to acidify the reaction mixture to pH 1 and ethyl acetate (150 ml) added. After shaking, the ethyl acetate phase was separated and the aqueous phase extracted with ethyl acetate. The combined ethyl acetate phase was washed once with brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo* to provide **1.17** as a amorphous solid (4.7805 g; occluded solvent).



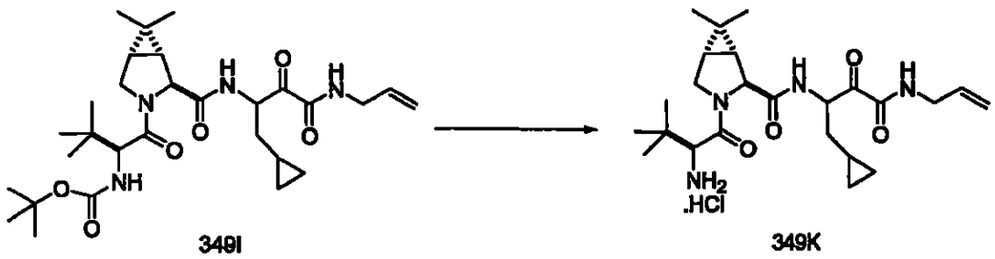
To a -20^0 C solution of the acid **1.17** (0.7079 g; 0.00192 mol.) and the amine salt (**12.04**; 0.5231 g; 1.16 equiv.) in CH_2Cl_2 (10 ml) was added HATU

(0.77 g; 1.05 equiv.) followed by diisopropylethylamine (0.8913 g; 1.2 ml; 3.59 equiv.). The reaction mixture was stirred at -20^0 C for ~16 hrs. It was then diluted with EtOAc (~150 ml) and washed successively with satd. $NaHCO_3$, 10% citric acid and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* provided a amorphous solid which was chromatographed over SiO_2 (42 g). Elution of the column with 50%-60% EtOAc in n-hexane provided in some of the fractions pure **349H** (0.7835 g).



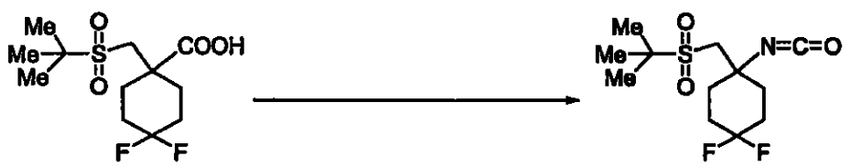
349H **349I**

A solution of the hydroxyamide **349H** (0.7835 g; 0.00142 mol.) in dry methylene chloride (32 ml) was treated with stirring and cooling (ice bath) with Dess-Martin reagent (1.5134 g; 2.5 equiv.). Ice bath was removed and the reaction mixture was allowed to stir at room temperature for 2.5 hrs. Saturated $Na_2S_2O_3$ (32 ml) was added to destroy excess oxidant and stirring continued until the cloudy solution turned clear two-phase system. The reaction mixture was then diluted with CH_2Cl_2 (~100 ml), the organic phase separated and washed once with satd. $NaHCO_3$, water then dried. Evaporation to dryness *in vacuo* provided **349I** (0.7466 g) as an amorphous solid.



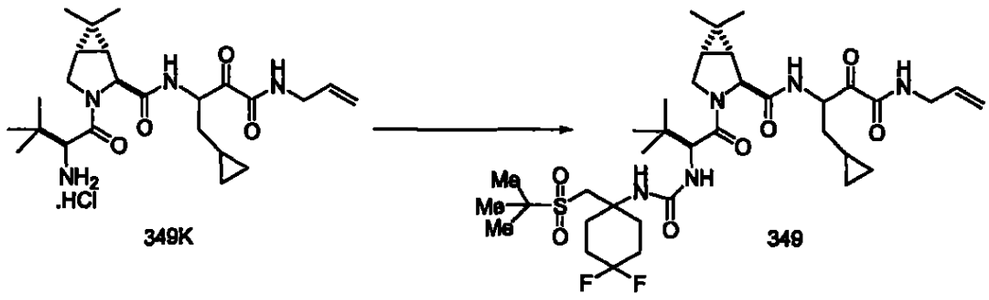
349I 349K

The tert.-butylcarbamate **349I** (0.7466 g) was treated with 4M HCl/dioxane (20 ml) and left in a stoppered flask for 45 minutes. Most of the dioxane was evaporated in-vacuo and the residue evaporated with n-hexane twice; the remaining residue was triturated with ether leaving **349K** (0.6341 g) as a free flowing solid.



349G 349J

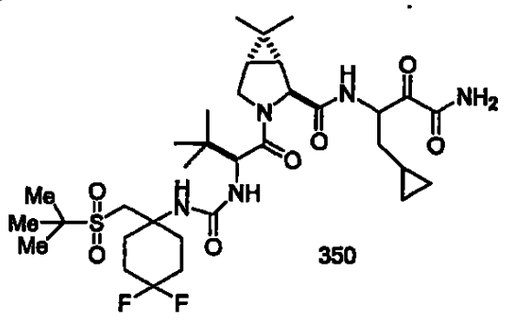
To a toluene solution (7.5 ml) of the acid **349G** (0.1 g; 0.0003351 mol.) were added Et_3N (0.0467 ml; 46.7 µl; 1 equiv.) followed by diphenylphosphoryl azide (0.072; 72 µl; 1equiv.). The reaction mixture was refluxed for 1 h. After cooling down, it was treated with ethyl acetate (~50 ml), the organic phase washed with saturated $NaHCO_3$ and concentrated *in vacuo* to provide **349J** (0.1 g).



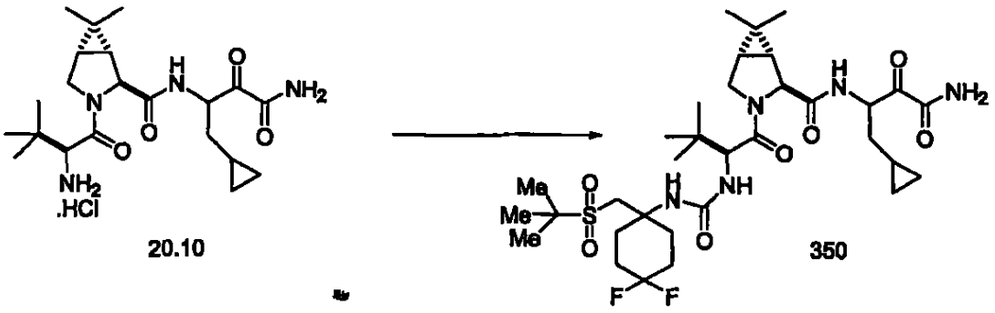
349K 349

To a stirred suspension of the amine hydrochloride **349K** (0.1 g; 0.000207 mol.) in methylene chloride (5 ml) was added diisopropylethylamine (0.135 g; 5 equiv.). After 1 minute was added the isocyanate **349J** (0.1 g; 0.0003385 mol.). The reaction mixture was stirred at room temperature for 2 hrs. It was then diluted with EtOAc and washed with 1N HCl, satd. $NaHCO_3$, dried over Na_2SO_4 and finally evaporated to dryness in-vacuo to provide an amorphous solid. It was subjected to preparatory TLC on silica gel plates using 40% acetone in n-hexane as eluent. The uv positive band was extracted with 60% acetone in methylene chloride to provide **349** (0.122 g) as an amorphous solid.

Synthesis of Compound 350:



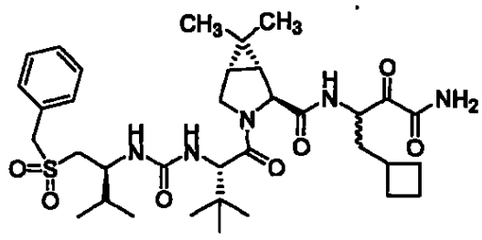
350



20.10 350

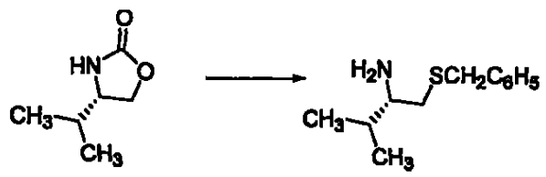
To a stirred suspension of the amine hydrochloride **20.10** (0.0966 g; 0.000223 mol.) in methylene chloride (5 ml) was added diisopropylethylamine (0.144 g; 5 equiv.). After 1 minute was added the isocyanate **349H** (0.1 g; 0.0003385 mol.). The reaction mixture was stirred at room temperature for 2 hrs. It was then diluted with EtOAc (~100 ml), then washed with 1N HCl, satd. $NaHCO_3$, dried over Na_2SO_4 and finally evaporated to dryness *In vacuo* to provide an amorphous white solid (0.1731 g). It was subjected to preparatory TLC on silica gel using 40% acetone in n-hexane as eluent. The uv positive band was extracted with 60% acetone in methylene chloride to provide **350** (0.0671 g) as an amorphous solid.

Example 145 Preparation of compound of formula I45:



145

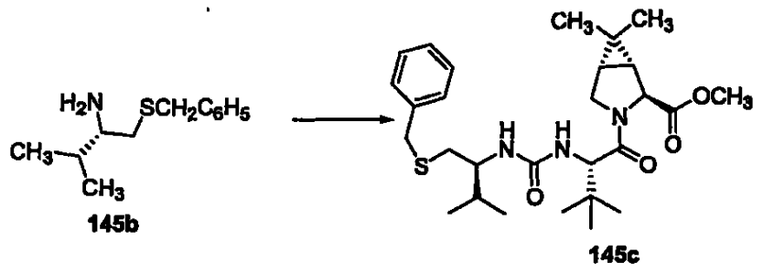
Step 1



145a 145b

1-Propanol was treated with metallic sodium (361 mg, 15.7 mmol) and stirred at RT for 1 h. After complete dissolution of sodium, benzylthiol (2.74 mL, 23.2 mmol) was added and the reaction mixture was stirred at RT for 0.5 h. (S)-4-isopropyl-oxazolidinone (Aldrich, 1g, 7.74 mmol) was added and the reaction mixture was heated at reflux for 16 h. The reaction mixture was concentrated in *vacuo* and the crude mixture was diluted with cold water and extracted with ether (3x150 mL). The combined organic layers were dried, filtered concentrated in *vacuo* to yield amine **145b.** It was converted to the hydrochloride salt with 4 M HCl and dried in high vacuum to yield **145b.HCl** (1.9 g).

Step 2

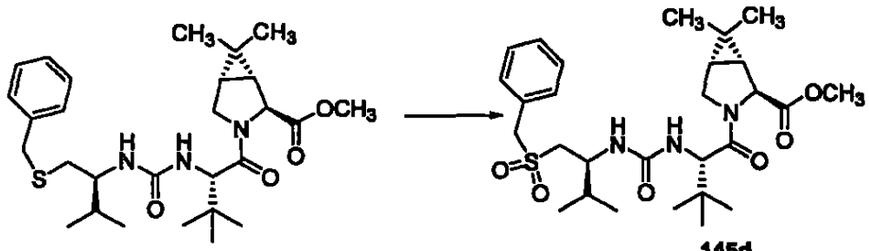


145b 145c

A solution of **145b.HCl** (1 g, 4.07 mmol) in CH_2Cl_2 (50 mL) and satd. $NaHCO_3$ (70 mL) at 0° C was treated with phosgene (15% in toluene 10 mL) and stirred at 0° C for 3 h. The reaction mixture was poured into a separatory funnel and the organic layer was separated. The organic layer was washed with cold $NaHCO_3$, brine and dried ($MgSO_4$). It was concentrated and used as it is in next step.

Amine hydrochloride salt (**1.04**; 865 mg, 2.7 mmol) was dissolved in CH_2Cl_2/DMF 1:1 and cooled to 0° C. The mixture was treated with $(C_2H_5)_3N$ (682 mg, 6.75 mmol) and isocyanate prepared as above (950 mg, 4.07 mmol) and stirred at RT overnight. The solvent was evaporated and the residue was dissolved in EtOAc. The organic layer was washed with aq. HCl, aq NaHCO3, brine. The reaction mixture was dried, filtered and concentrated in *vacuo*. The residue was purified by chromatography (SiO_2, EtOAc/Hexanes 1:3) to yield **145c** (880 mg).

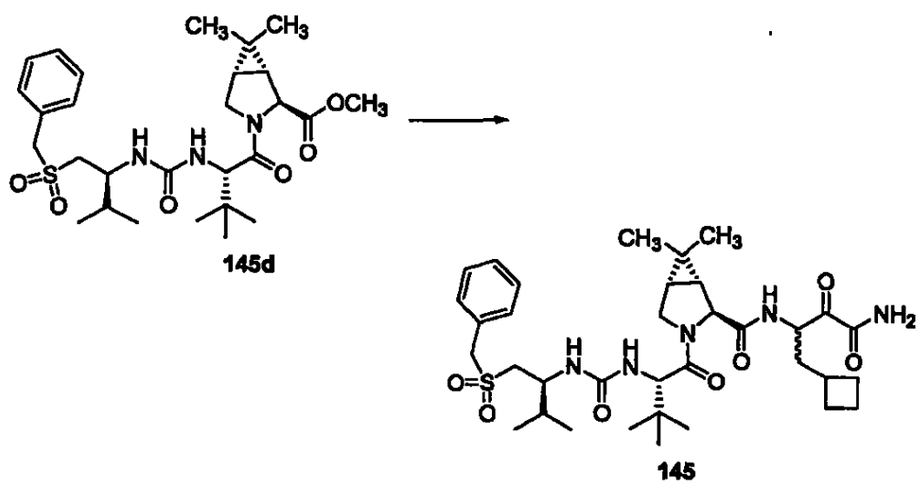
Step 3



145c **145d**

A solution of **145c** (500 mg, 0.9 mmol) in 1,2 dichloroethane (10 mL) was treated with MCPBA (70%, 500 mg,) and 0° C and diluted with ether and aq. solution of $Na_2S_2O_3$. The organic layer was separated and washed extensively with aq. saturated NaHCO3 and brine. The reaction mixture was dried (MgSO4) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hexane 2:3) to yield **145d** (530 mg). MS (ESI) 550 [$(M+1)^+$, 100], 381 (95), 353 (20).

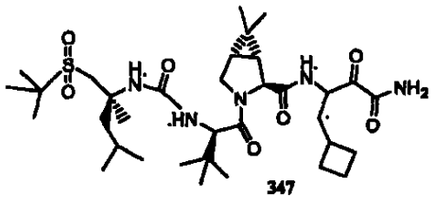
Step 4



145d **145**

The conversion of **145d** to **145** was identical to the procedure described in the conversion of **284B** to **284D** and **108D** to **108** MS (ESI) 690 [(M+1)$^+$, 100), 381 (30).

Preparation of Intermediate of Formula 347:



347

Step1:

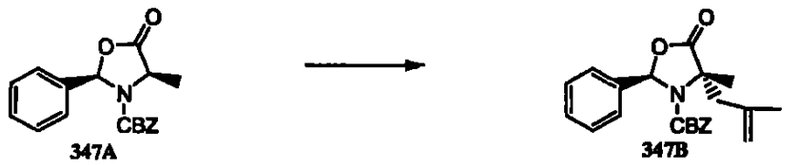


347A

Dimethyl benzaldehyde acetal (10.0 mL, 67.2 mmol) was added to a cooled solution of CBZ-*D*-alanine (15.0 g, 67.2 mmol) in Et_2O (180 mL), followed by $BF_3.Et_2O$ (50.6 mL, 403.2 mmol) over 15 min. The reaction

mixture was stirred at -20 °C for 4 days and quenched by addition of ice cold saturated $NaHCO_3$ (350.0 mL). The organic layer was diluted with Et_2O (500 mL), separated, washed with $NaHCO_3$ (5% aqueous solution), brine, dried over $MgSO_4$, filtered and concentrated. The crude was recrystallized using Et_2O/hexane to yield **347A** (13.6 g, 65%).

Step 2



347A **347B**

THF(48.0 mL) was added to a flame dried flask and cooled to -35 °C. KHDMS(0.5 M solution in PhMe, 42.0 mL, 21 mmol) was added to it, followed by dropwise addition of a mixture of **347A** (6.22g, 20.0 mol) and 3-bromo-2-propene (2.02 mL, 20 mmol) maintaining the internal temperature between -30 and -35 °C. The reaction mixture was stirred at -35 °C for 2 h, then allowed to warm up over 2.5 h, quenched by addition of ice cold saturated $NaHCO_3$ (400.0 mL). The organic layer was diluted with Et_2O (600 mL), separated, washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude was purified over SiO_2 using CH_2Cl_2 to yield **347B** (14.2 g, 90%).

Step 3



347B **347C**

To a solution of **347B** (10.7 g, 29.4 mmol) in MeOH (200 mL) was added LiOH (4N, 15 mL) and stirred at RT for 30 min, diluted with H_2O (500 mL), extracted with EtOAc (4 x 400 mL), washed with brine, dried over

$MgSO_4$, filtered and concentrated. The crude was purified over SiO_2 using CH_2Cl_2 to yield **347C** (8.65 g, 88%).

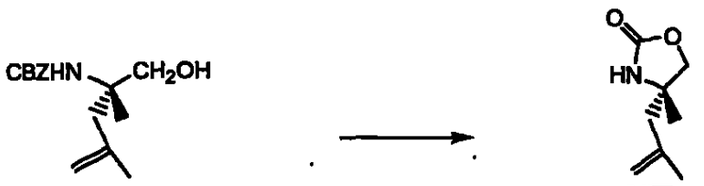
Step 4



347C **347D**

To a ice-cold solution of **347C** (8.56 g, 29.4 mmol) in EtOH (100 mL) was added $LiBH_4$ (960 mg, 44.1 mmol) and stirred at RT for 12h, another portion of $LiBH_4$ (960 mg) was added to it at 5 °C and stirred at RT for 4h, diluted with H_2O (100 mL) and MeOH(100 mL), evaporated to dryness, dissolved in H_2O (100 ml), extracted with EtOAc (500 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude was purified over SiO_2 using EtOAc (1-8%) in CH_2Cl_2 to yield **347D** (4.7 g, 60%).

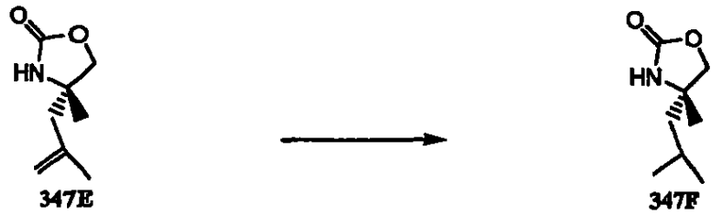
Step 5



347D **347E**

t-BuOK (1M in THF, 3.85 mL) was added to a cooled (-5 °C) solution of **347D** (4.06 g, 15.4 mmol) in THF (20 mL) and stirred at that temperature for 2h. The reaction mixture was concentrated, redissolved in EtOAc (250 mL) and NaOH (2N, 50 mL). The organic layer was diluted with EtOAc (600 mL), separated, washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude was purified over SiO_2 using 10% CH_2Cl_2 in EtOAc to yield **347E** (1.4 g).

Step 6



347E 347F

347E (1.37 g, 8.82mmol) was dissolved in EtOH (25 mL) and Pd-C (10% by weight, 275.0 mg) was added to it. The reaction mixture was stirred under a hydrogen atmosphere for 12h, filtered, concentrated and purified over SiO_2 using 10% CH_2Cl_2 in EtOAc to yield **347F** (1.04g, 75%).

Step 7



347F 347G

347F (2.58 g, 16.4mmol) was dissolved in PrOH (40 mL) and NaSBu-*t*(10.2 g, 82 mmol) was added to it. The reaction mixture was refluxed for 136 h, cooled, evaporated and redissolved in EtOAc, washed with H_2O and the organic layer dried over $MgSO_4$, filtered and concentrated. The crude was purified over SiO_2 using 30% acetone in CH_2Cl_2 to yield **347G** (0.6 g, 19%) and **347F** (1.1g).

Step 8

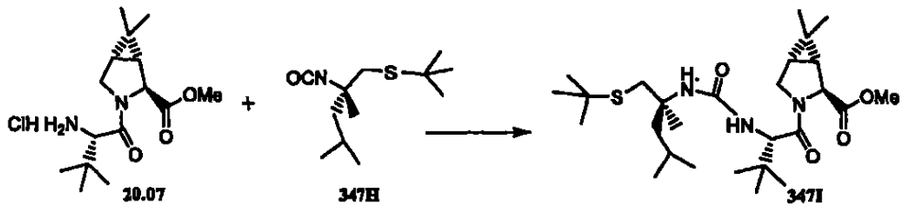


347G 347H

Saturated $NaHCO_3$ was added to an ice-cold solution of **347G** (0.6 g, 3.0 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred vigorously for

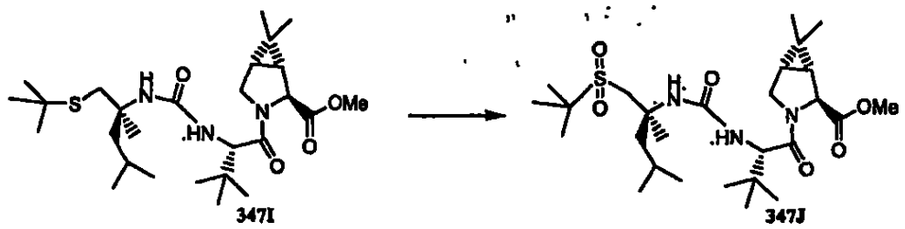
10 min. and $COCl_2$ (1.85 M solution in PhMe, 4.51 mL) was added to it and stirring was continued at room temperature for 1h. The organic layer was dried over MgSO4, filtered and concentrated to half the volume to yield **347H** as a solution in CH_2Cl_2.

Step 9



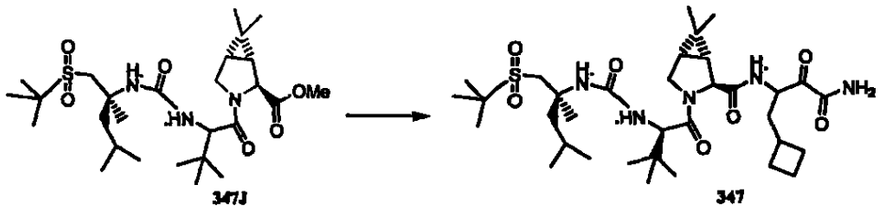
To a cooled solution (O ^{0}C) of **347H** (685 mg, 3.0 mmol) in DMF (10.0 mL) was added **20.07** (1.05 g, 3.34 mmol), followed by DIPEA (1.45 mL, 8.35 mmol). The reaction mixture was stirred at room temperature for 1.2 h, diluted with ethyl acetate, washed with 3% citric acid, brine, dried over $MgSO_4$, filtered, concentrated and purified over SiO_2 using acetone/CH_2Cl_2 (1:9) to yield **347I** (1.57g).

Step 10



To a cooled solution (O ^{0}C) of the **347I** (1.5 g, 3.34 mmol) in CH_2Cl_2 (100.0 mL) was added ***m*-CPBA** (2.51g, 10.02 mmol). The reaction mixture was warmed to room temperature over 12 h, diluted with CH_2Cl_2 (300.0 mL), washed with brine, dried over $MgSO_4$, filtered, concentrated and purified over SiO_2 using acetone/CH_2Cl_2 (1:9) to yield **347J** (1.57g).

Step 11



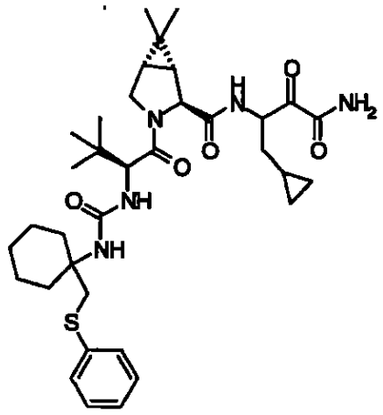
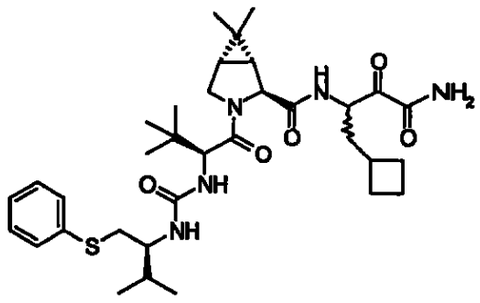
347J 347

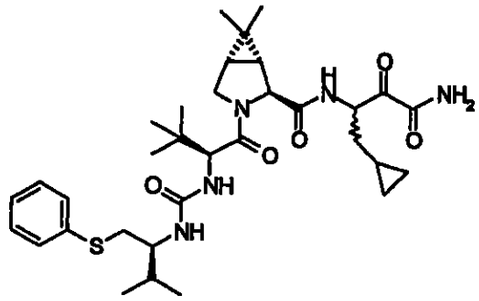
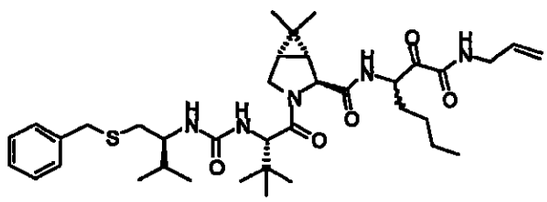
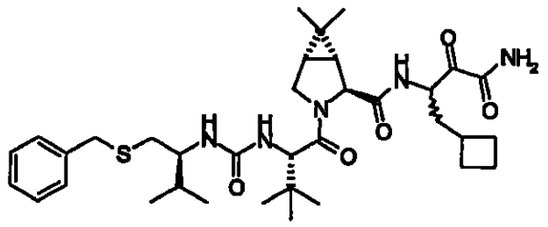
The conversion of **347J** to **347** was similar in procedure to those described in the conversion of **284B** to **284D** and **108D** to **108** MS(LCMS) calcd. 681.94, found (MH^+) 683.2.

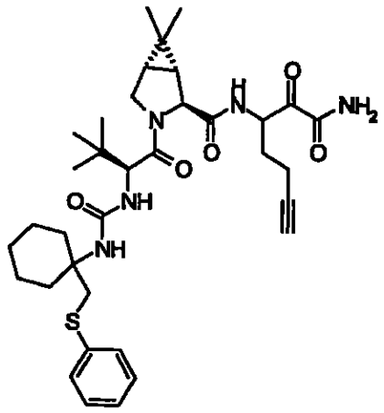
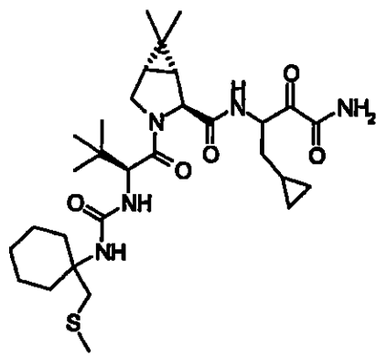
Table 3 lists some of the inventive compounds and their HCV serine protease inhibitory activity ranges, as determined by the assay described later. The activity is shown as Ki* ranges (nanoMolar), which are: A = <75 nM; B = 75 - 250 nM; and C = >250 nM.

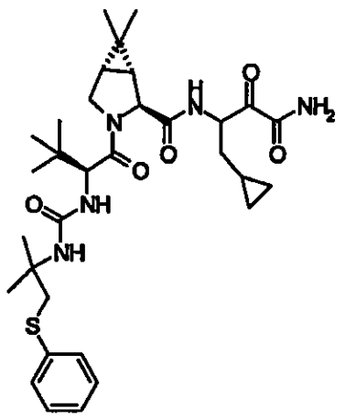
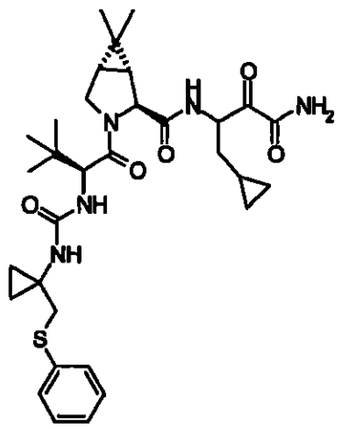
Table 3

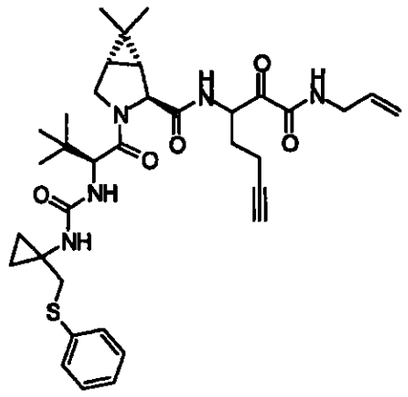
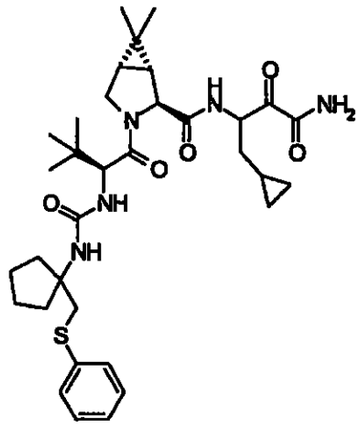
Sulfide Compounds

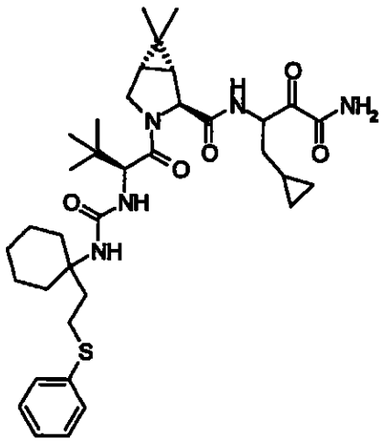
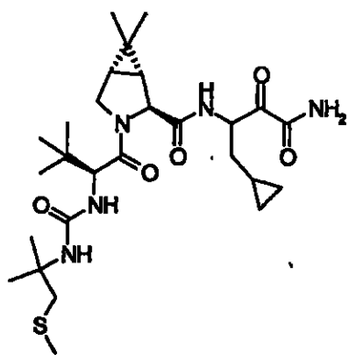
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
	[Ki* ranges are: A = <75 nM; B = 75 - 250 nM; C = >250 nM]		
102		LCMS; MH^+, 654.1	A
103			B

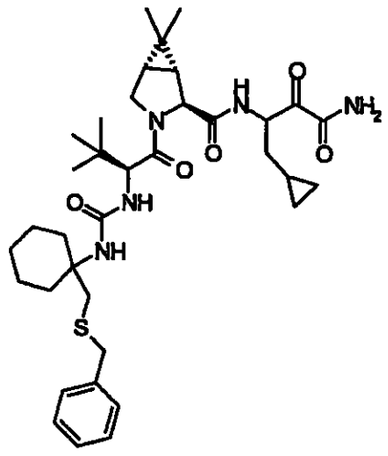
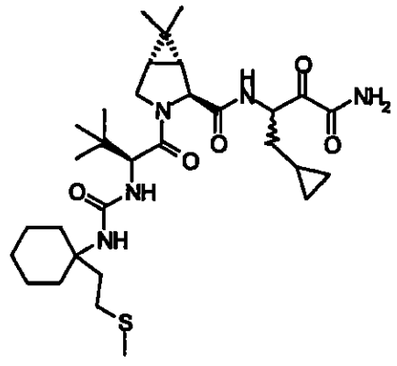
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
104			A
105			C
106			B

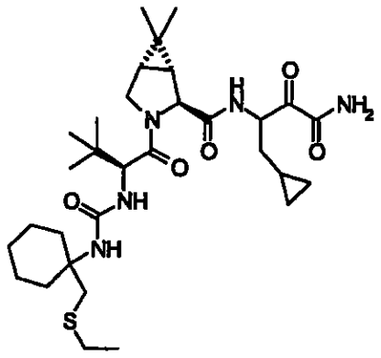
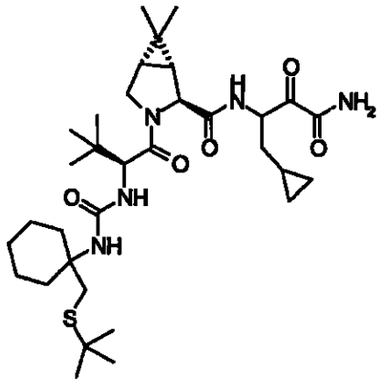
Prep. Ex.	COMPOUND	Select Mass Spectra Data	KI* range
107		FABMS, $(M+TG)^+$, 760.5. TG= thioglycerol	A
108			A

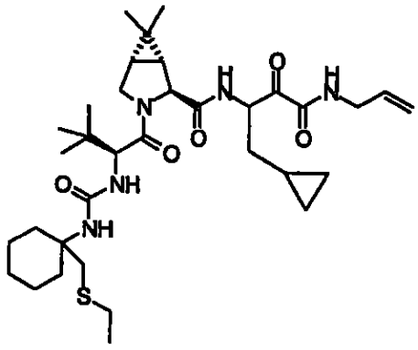
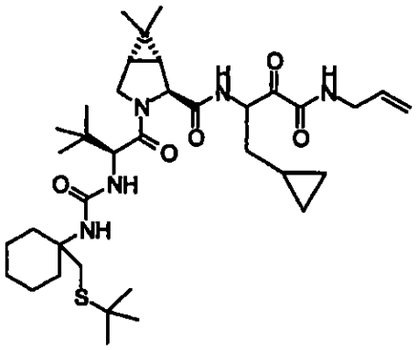
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
109			A
110			A

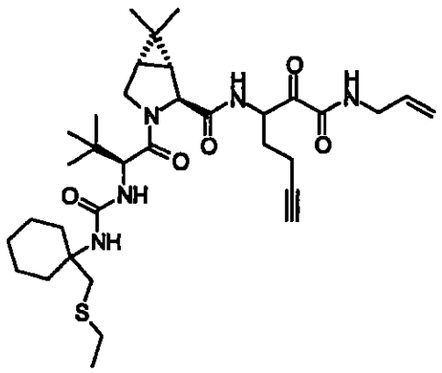
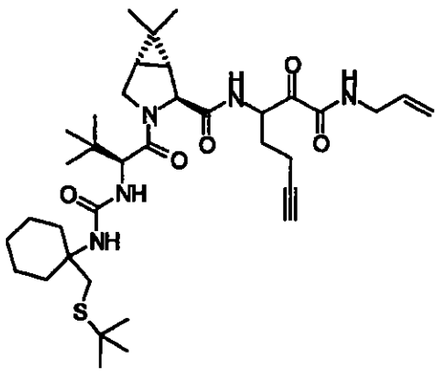
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
111		FABMS: (MH)+, 650.3.	B
112			A

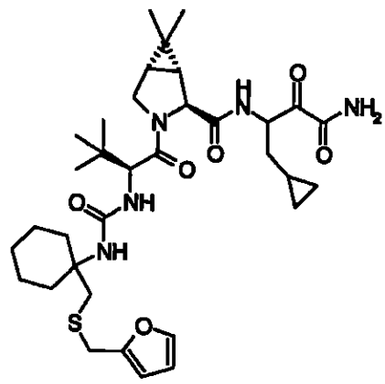
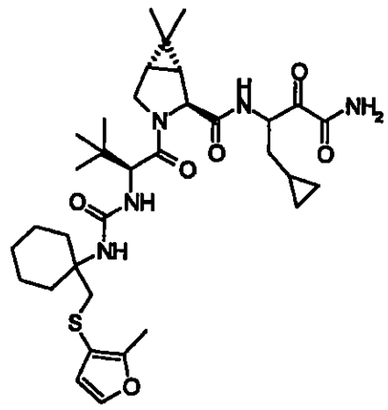
Prep. Ex.	COMPOUND	Select Mass Spectra Data	KI* range
113		FABMS: $(MH)^+$,668.3	A
114			A

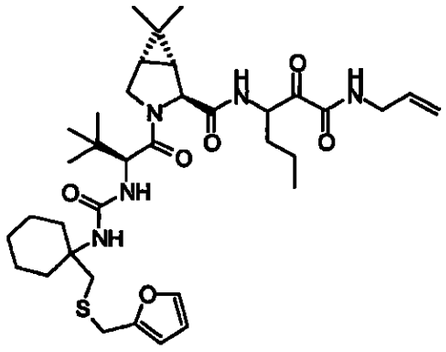
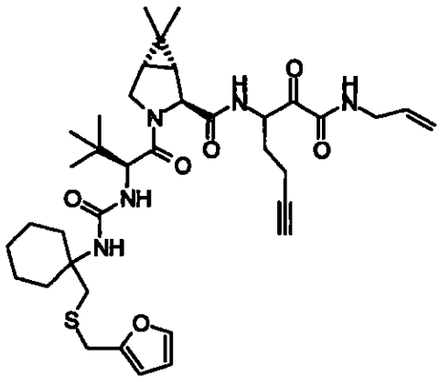
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
115			A
116		LCMS; MH+, 606.1.	A

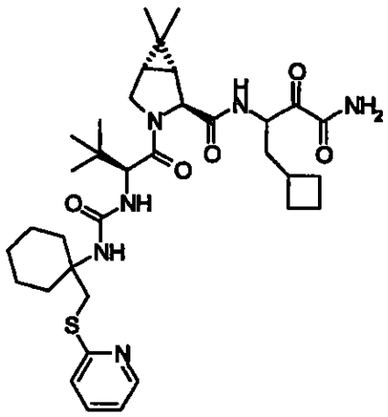
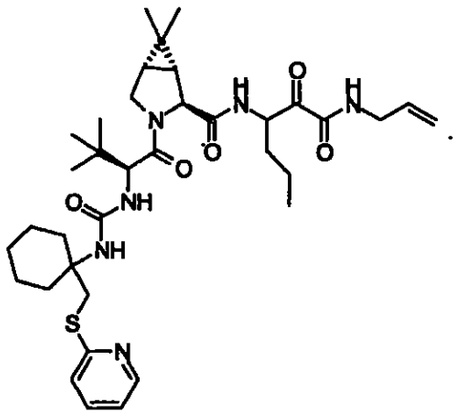
Prep. Ex.	COMPOUND	Select Mass Spectra Data	KI* range
117			A
118			A

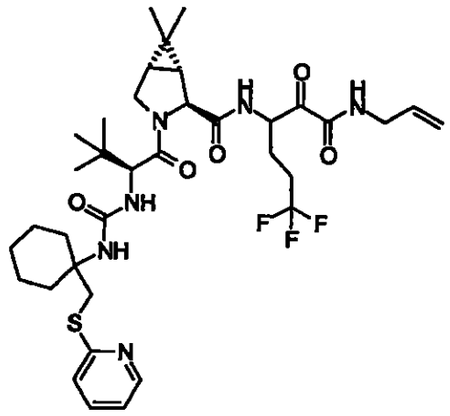
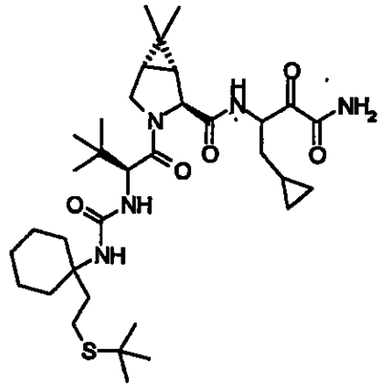
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
119			B
120			C

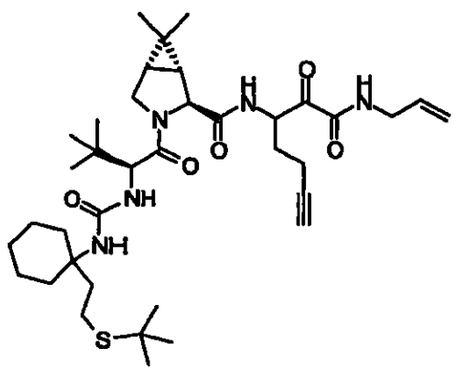
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
121		FABMS; MH^+, 644.2	A
122		FABMS; MH^+, 672.5.	A

Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
123			A
124			B

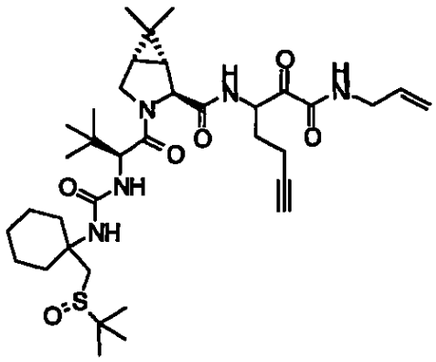
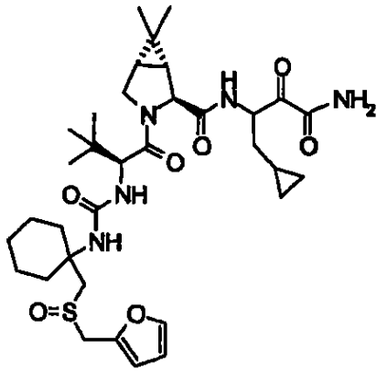
Prep. Ex.	COMPOUND	Select Mass Spectra Data	KI* range
125			B
126			A

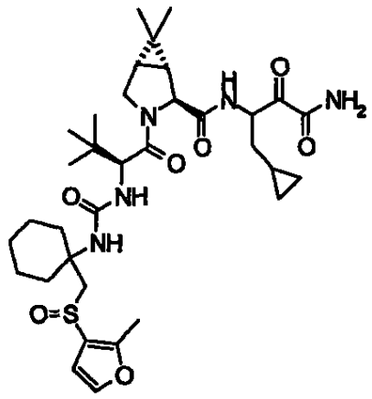
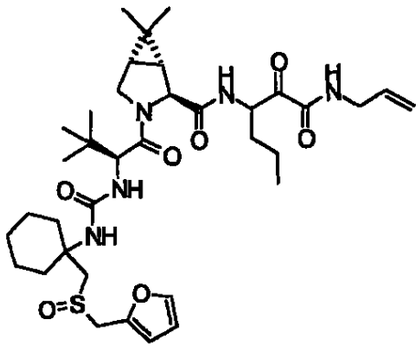
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
127			A
128			B

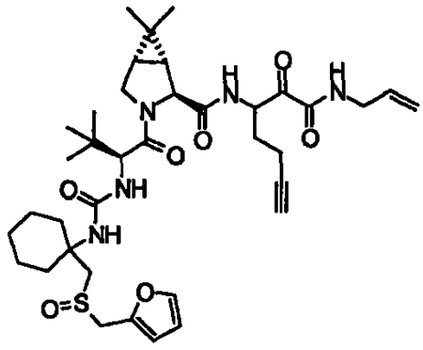
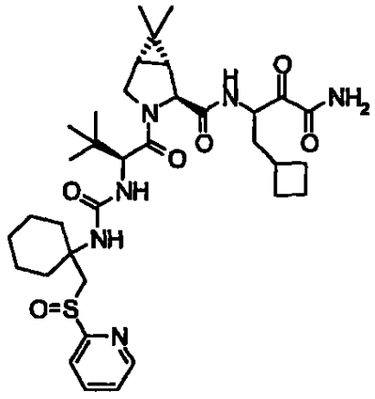
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
129			C
130			B

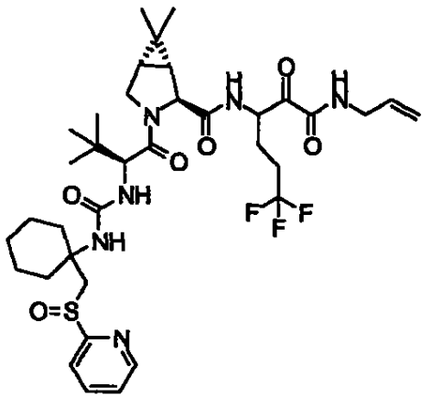
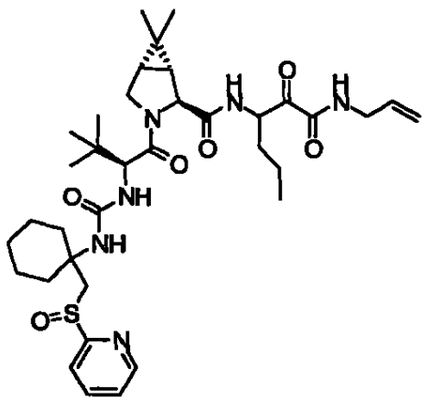
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
131			B

Sulfoxide Compounds

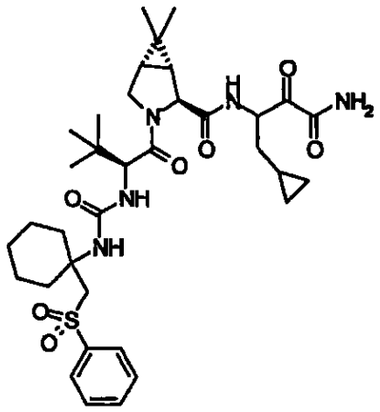
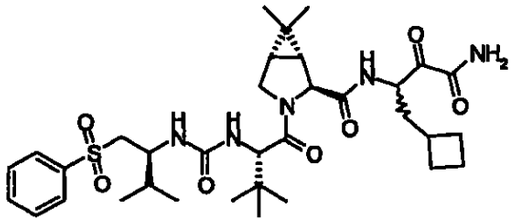
Prep. Ex.	COMPOUND	Select Mass Spectral Data	KI* range
	[Ki* ranges are: A = <75 nM; B = 75 - 250 nM; C = >250 nM]		
132		FABMS; MH^+, 688.5.	A
133			A

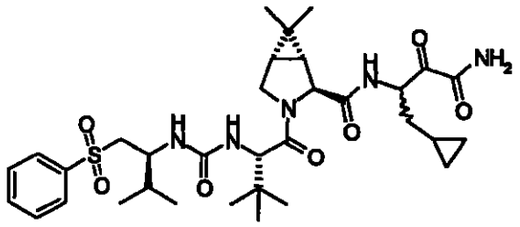
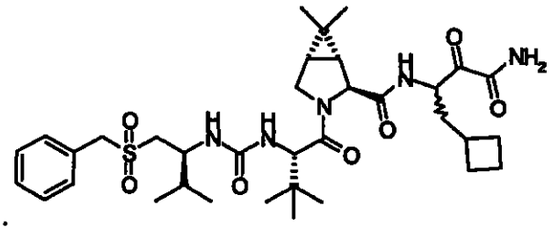
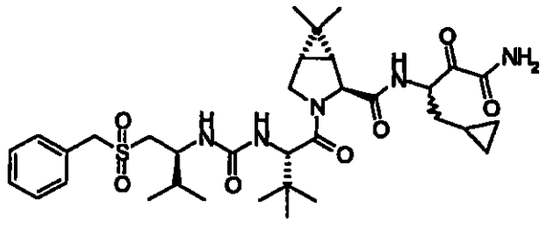
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
134			A
135			A

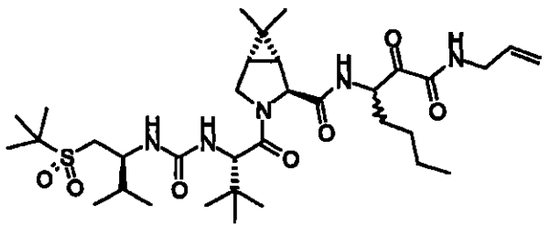
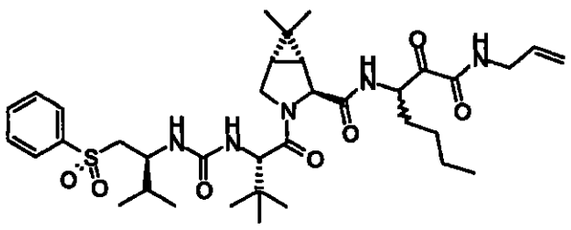
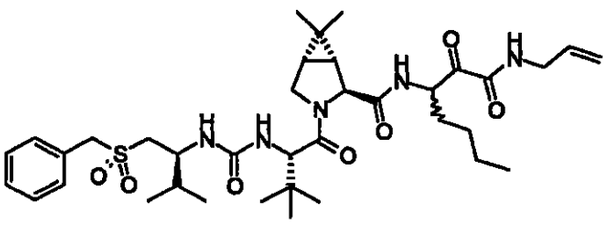
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
136			A
137			A

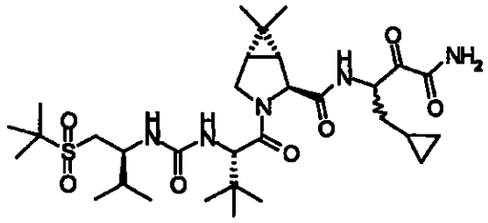
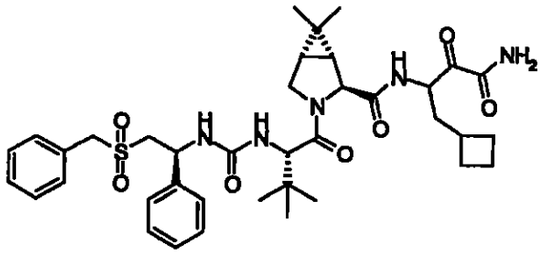
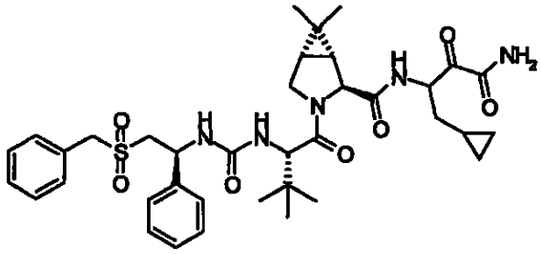
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
138			B
139			A

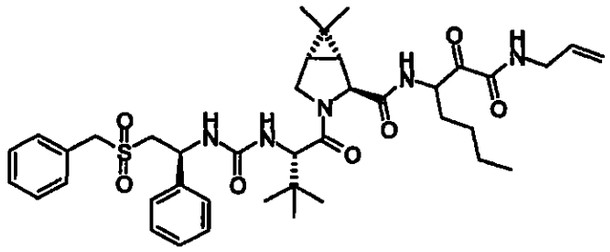
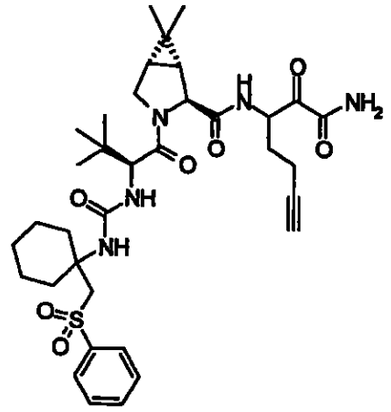
Sulfone Compounds

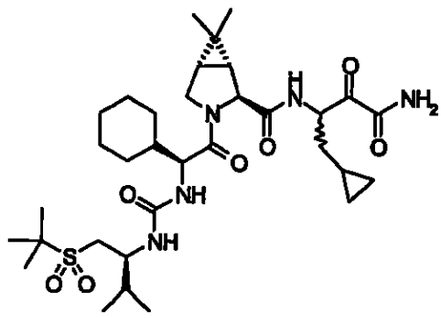
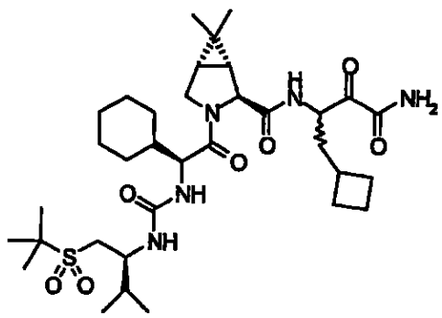
Prep. Ex	COMPOUND	Select Mass Spectral Data	Ki* range
	[Ki* ranges are: A = <75 nM; B = 75 - 250 nM; C = >250 nM]		
142		LCMS: MH^+, 686.1.	A
143			A

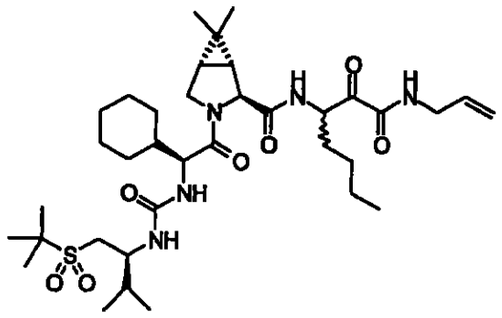
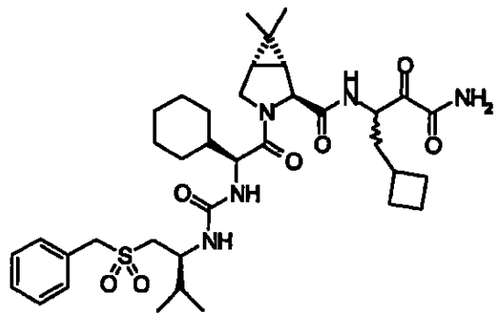
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
144			A
145			A
146			A

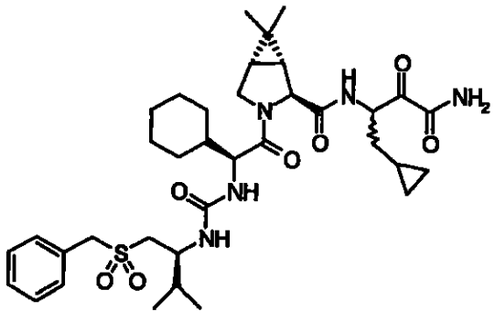
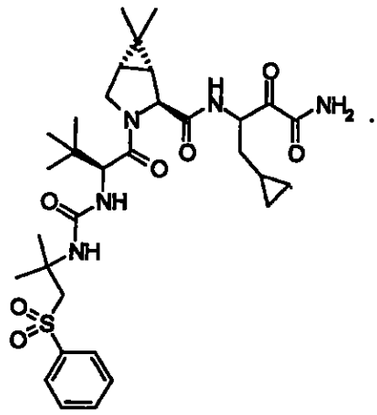
Prep. Ex.	COMPOUND	Select Mass Spectral Data	KI* range
147			B
148			B
149			B

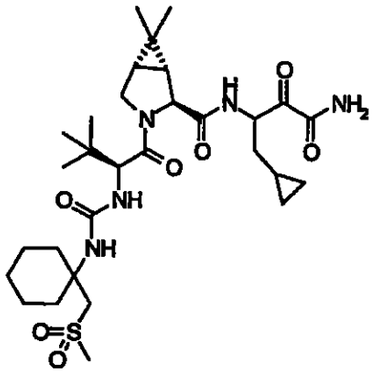
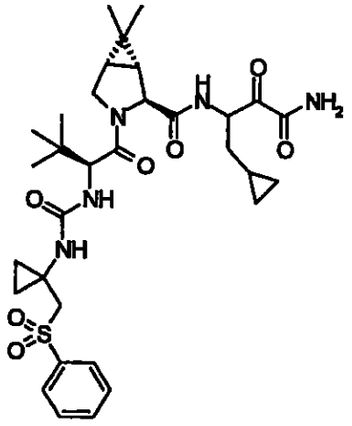
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
150			A
151			B
152			B

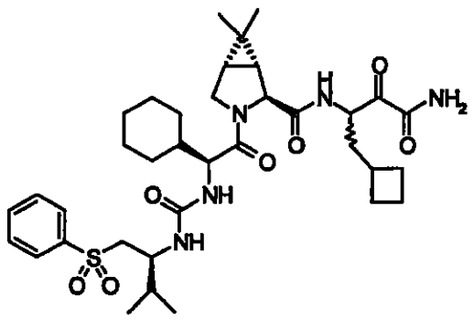
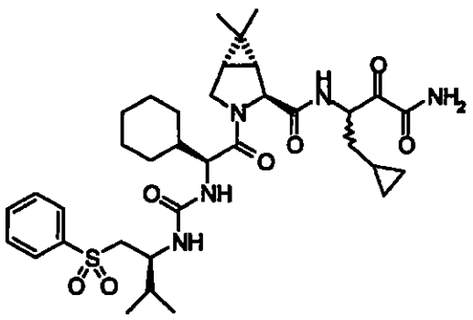
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
153			C
154		FABMS; MH^+, 684.2.	A

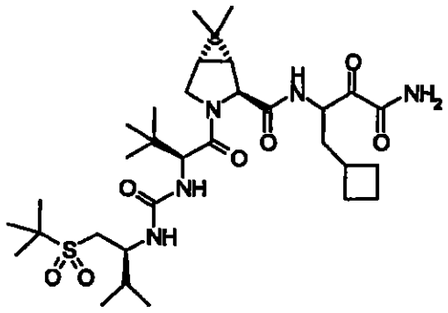
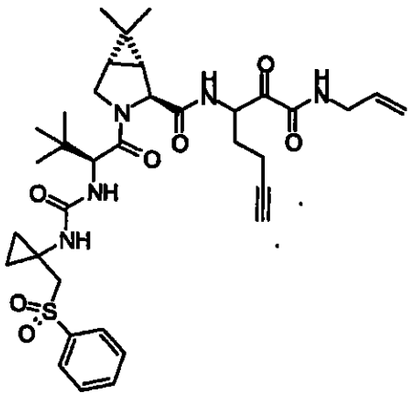
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
155			A
156			A

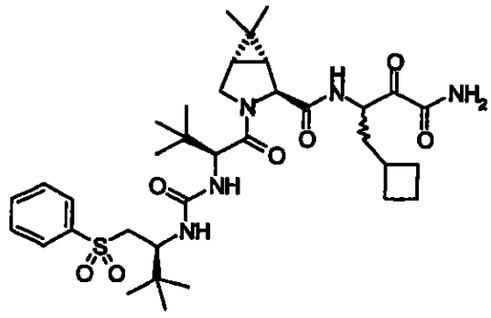
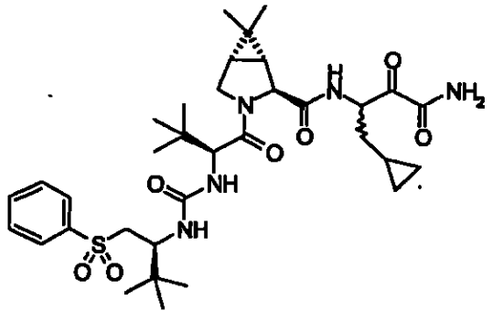
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
157			A
158			A

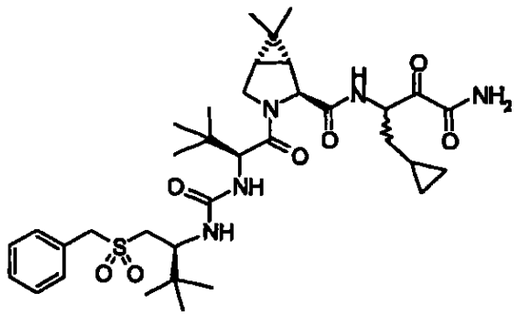
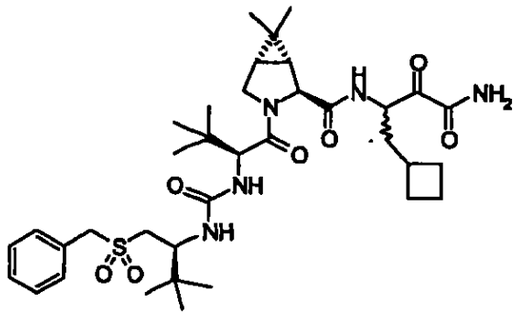
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
159			A
160			A

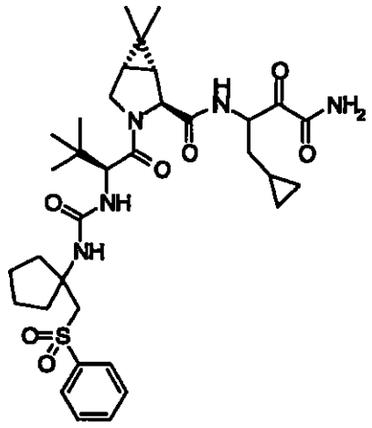
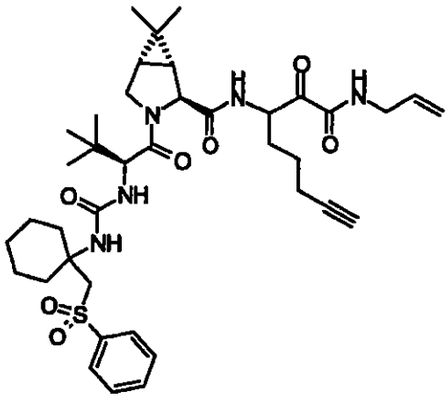
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
161			A
162			A

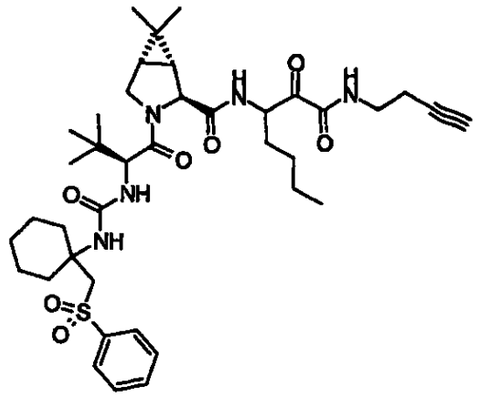
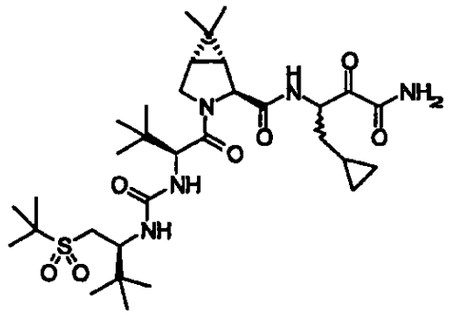
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
163			A
164			A

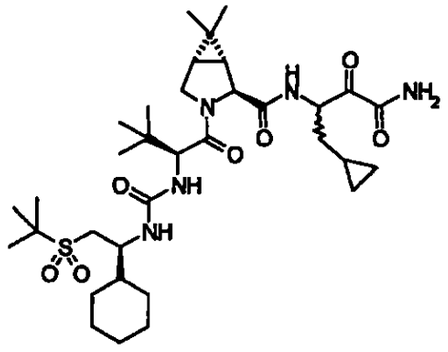
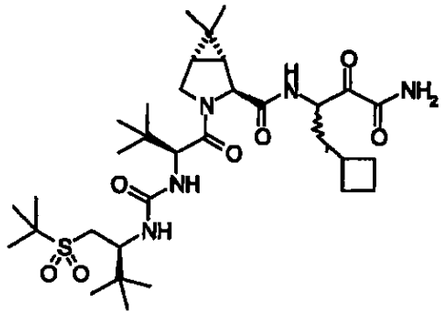
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
165			A
166		FABMS; MH^+, 682.3.	B

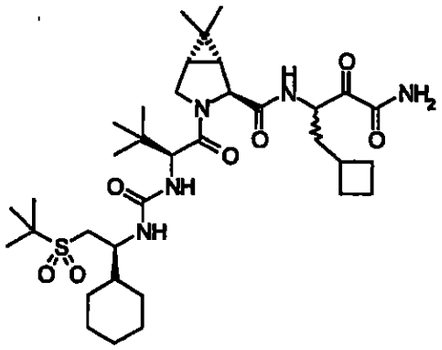
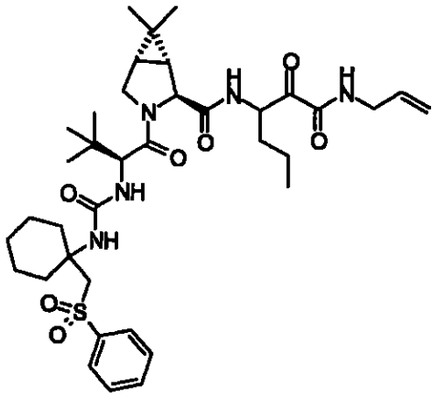
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
167			A
168			A

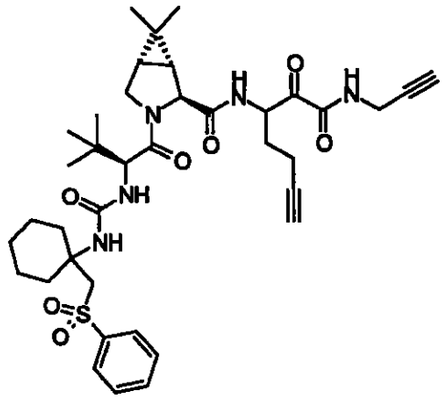
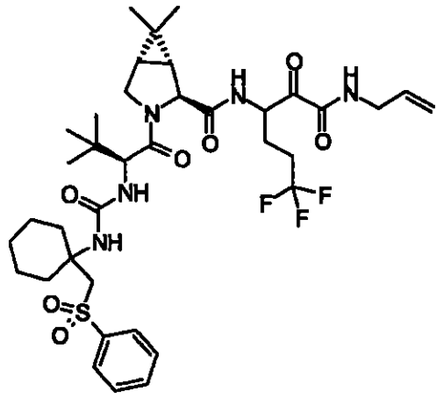
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
169			A
170			A

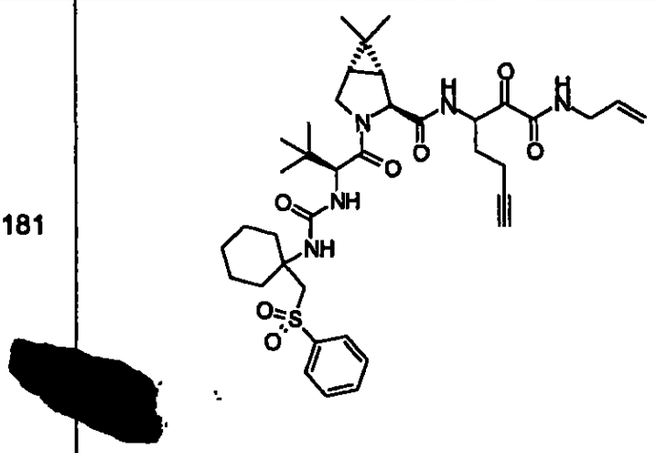
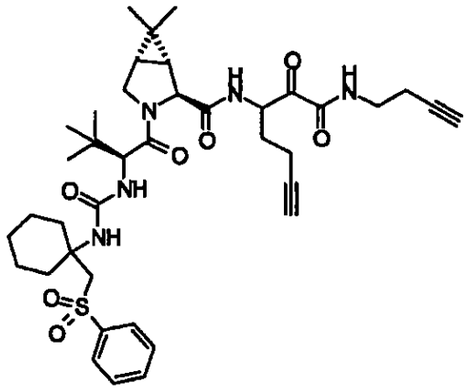
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
171			A
172		LCMS; MH^+, 738.2.	B

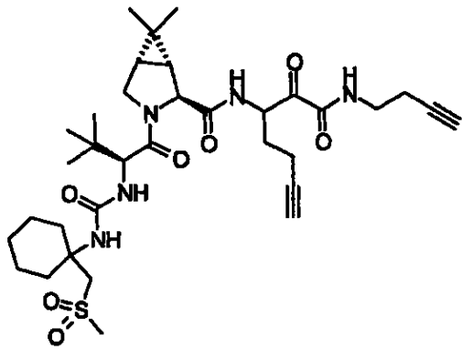
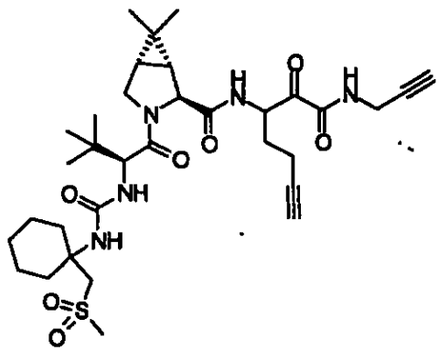
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
173			A
174			A

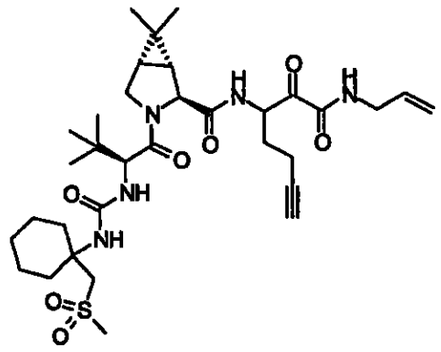
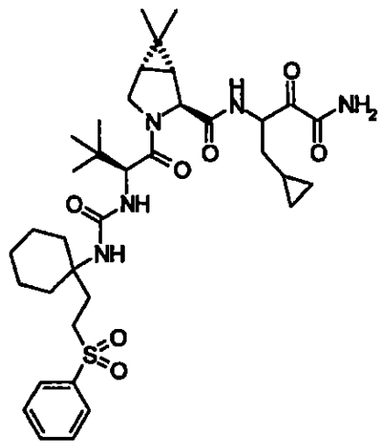
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
175			A
176			A

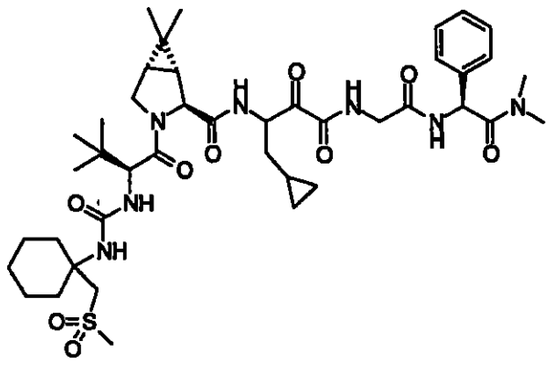
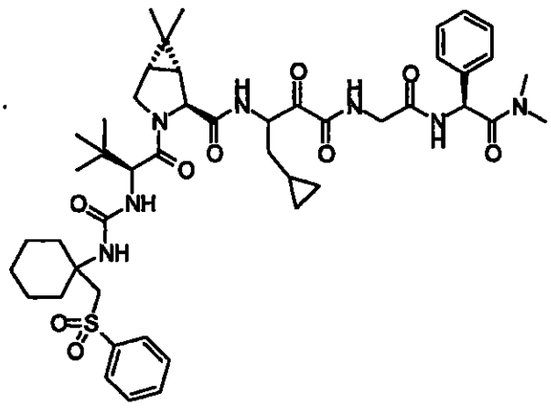
Prep. Ex.	COMPOUND	Select Mass Spectral Data	KI* range
177			A
178		LCMS; MH^+, 714.1.	A

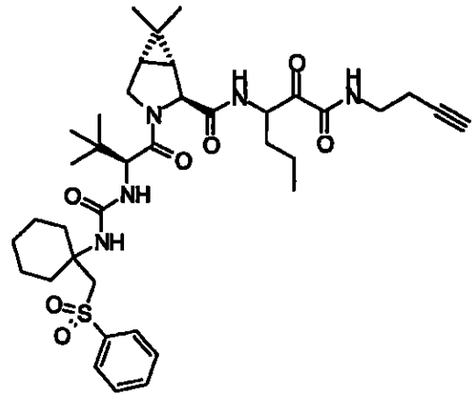
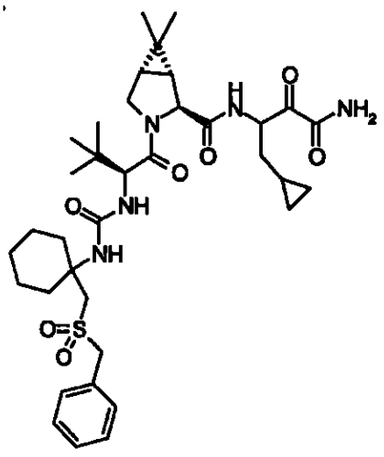
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
179			A
180			A

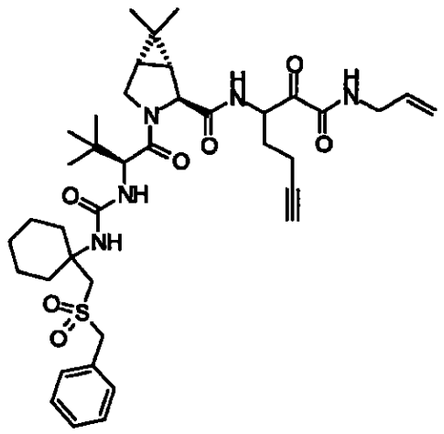
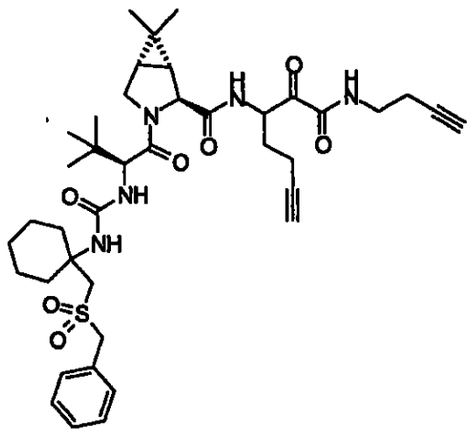
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
181		FABMS; MH^+, 724.6.	A
182		FABMS; MH^+, 736.5.	A

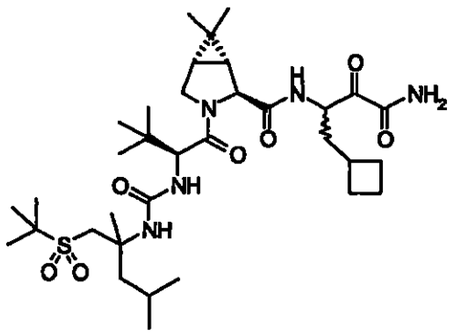
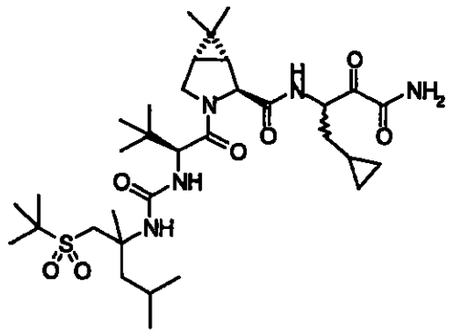
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
183			A
184			A

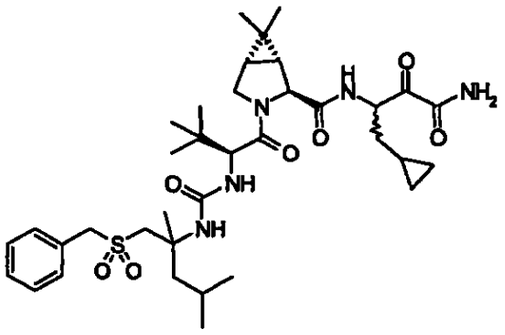
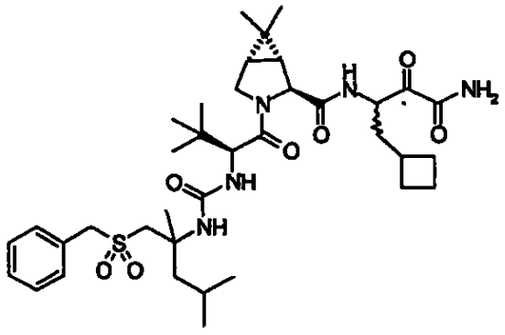
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
185		FABMS; MH^+, 662.5.	A
186		FABMS; MH^+, 700.3.	A

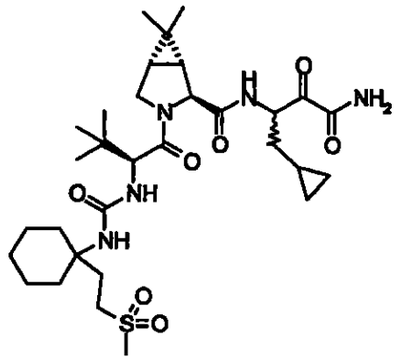
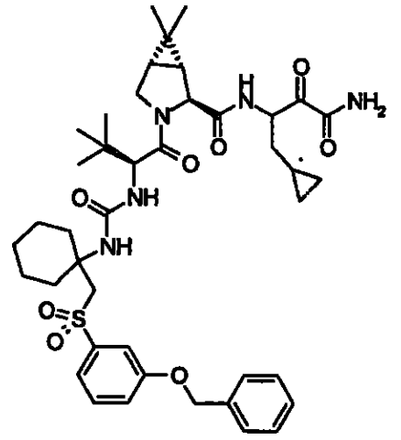
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
187			A
188			A

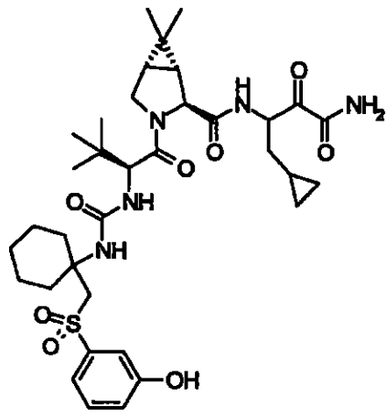
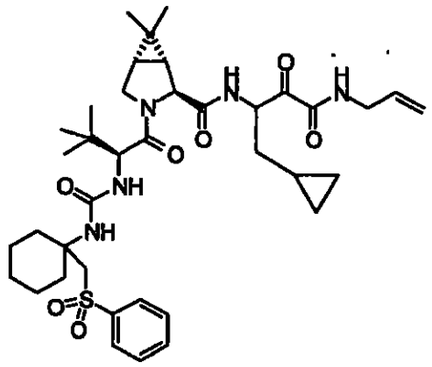
Prep. Ex.	COMPOUND	Select Mass Spectral Data	KI* range
189			A
190			A

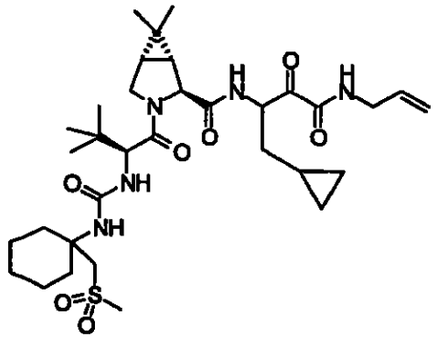
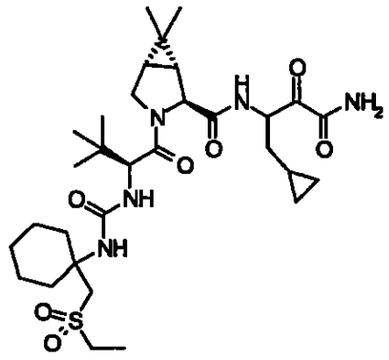
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
191		FABMS; MH^+, 738.4.	A
192			A

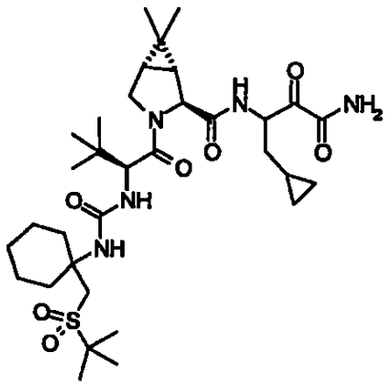
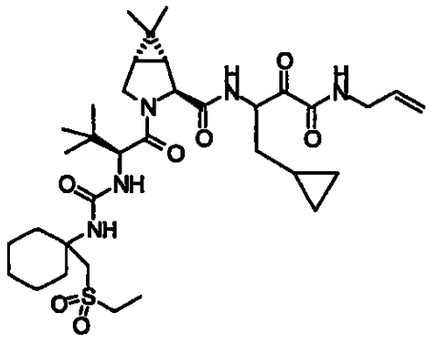
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
193			A
194			A

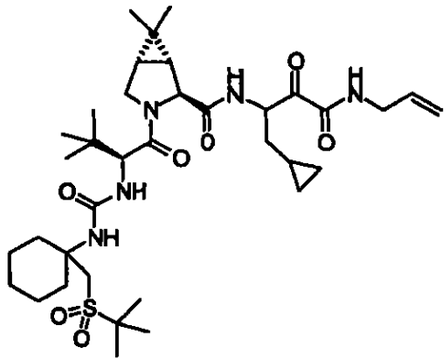
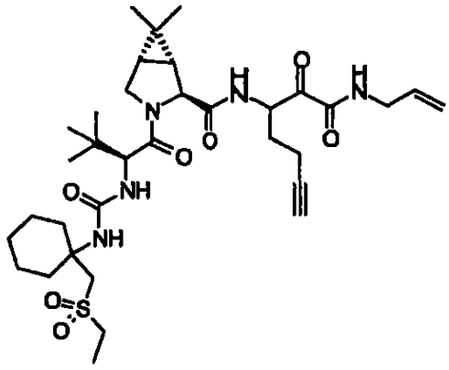
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
195			A
196			A

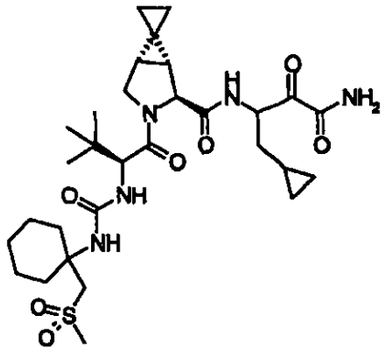
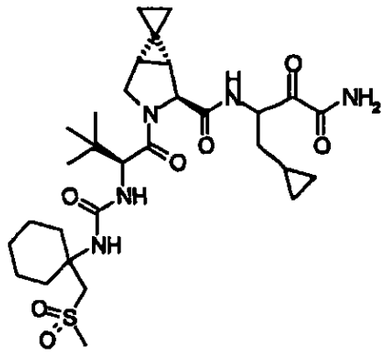
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
197		FABMS; MH^+, 638.3.	A
198		LCMS; MH^+, 792.2.	A

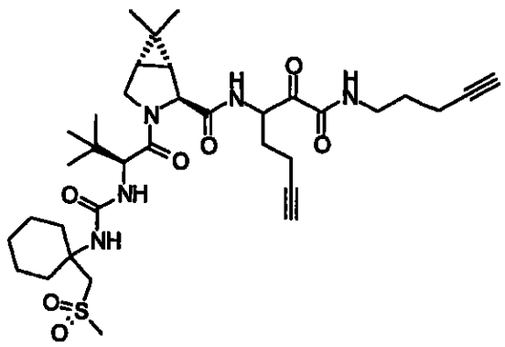
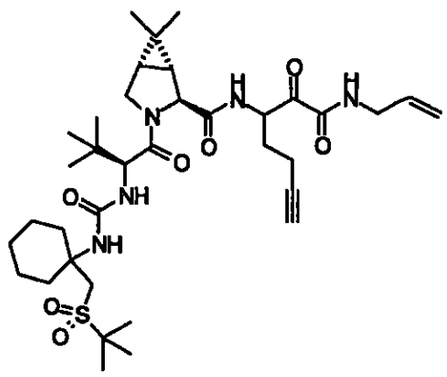
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
199		LCMS: MH^+, 702.2.	A
200		FABMS; MH^+, 726.5.	A

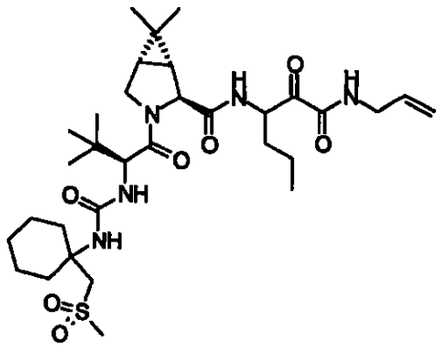
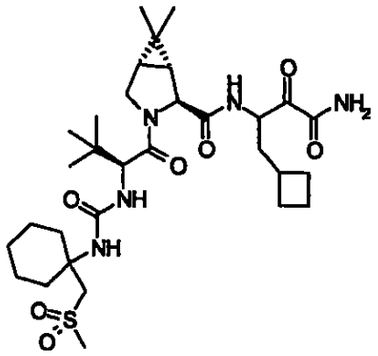
Prep. Ex.	COMPOUND	Select Mass Spectral Data	KI* range
201			A
202			A

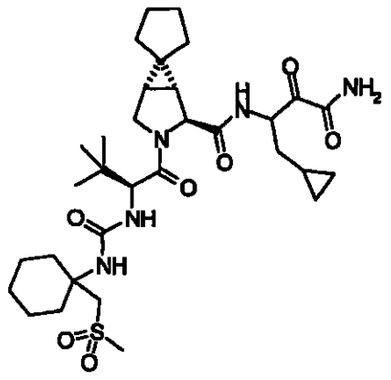
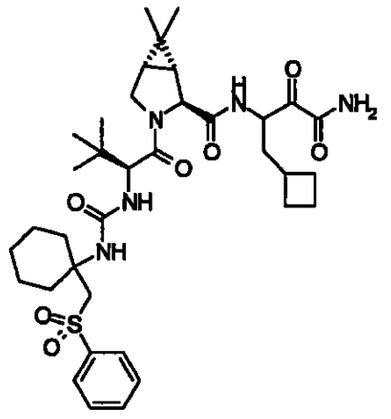
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
203			A
204			A

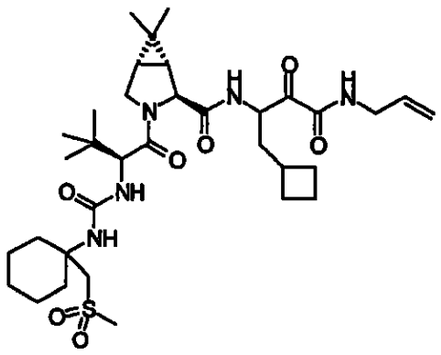
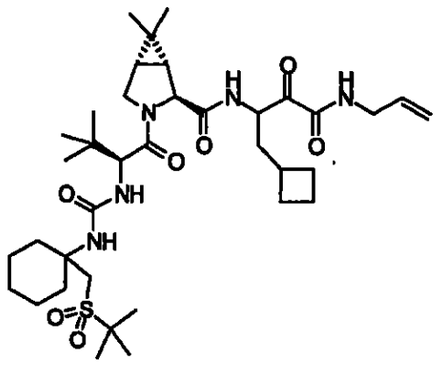
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
205			A
206		FABMS; MH^+, 676.7.	A

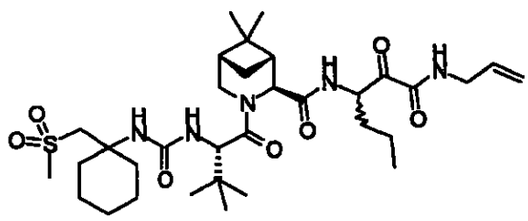
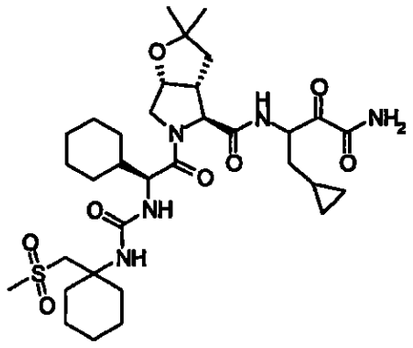
Prep. Ex.	COMPOUND	Select Mass Spectral Data	KI* range
207			A
208			A

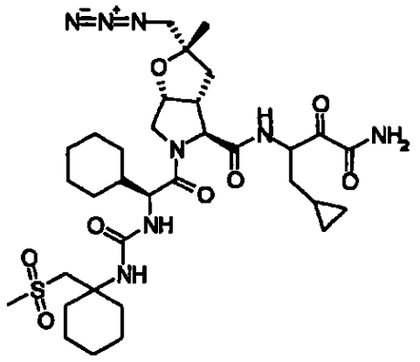
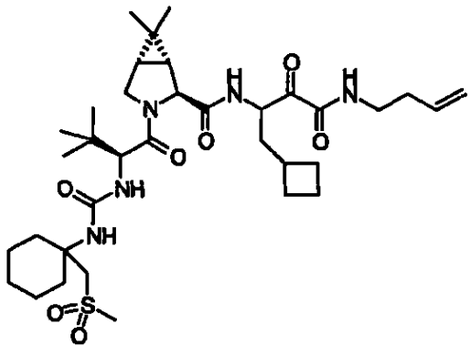
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
209		FABMS; MH^+, 688.3.	A
210		FABMS; MH^+, 704.4.	A

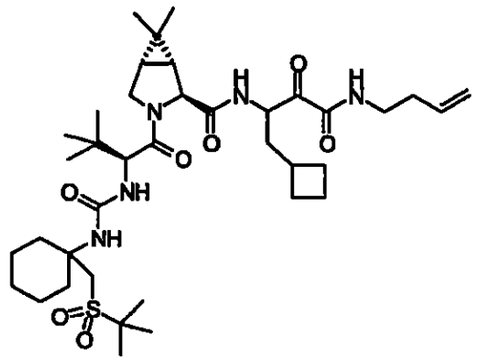
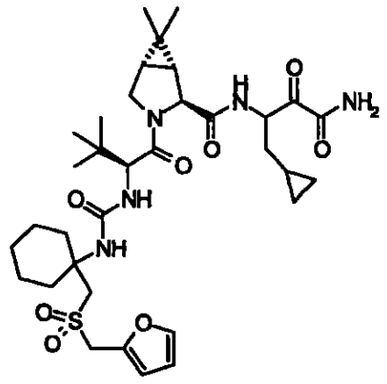
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
211			A
212			A

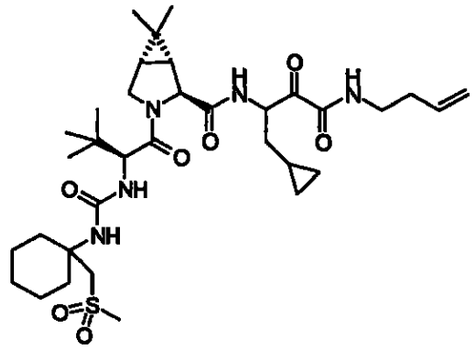
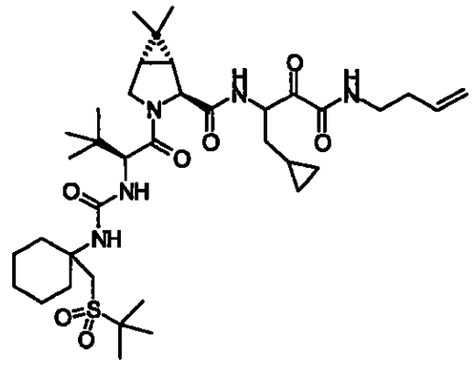
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
213			A
214			A

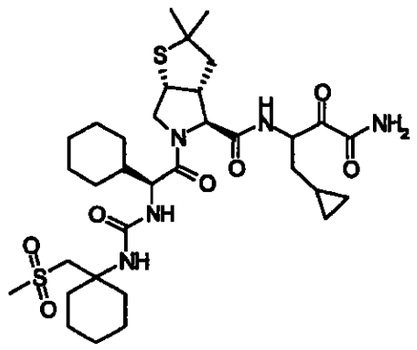
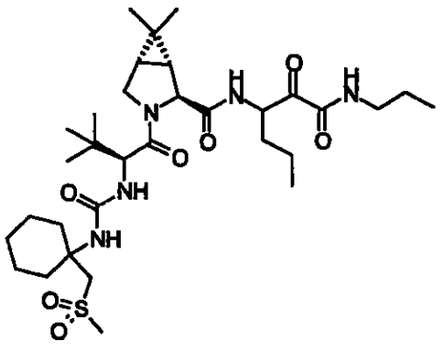
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
215		FABMS; MH^+, 678.6.	A
216		FABMS; MH^+, 720.6.	A

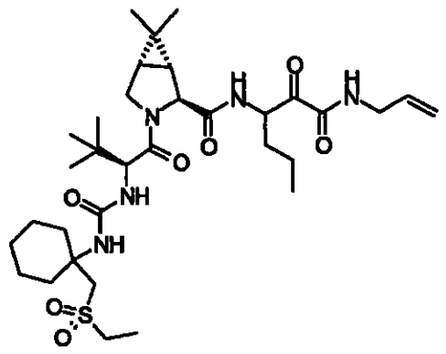
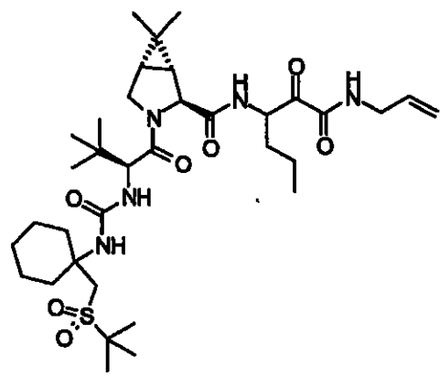
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
217			A
218			A

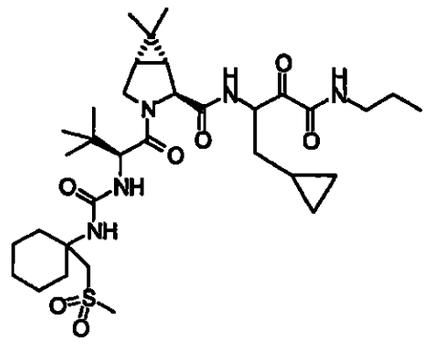
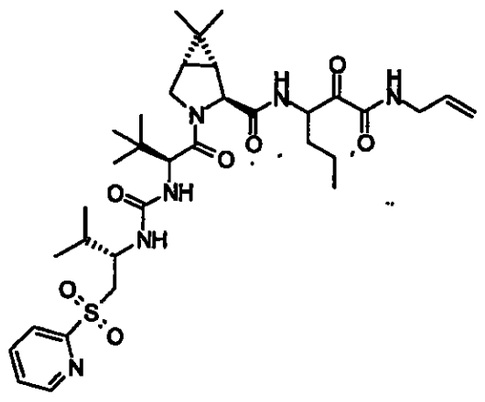
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
219			A
220		FABMS; MH^+, 692.5.	A

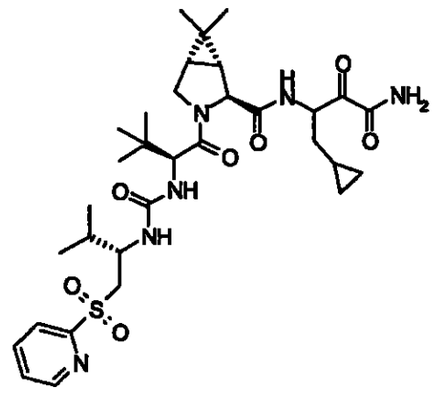
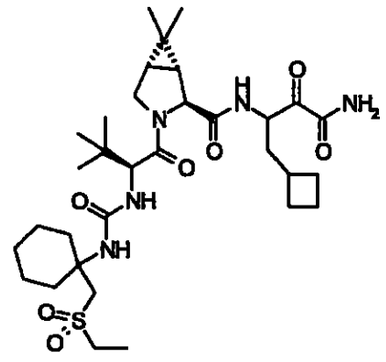
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
221		FABMS; MH^+, 734.5.	A
222			A

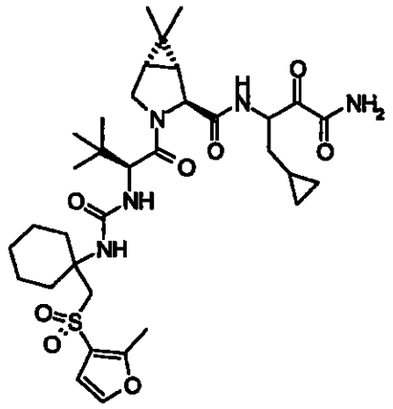
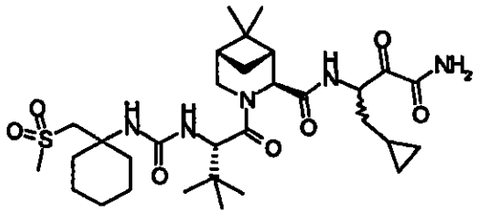
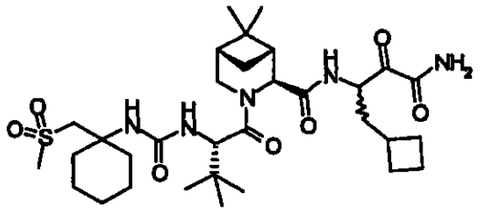
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
223		FABMS; MH^+, 678.4.	A
224		FABMS; MH^+, 720.8.	A

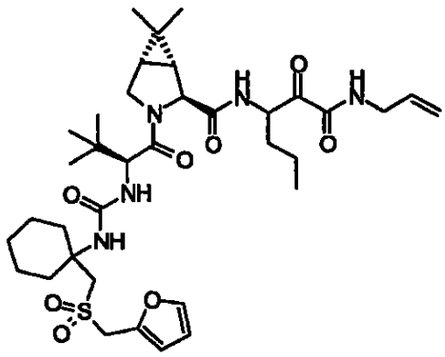
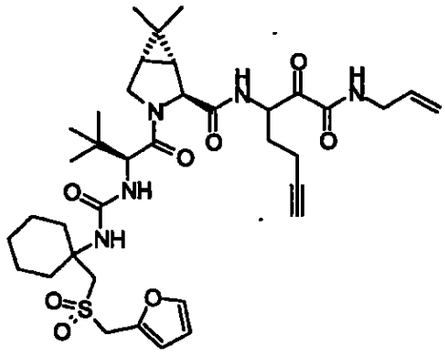
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
225			B
226		LCMS; MH^+, 654.1.	A

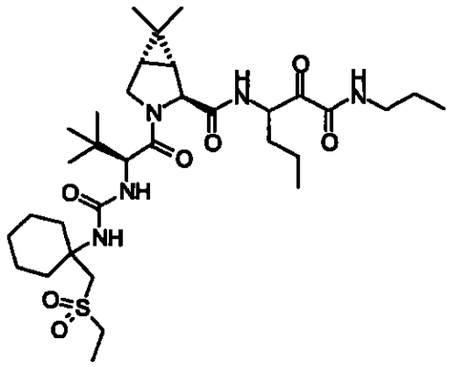
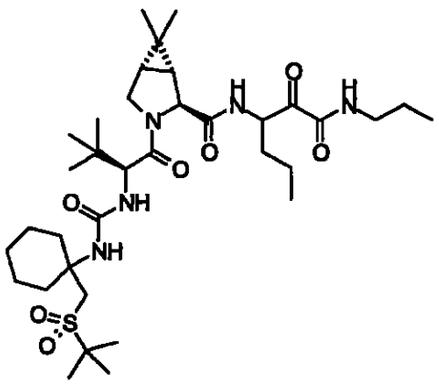
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
227			A
228			A

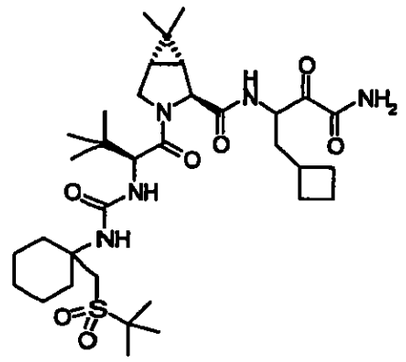
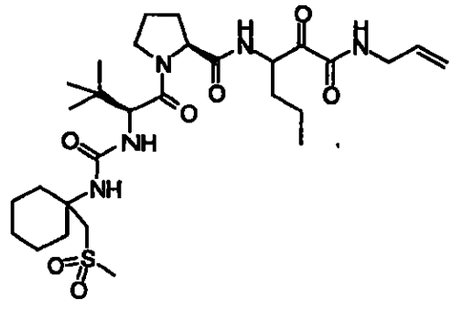
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
229		FABMS; MH+, 666.5.	A
230			C

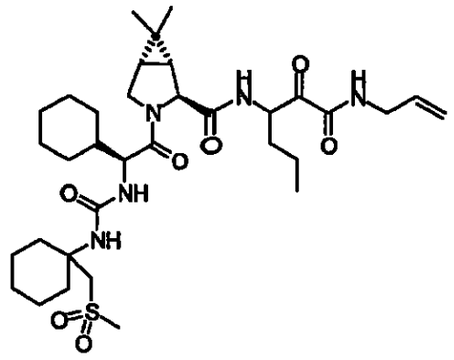
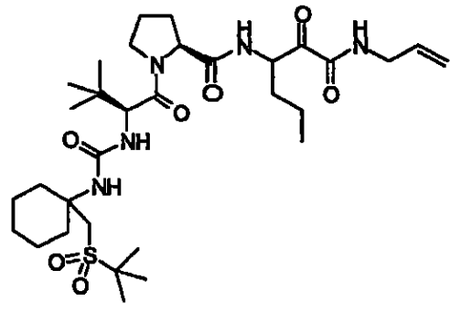
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
231			A
232			A

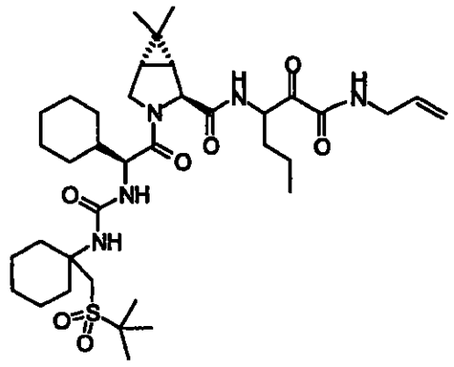
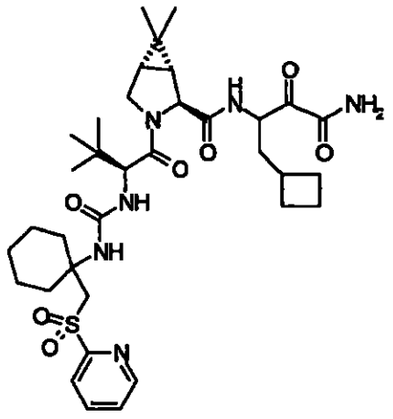
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
233			A
234			C
235			A

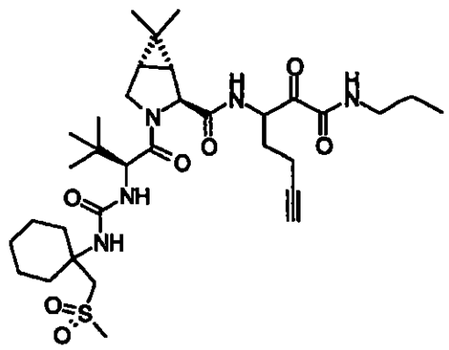
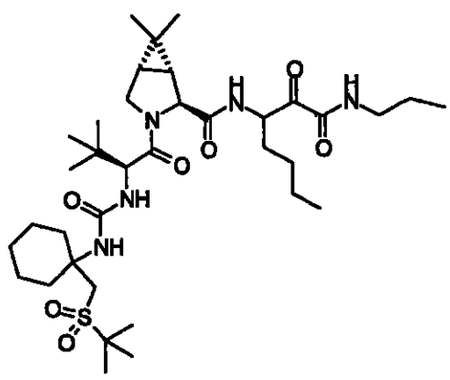
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
236			A
237			A

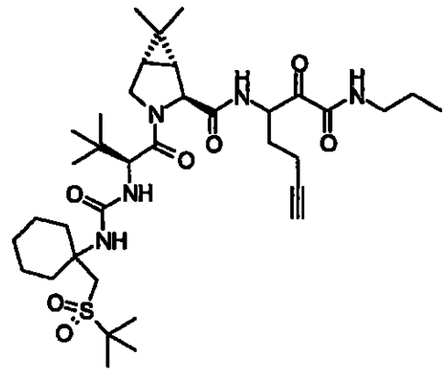
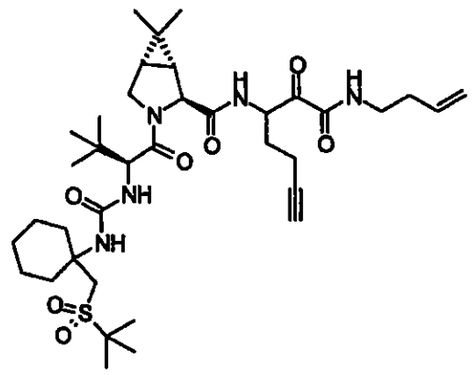
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
238			A
239			A

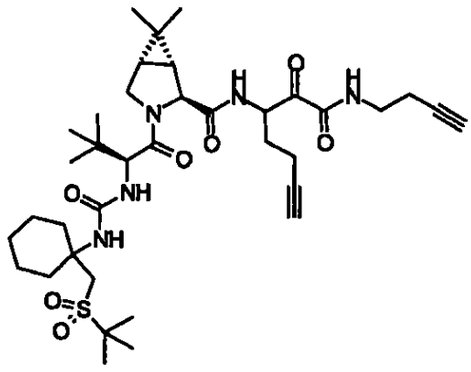
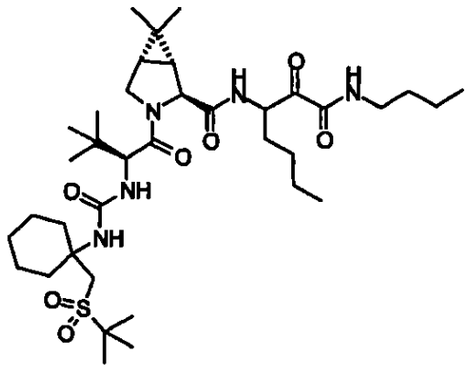
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
240			A
241			C

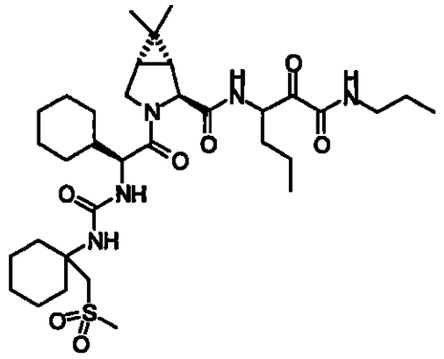
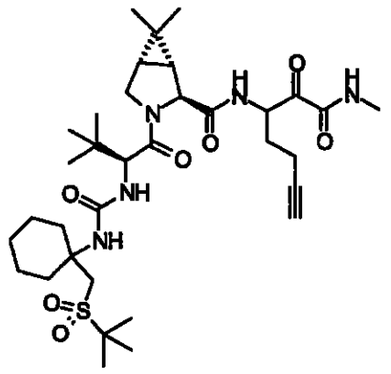
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
242			A
243			C

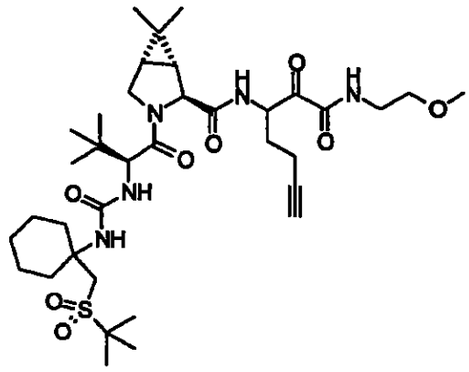
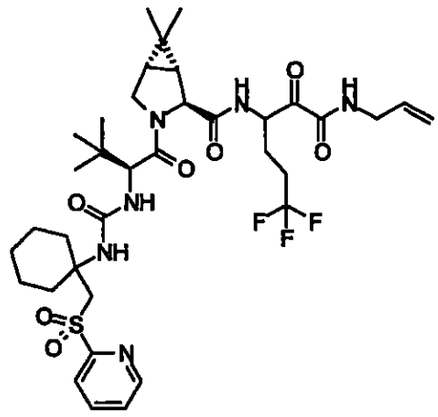
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
244			A
245			A

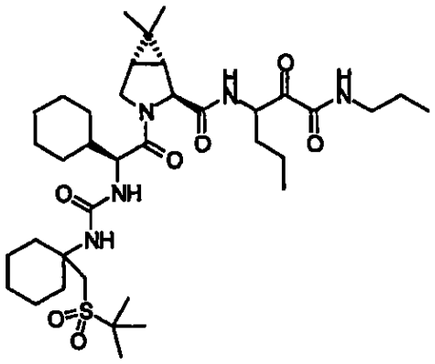
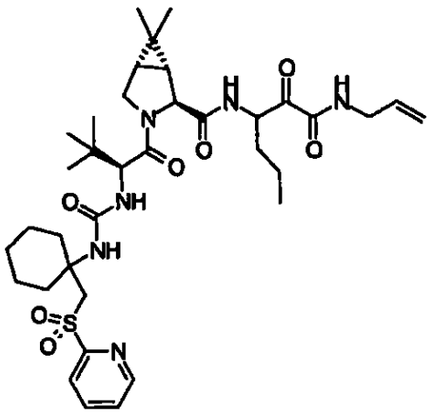
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
246		FABMS; MH^+, 664.2.	A
247		FABMS; MH^+, 710.3.	A

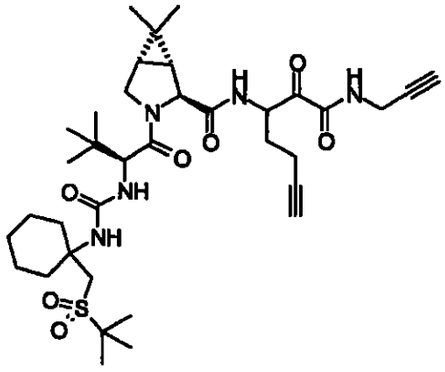
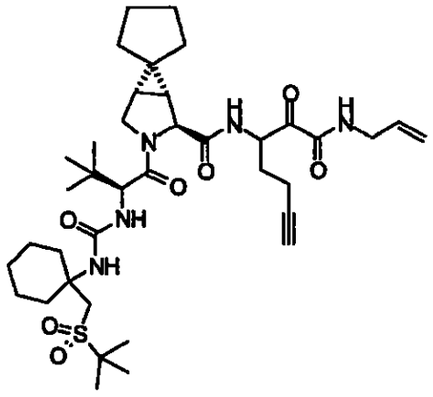
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
248		FABMS; MH^+, 706.5.	A
249		FABMS; MH^+, 718.2.	A

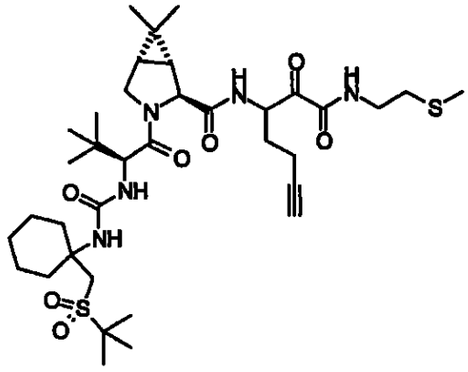
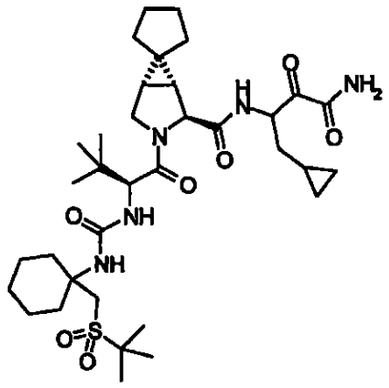
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
250			A
251		FABMS; MH^+, 724.5.	A

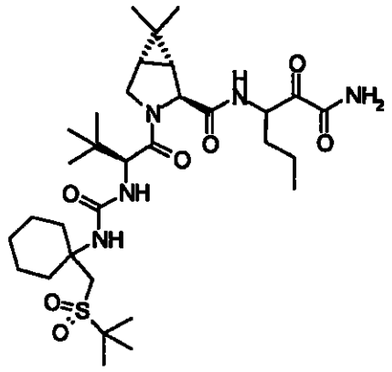
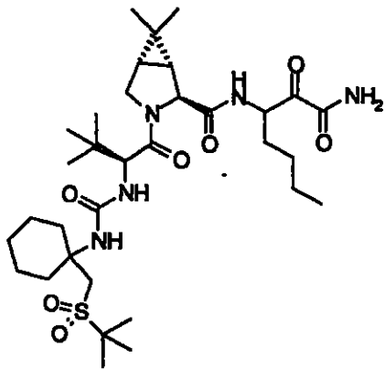
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
252		FABMS; MH^+, 680.4.	A
253			A

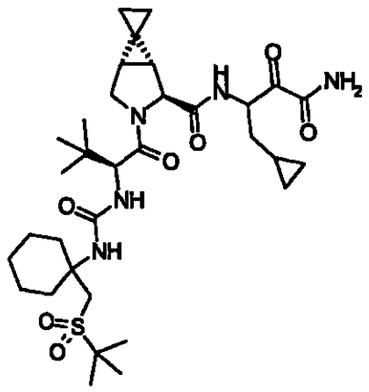
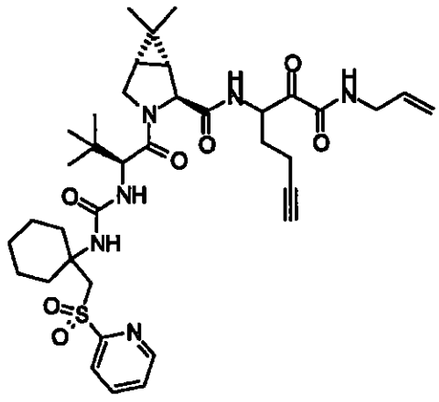
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
254		FABMS; MH^+, 722.1.	A
255			A

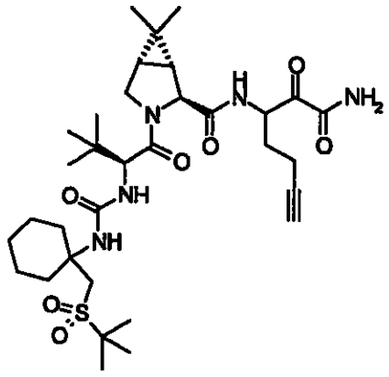
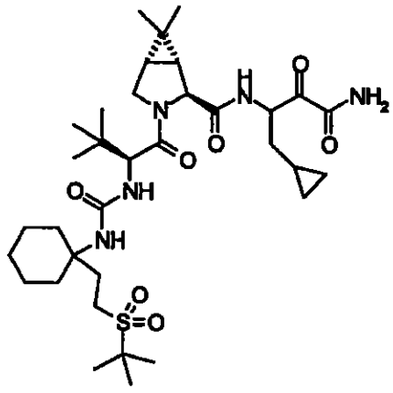
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
256			A
257			A

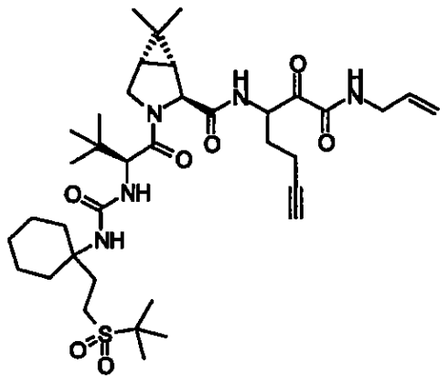
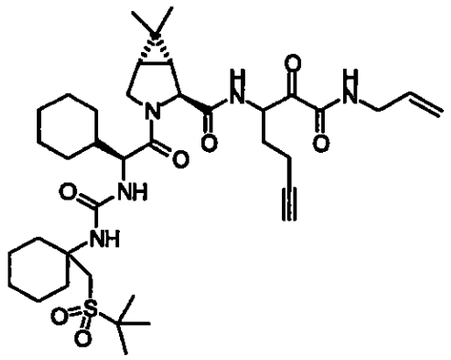
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
258		FABMS; MH+, 702.3.	A
259		FABMS; MH^+, 730.5.	A

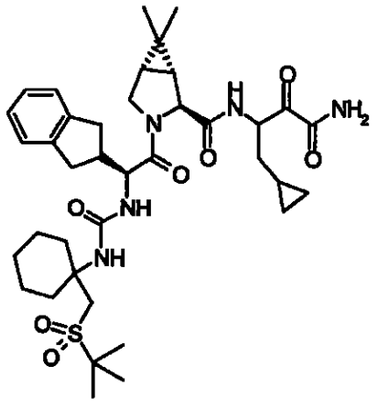
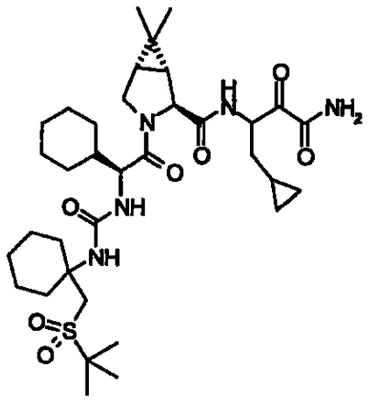
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
260		FABMS; MH^+, 738.4.	A
261		FABMS; MH^+, 692.5.	A

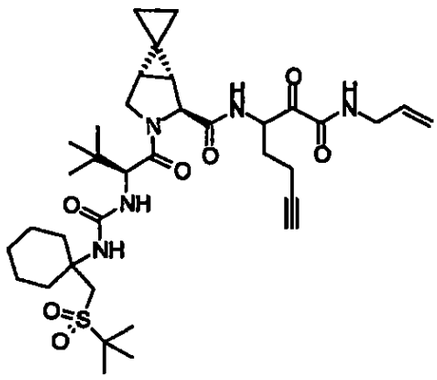
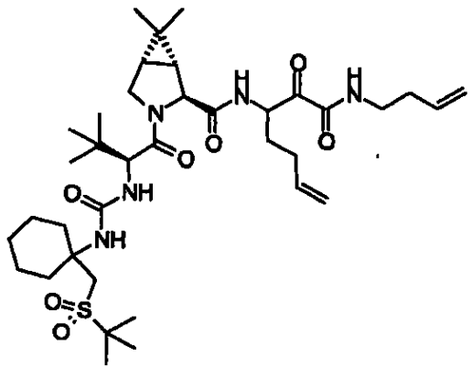
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
262			A
263			A

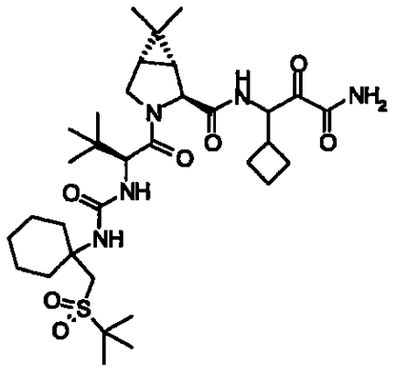
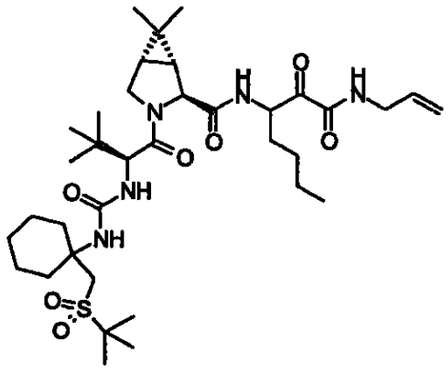
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
264		FABMS; MH^+, 664.4.	A
265			A

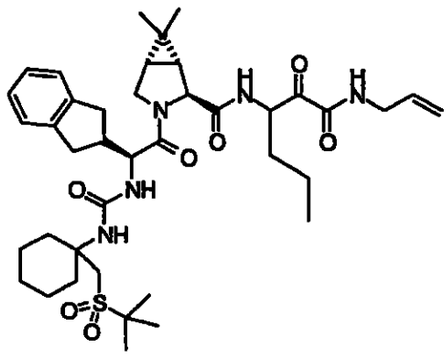
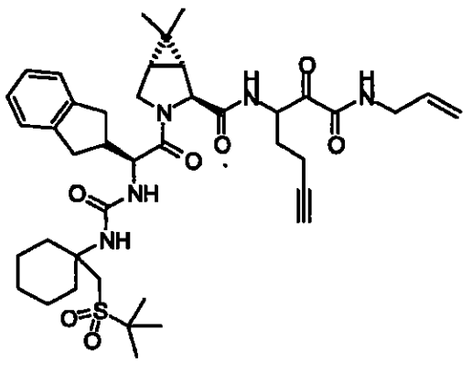
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
266		FABMS; MH^+, 664.2.	A
267			B

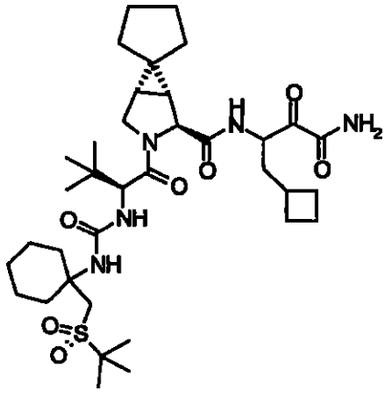
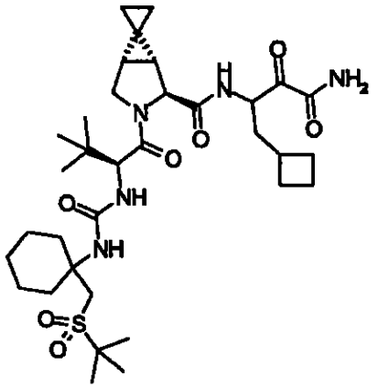
Prep. Ex.	COMPOUND	Select Mass Spectral Data	KI* range
268			B
269			A

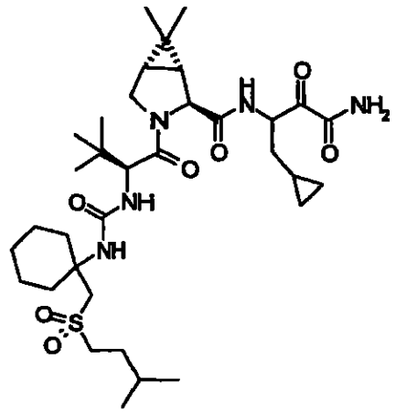
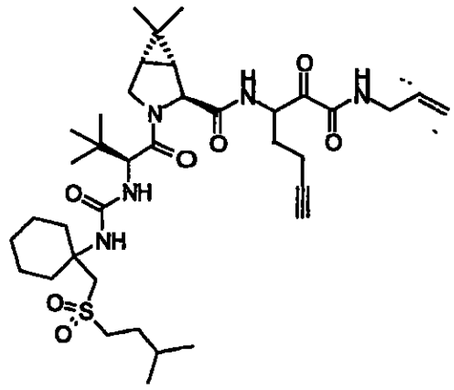
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
270			A
271			A

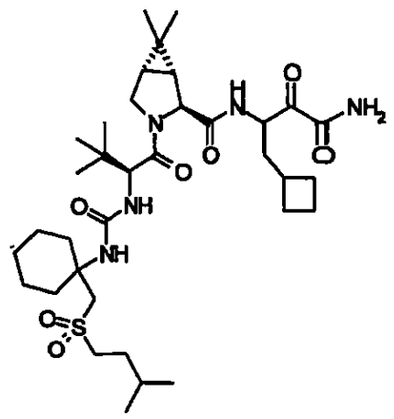
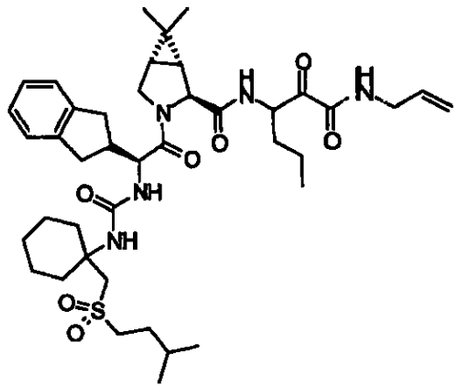
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
272		FABMS; MH^+, 702.3.	A
273		FABMS; MH^+, 720.5.	A

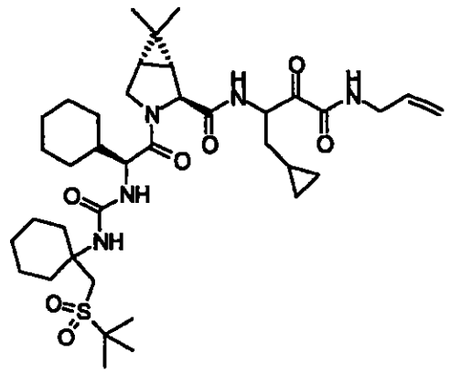
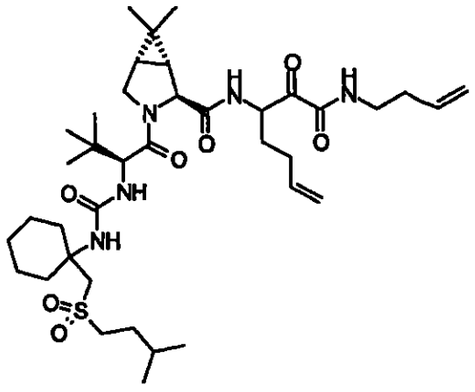
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
274			A
275			A

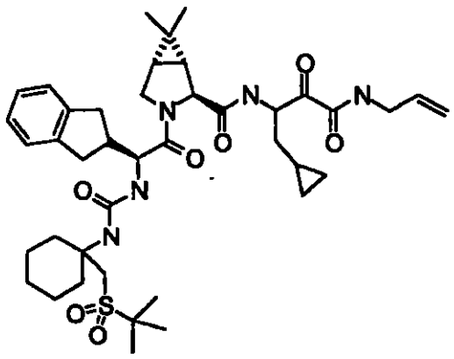
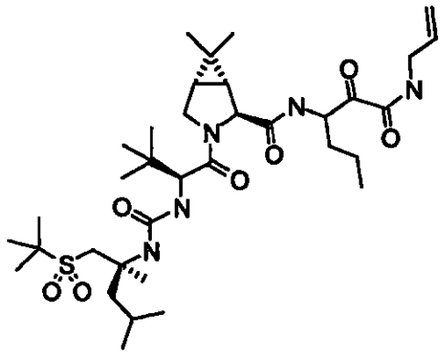
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
276			A
277		FABMS; MH^+, 764.8.	A

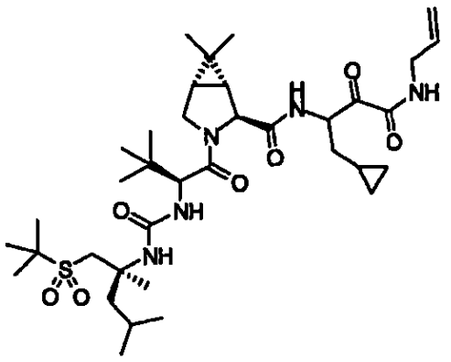
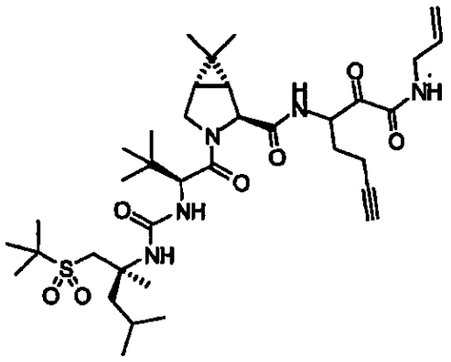
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
278		LCMS; MH^+, 706.2.	A
279		FABMS; MH^+, 678.2.	A

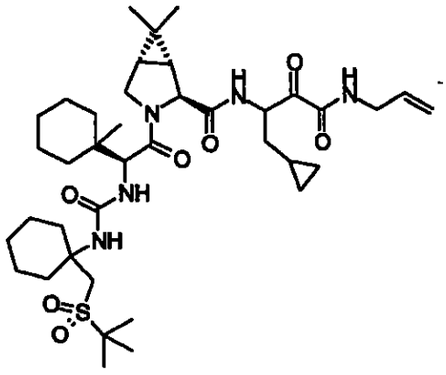
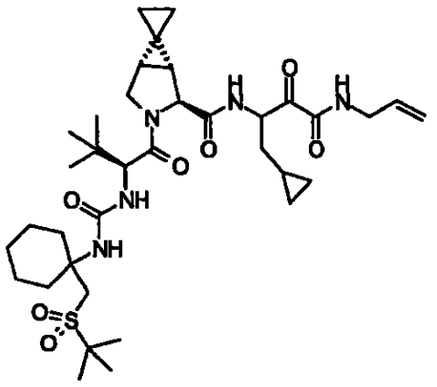
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
280			A
281			A

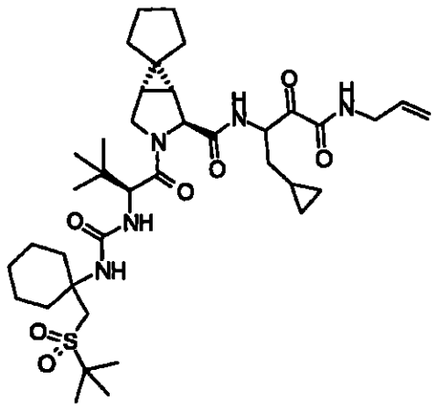
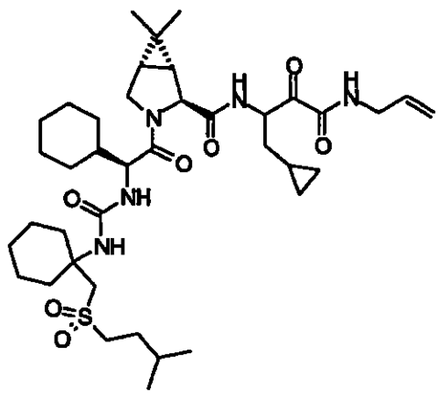
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
282			A
283			A

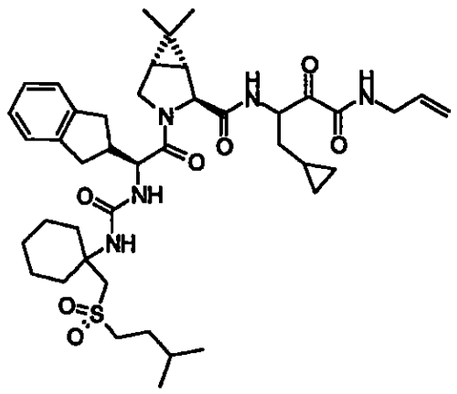
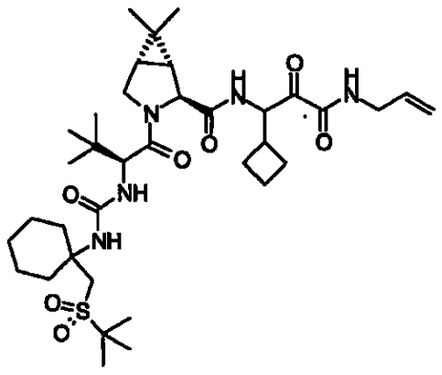
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
284			A
285			A

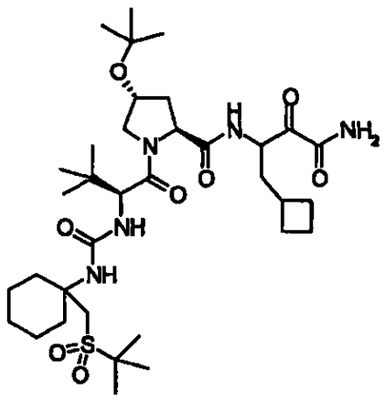
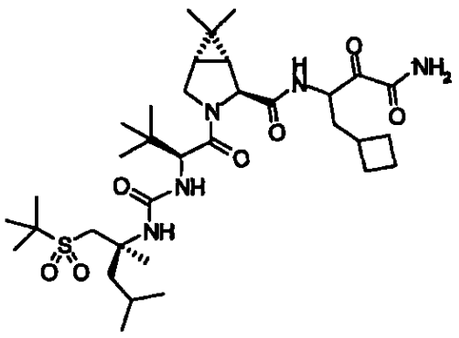
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
286		LCMS; MH^+, 766.2.	A
287			C

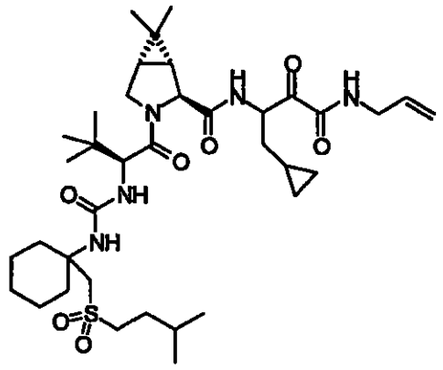
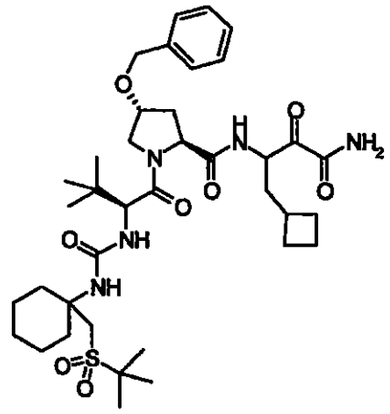
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
288			C
289			B

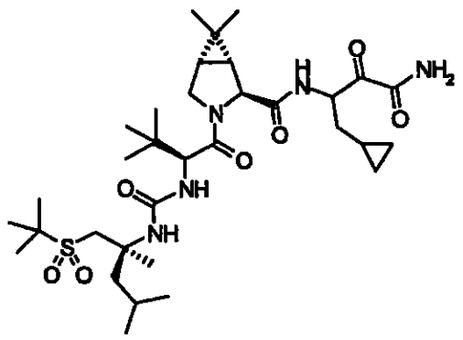
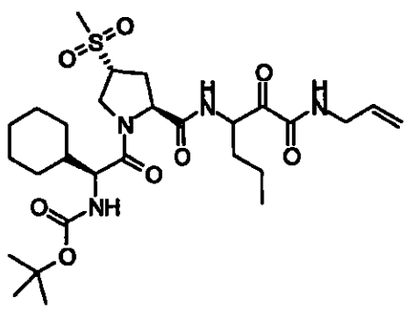
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
290			A
291			A

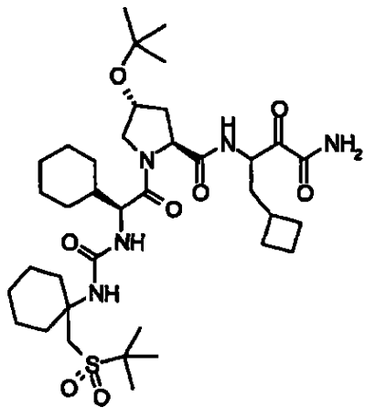
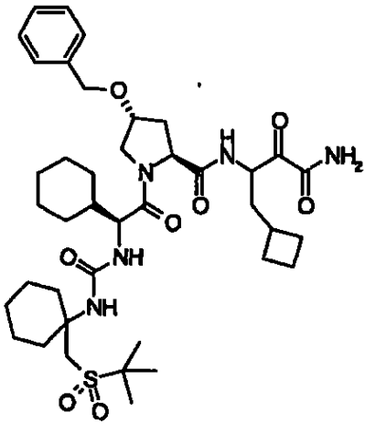
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
292			A
293			A

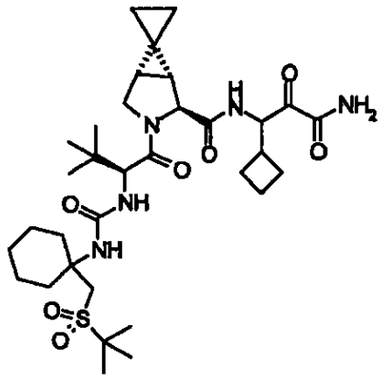
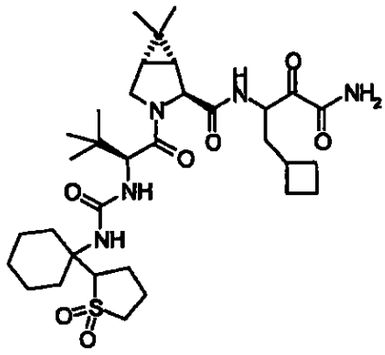
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
294			A
295			B

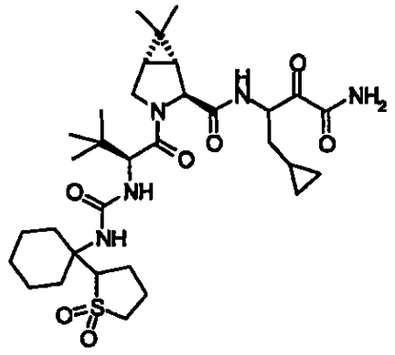
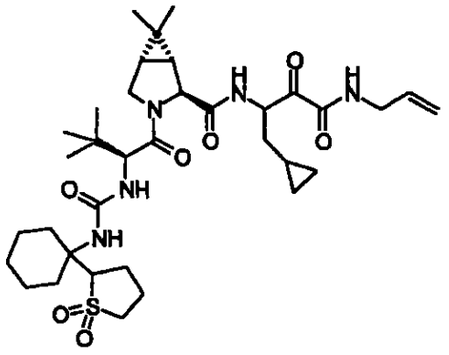
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
296		LCMS; MH^+, 712.3.	A
297			A

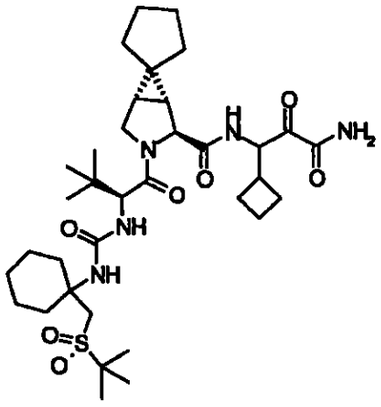
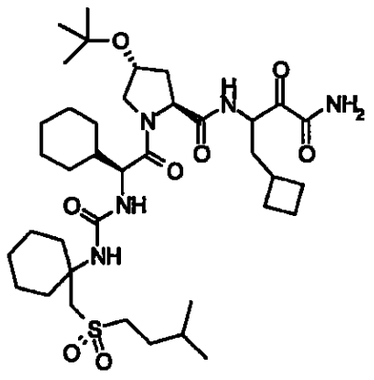
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
298			A
299		LCMS; MH^+, 746.2.	A

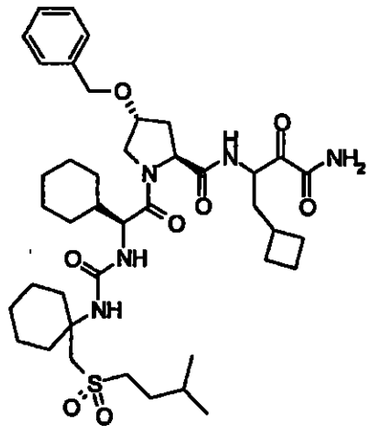
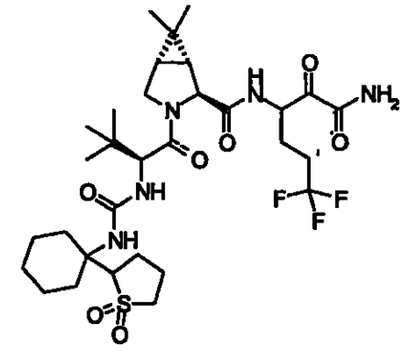
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
300			B
301			A

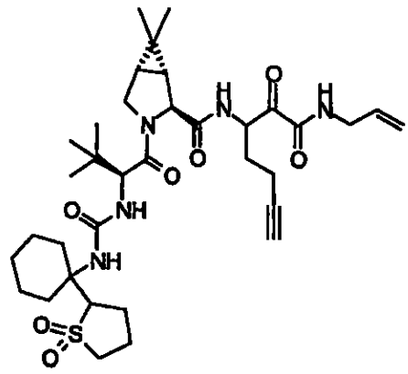
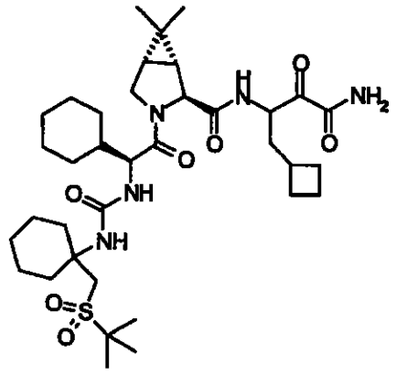
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
302			A
303			B

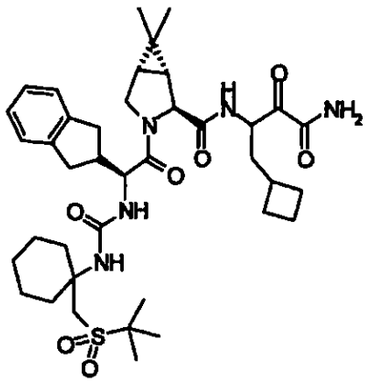
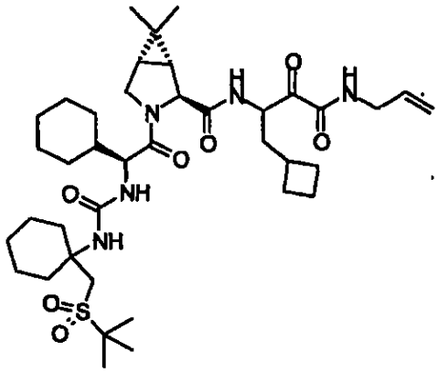
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
304		LCMS; MH^+, 664.1.	C
305			B

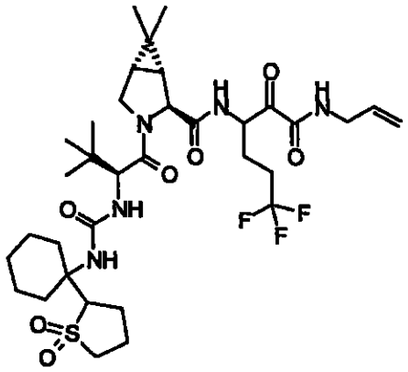
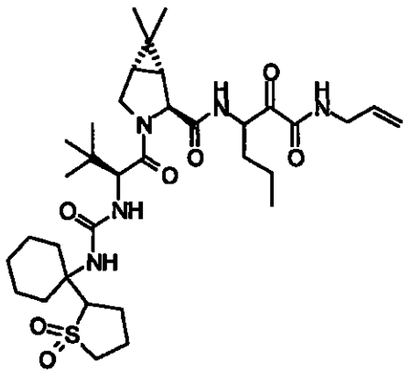
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
306			A
307			A

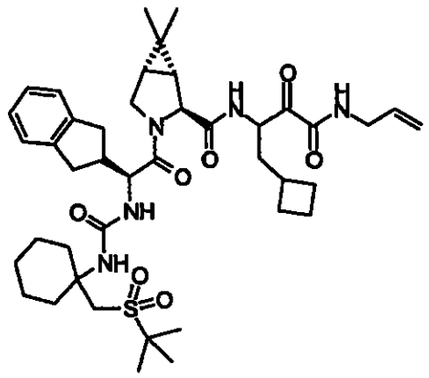
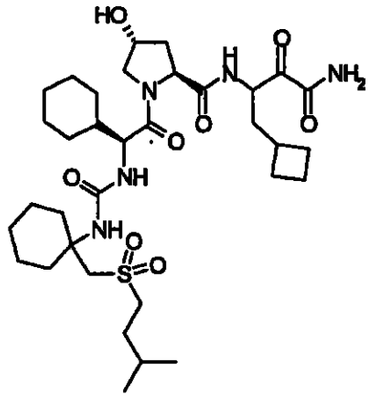
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
308		LCMS; MH^+, 692.1.	A
309			A

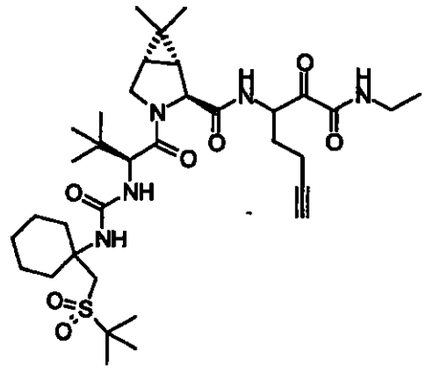
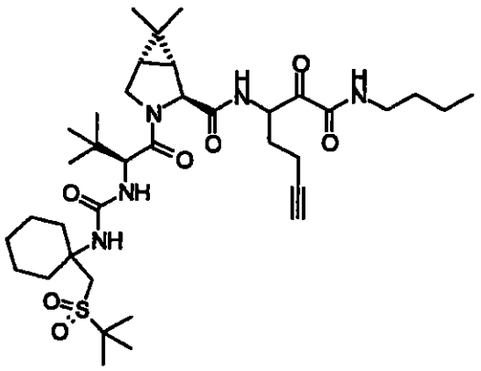
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
310			A
311			A

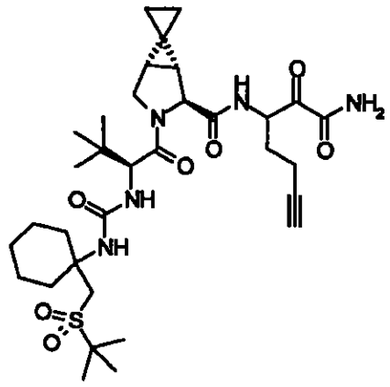
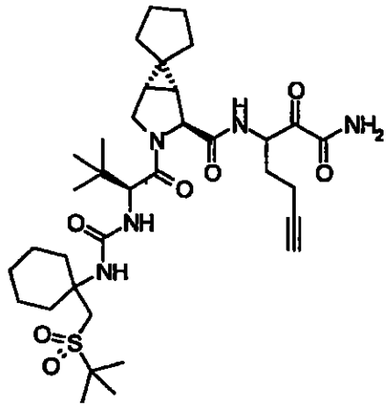
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
312			A
313			A

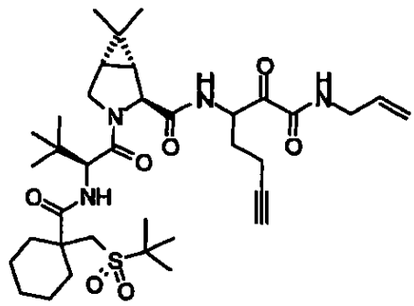
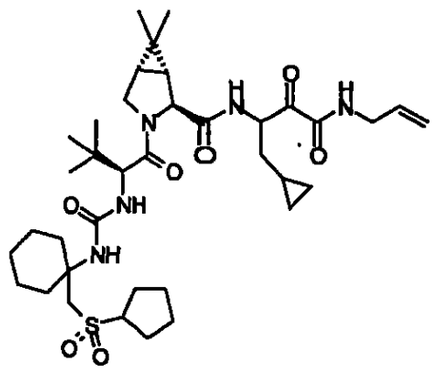
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
314			A
315			A

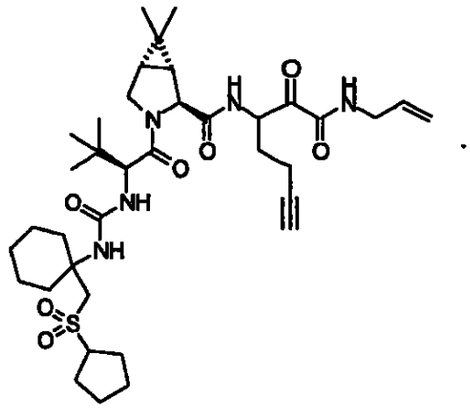
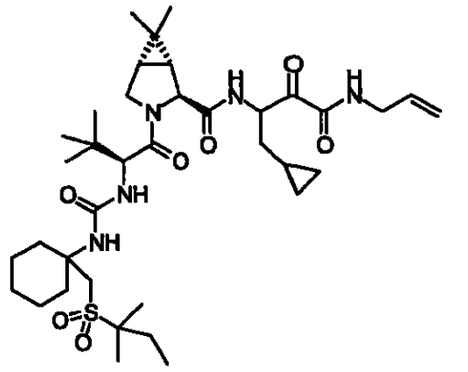
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
316			A
317			A

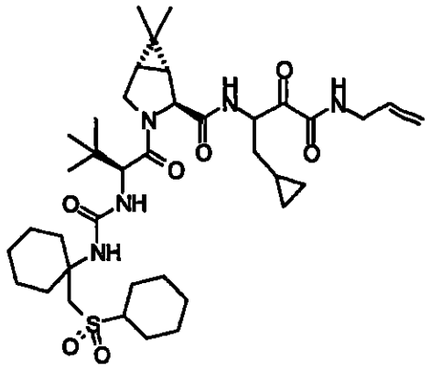
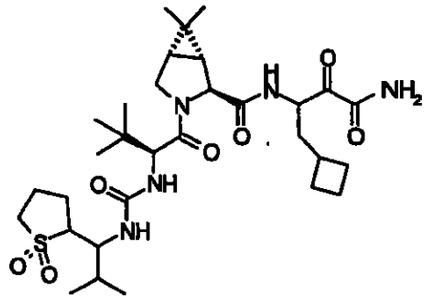
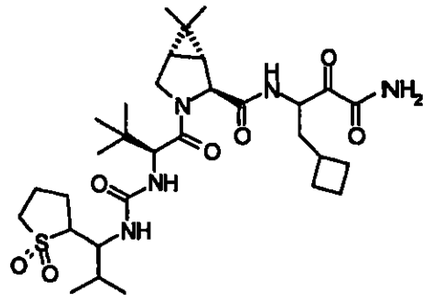
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
318			A
319			A

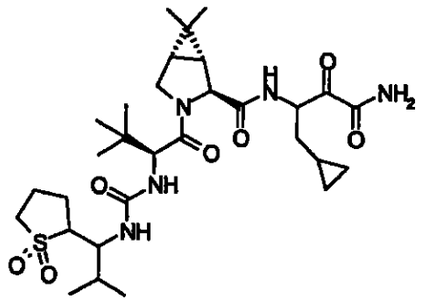
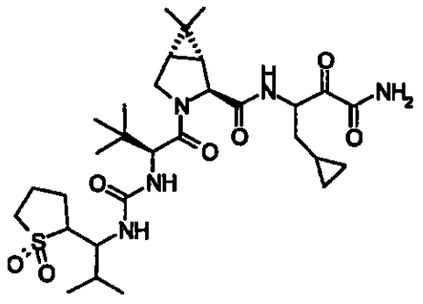
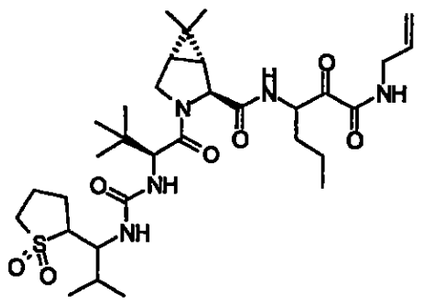
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
320		692.3LC MS; MH^+, 692.2.	A
321		LCMS; MH^+, 720.2.	B

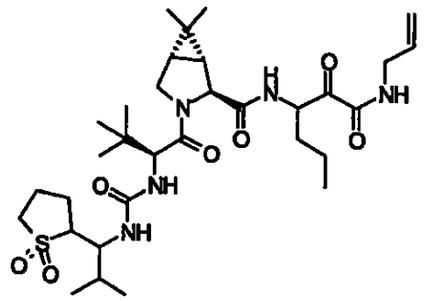
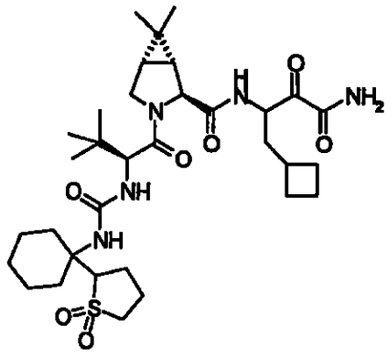
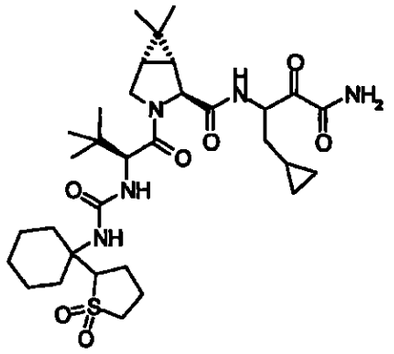
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
322			B
323			A

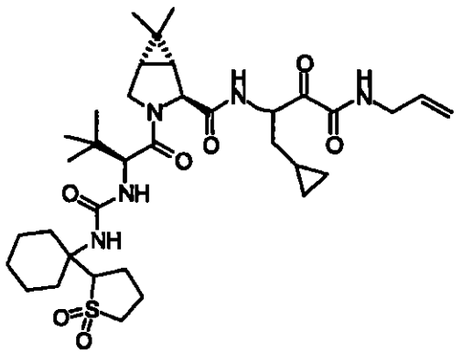
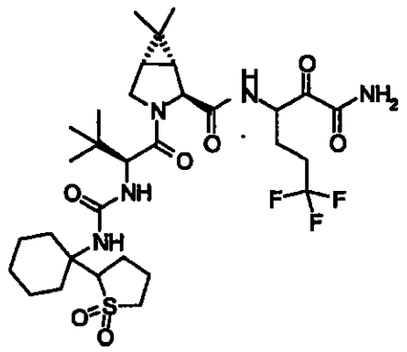
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
324			A
325			A

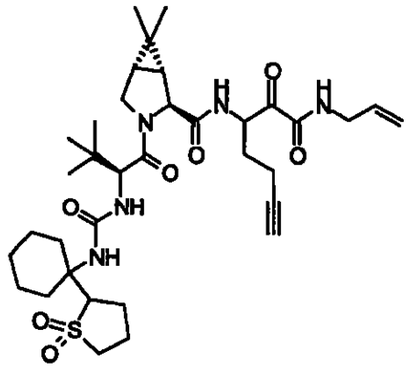
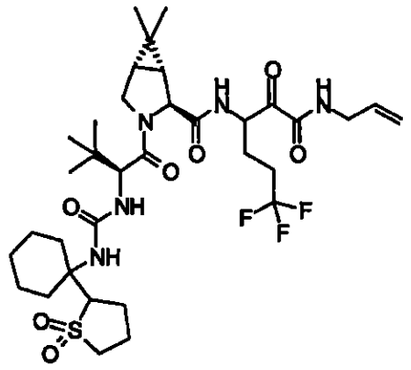
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
326			A
327		LCMS; MH^+, 720.2.	C

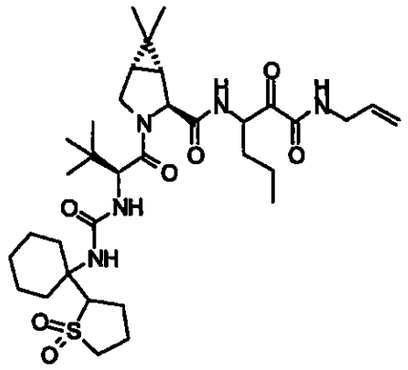
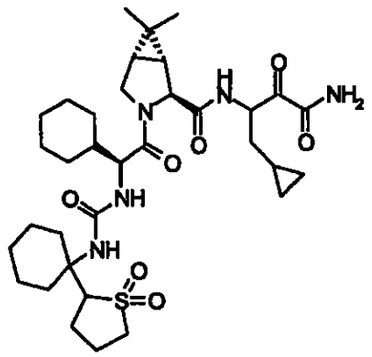
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
328			NA
329			A
330			C

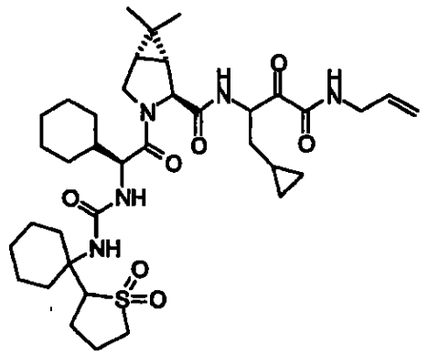
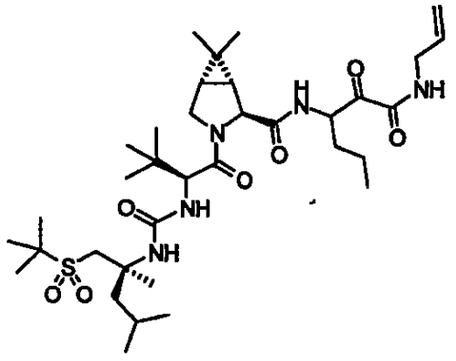
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
331			A
332			C
333			C

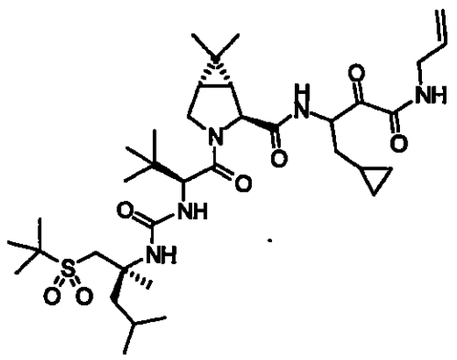
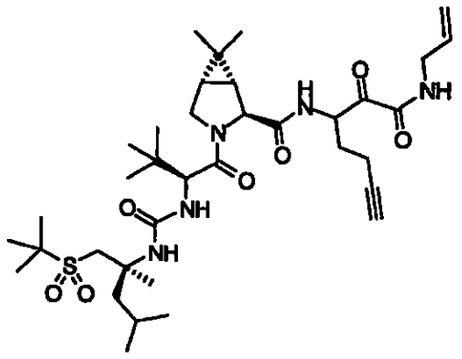
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
334			A
335			A
336			A

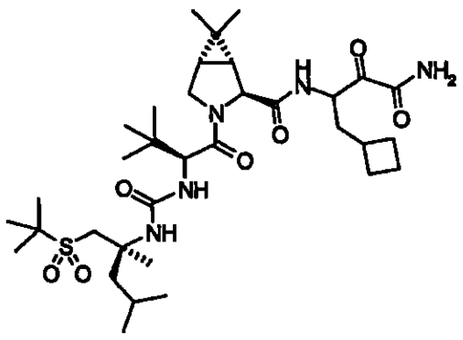
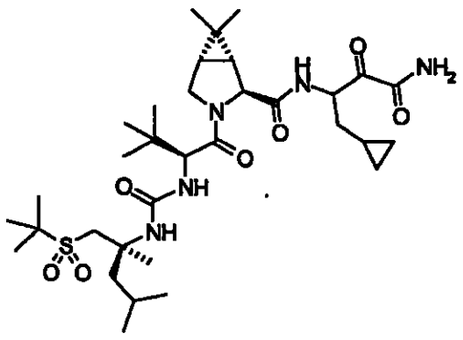
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
337			A
338			A

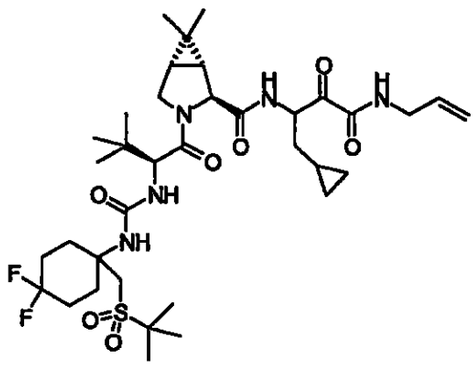
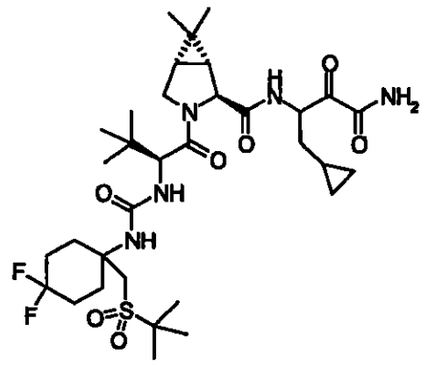
Prep. Ex.	COMPOUND	Select Mass Spectral Data	KI* range
339			A
340			A

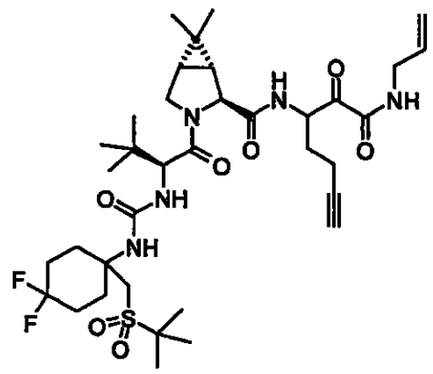
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
341			A
342			A

Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
343			A
344			C

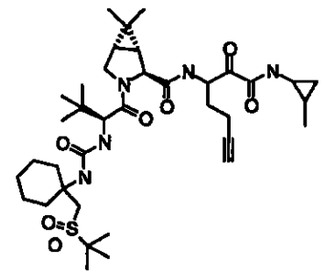
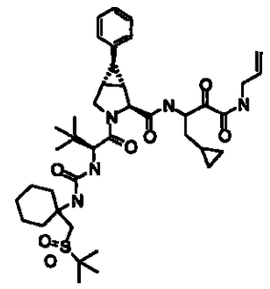
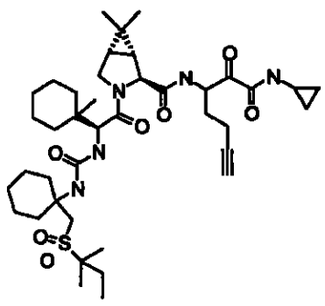
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
345			C
346			B

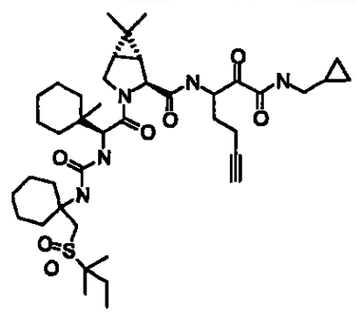
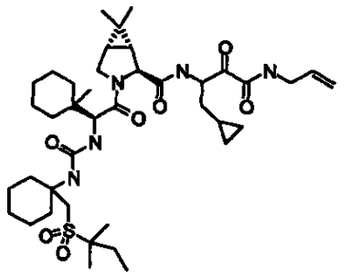
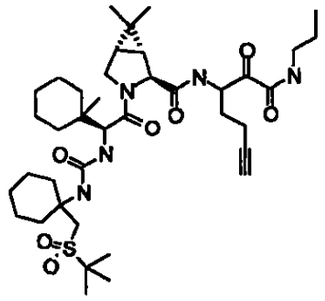
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348			B

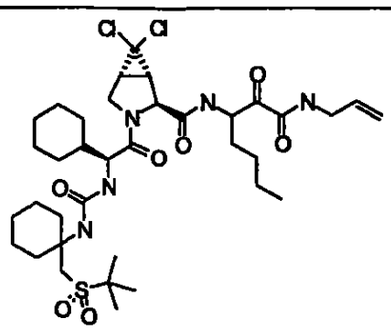
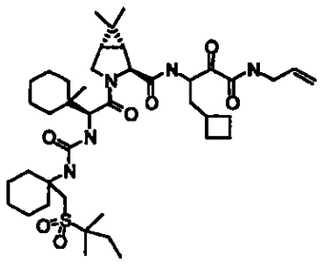
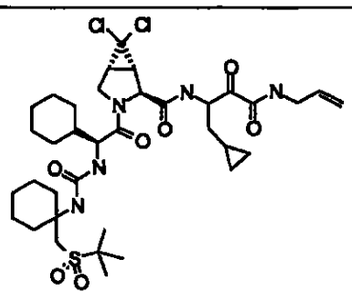
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350			A

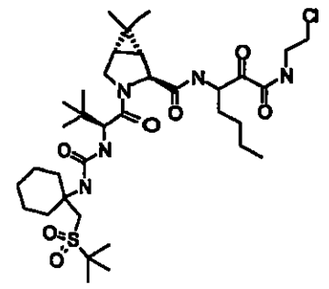
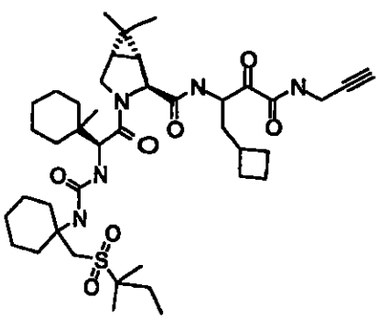
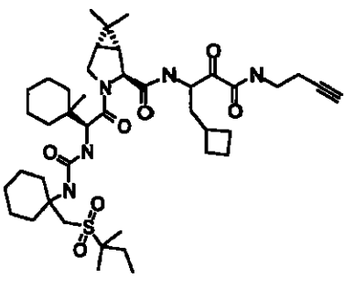
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
351			A

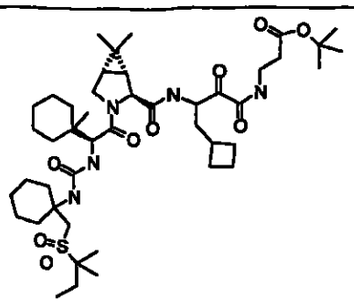
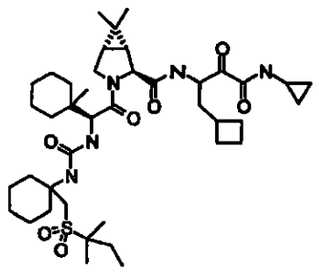
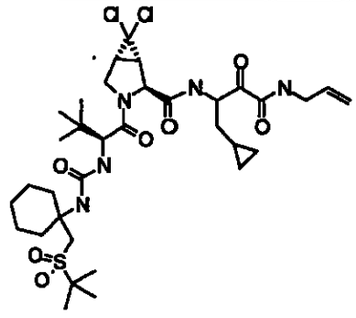
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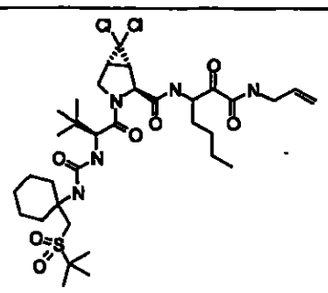
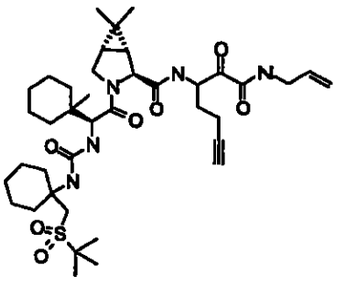
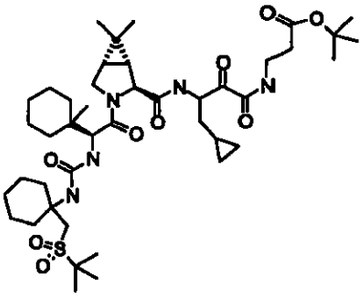
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	C	754.0095
	7	758.0414

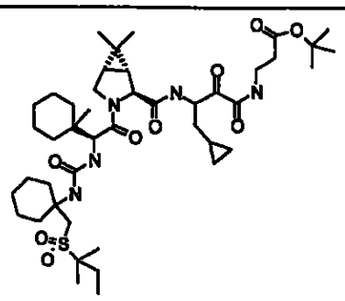
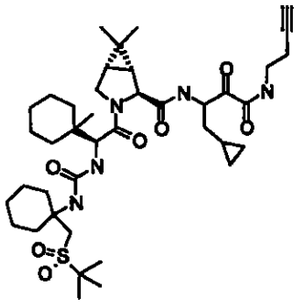
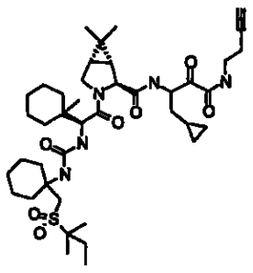
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	14	760.0574
	4	746.0303

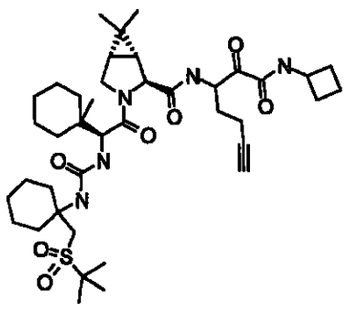
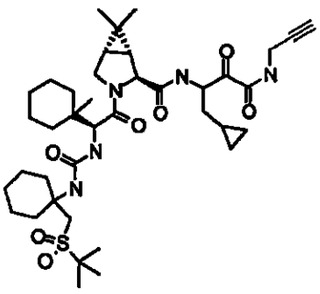
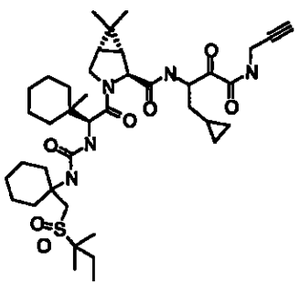
	5	774.855
	37	774.0844
	18	772.8391

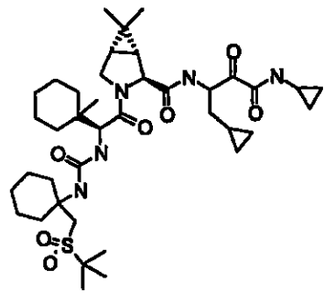
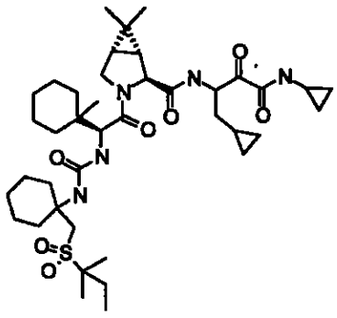
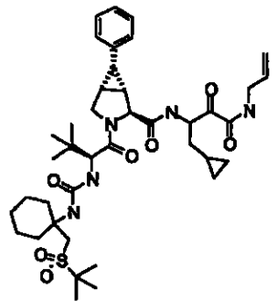
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	34	772.0685
	48	786.0956

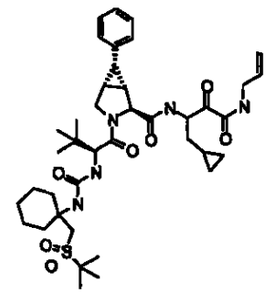
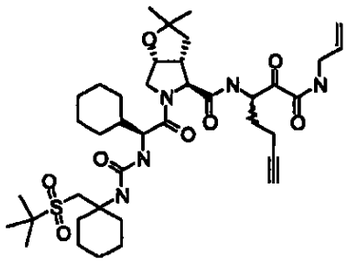
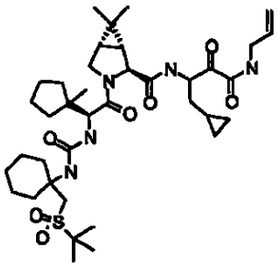
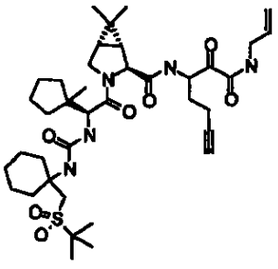
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	54	774.0844
	9	746.8008

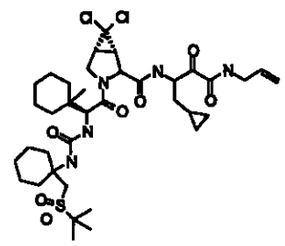
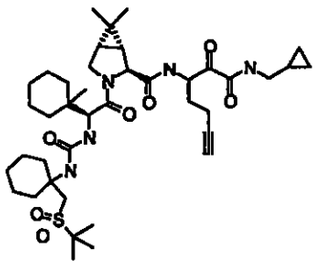
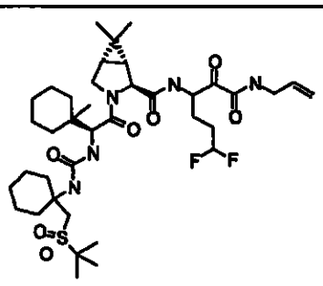
	8	748.8168
	5	744.0143
	17	834.1374

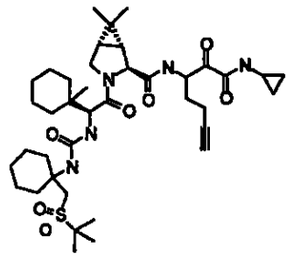
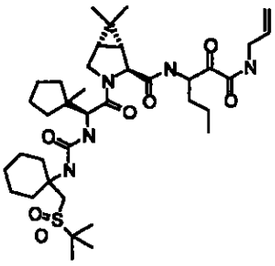
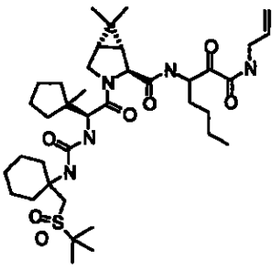
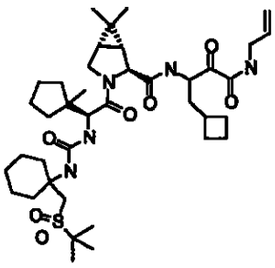
	19	848.1645
	17	758.0414
	20	772.0685

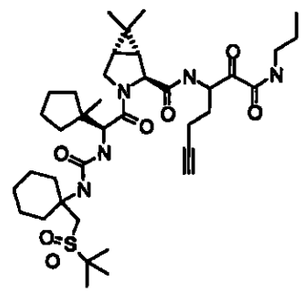
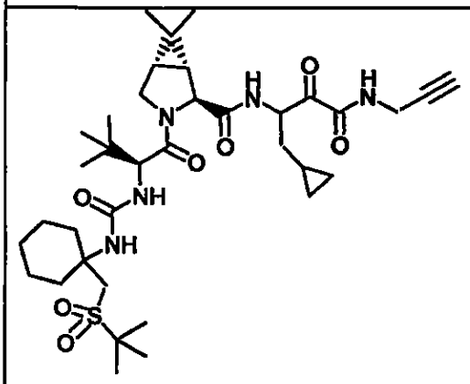
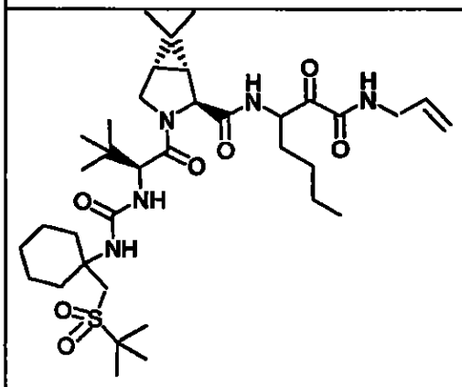
	10	758.0414
	8	744.0143
	17	758.0414

	12	746.0303
	13	760.0574
	C	754.0095

	C	754.0095
	23	760.0137
	12	732.0032
	2.4	729.9872

	B	786.8661
	4	758.0414
	6	770

	6	744.0143
	22	719.992
	22	734.0191
	34	746.0303

	13	732.0032
		
		

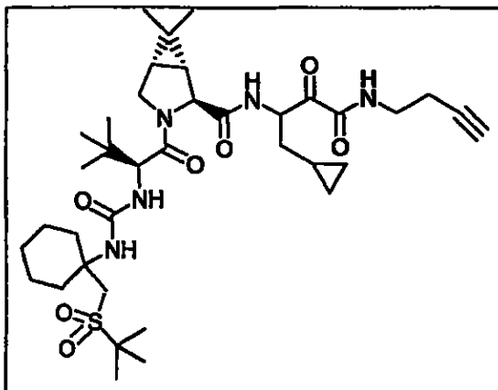
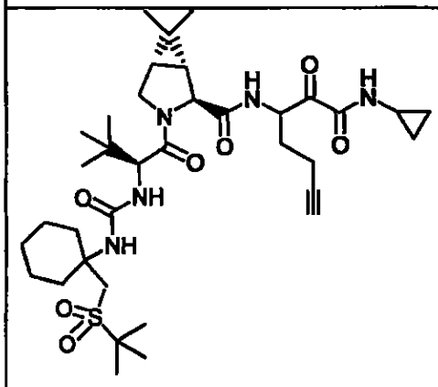
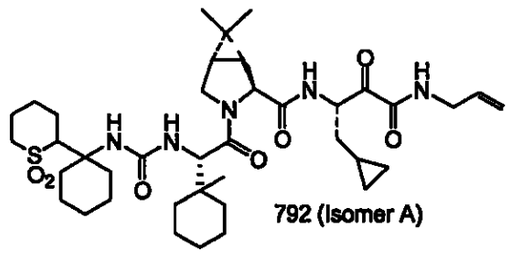
		
		

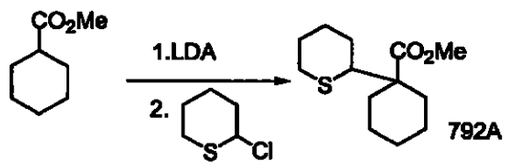
Table 3A lists additional compounds made in accordance with this invention. The following experimental procedures describe the preparation of the compounds shown in **Table 3A** which follows the experimentals.

Example 792



792 (Isomer A)

Step1

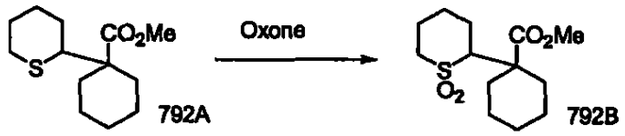


To a solution of pentamethylene sulfide (10.09g) in dry benzene (120ml)was added, portionwise (over a period of 40 min.) , N-chlorosuccinimide (13.02g) while maintaining the internal temperature below 9^{0}C. The resulting reaction mixture was stirred below 15^{0}C for 45 min. The precipitate was filtered and the supernatant was concentrated under reduced pressure. The residue was diluted with cold hexane, filtered and the supernatant concentrated under reduced pressure to provide the chloride as a yellow oil (11.88g).

To diisopropylamine (12.5ml) in anhydrous THF (15ml) was added n-BuLi (53ml of a 1.6M solution in hexanes) at -78^{0}C, under an atmosphere of nitrogen, and the resulting mixture was maintained at this temperature for a period of 15 min., before the addition of methyl cyclohexanecarboxylic acid (12.47ml) and the reaction was maintained at -78^{0}C for a further 40 min. The chloride in anhydrous THF (50ml) was added to the reaction mixture and the flask was removed from the cooling bath and allowed to warm slowly to room temperature. The reaction was quenched with 5% aq. KH_2PO_4 (100ml) containing conc. aq. HCl (2.7ml). The organics were extracted into

Et_2O/EtOAc, dried ($MgSO_4$) and concentrated under reduced pressure to yield a residue which was purified by silica gel column chromatography using 0-2% EtOAc in hexanes as eluent. Gave the bicycle (792A; 8.12g) as a yellow oil.

Step 2

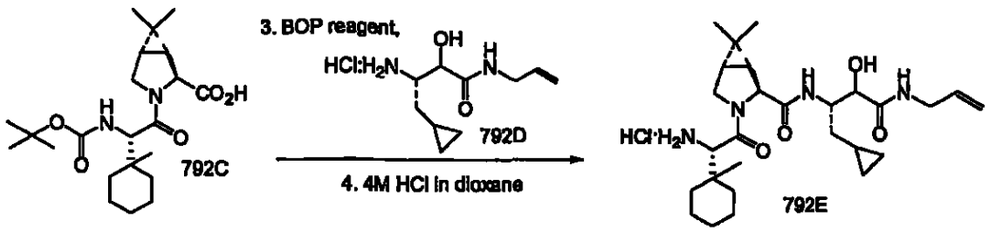


792A 792B

A solution of the sulfide (792A; 0.780g) in 50% aq. MeOH (8ml) was cooled to 0°C and added to a cooled (0°C) suspension of oxone (5.97g) in 50% aq. MeOH (8ml) and the reaction was allowed to warm to room temperature overnight before partitioning between methylene chloride and water. The aqueous layer was further extracted with methylene chloride and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using (25-35%) EtOAc in hexanes to give the sulfone (792B; 0.1598g) . The reaction was repeated using the sulfide (792A; 8.12g), oxone (62.06g), methanol (30ml), water (30ml) to give the sulfone (792B; 4.73g).

The racemic mixture (792B; 0.4925g) was further purified by chiral HPLC using a preparatory Chiralpak AS column using 40% i-PrOH in hexanes (45ml/min; monitored at 218nm. Gave (792B-enantiomer A; 0.247g; retention time 37 min.) followed by (792B-enantiomer B; 0.249g; retention time 63min).

Steps 3 and 4:



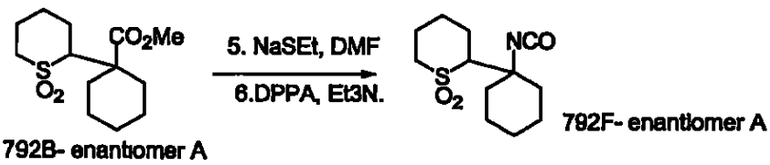
Step 3

To a solution of the carboxylic acid (792C; 0.172g) and the hydrochloride salt (792D) in dichloromethane (5ml) was added BOP reagent (0.246g) followed by triethylamine (0.232ml) and the resulting reaction mixture was stirred overnight at room temperature. The reaction mixture was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. $NaHCO_3$, water, dried ($MgSO_4$) and the volatiles were removed under reduced pressure to yield a residue which was used in step 4 without purification.

Step 4

To the residue from step 3 was added 4M HCl in dioxane (10ml) and the solution was allowed to stand at room temperature for a period of 2h. The volatiles were removed under reduced pressure to yield the hydrochloride salt (792E), used without purification.

Steps 5 and 6



792B- enantiomer A

792F- enantiomer A

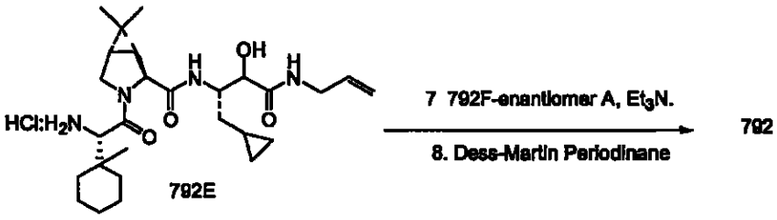
Step 5

To a solution of the methyl ester (792B-enantiomer A; 0.100g) was dissolved in anhydrous DMF (1ml) and sodium ethanethiolate (0.122g) was added and the reaction mixture was allowed to stir at room temperature for approx 72h. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with water (X4), dried ($MgSO_4$) and the volatiles were removed under reduced pressure.

Step 6

To the residue from step 5 was dissolved in anhydrous toluene (2ml) and DPPA (0.083ml) and Et_3N (0.054ml) were added and the reaction was heated to 120°C, under an atmosphere of nitrogen for 1h. After cooling, the reaction was partitioned between EtOAc and sat. aq. $NaHCO_3$ The organic phase was separated, dried ($MgSO_4$) and the volatiles were removed under reduced pressure to provide the isocyanate (792F-enantiomer A), used without purification.

Steps 7 and 8



Step 7

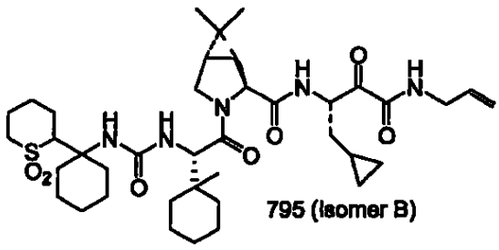
To the hydrochloride salt (792E; 0.050g) in dichloromethane (3ml) was added triethylamine (0.100ml) followed by the isocyanate (792F; approx. 0.040g) in toluene (1ml) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried ($MgSO_4$). The volatiles were removed under

reduced pressure to yield a residue which was usedwithout purification in step 8.

Step 8

The residue from step 7 was dissolved in dichloromethane (3ml) and Dess-Martin peridinane (0.100g) was added and the reaction was stirred at room temperature for 1h. The reaction was partitioned between EtOAc and 10% aq. sodium thiosulfate. The organic phase was separated, washed with sat. aq. sodium bicarbonate, dried ($MgSO_4$) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-hexanes (1:1) as eluent to give the keto-amide (792; 0.0436g) as a white solid.

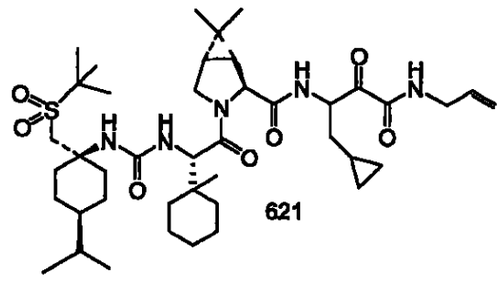
Example 795



795 (isomer B)

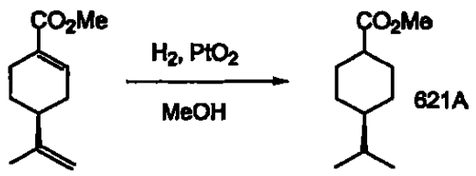
Using the procedures described for the preparation of 792, 792B-enantiomer B was transformed into the corresponding isocyanate as described in steps 5 and 6. Further by utilizing 792E and steps 7 and 8 and the isocyanate derived from 792B-enantiomer B, 795 was produced.

Example 621:



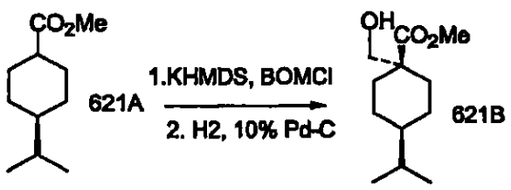
621

Steps 1



To Methyl Perillate (3g) in methanol (20ml) was added PtO_2 (0.3g) and the resulting suspension was placed under anatmosphere of hydrogen (balloon) overnight. The suspension was filtered through a pad of celite and the solid was washed thoroughly with methanol. The filtrate was concentrated under reduced pressure to yield the cyclohexane (621A; 2.93g), a mixture of diastereomers, as a colorless oil.

Steps 2 and 3



Step 2

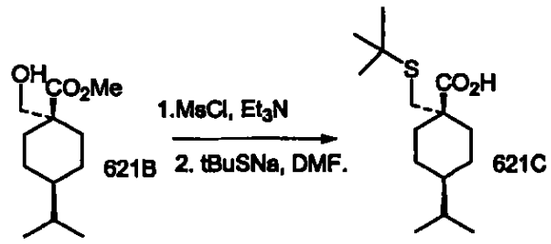
The carboxylic esters (621A;3.75g) were dissolved in anhydrous diethyl ether (50ml) and cooled to -78^{0}C, under an atmosphere of nitrogen. KHMDS (69ml of a 0.5M solution in toluene) was added dropwise and the resulting mixture was stirred for a further 15 min., before the addition of BOMCl (1.7eq.) and the reaction flask was removed from the cooling vessel and allowed to

warm slowly to room temperature. Water (approx. 10ml) was added and the mixture was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried ($MgSO_4$), and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc:Hexanes (1:20) as eluent, providing the intermediate benzyl ether (3.01g), a colorless oil.

Step 3

To the benzyl ether from step 2 (2g) was added methanol (10ml) followed by 10% Pd-C (1g) and the black suspension was placed under an atmosphere of hydrogen (balloon) overnight. The reaction was filtered through a pad of celite and the solid was washed thoroughly with methanol. The filtrate was concentrated to provide the desired alcohol (621B;1.362g) as a colorless oil.

Steps 4 and 5



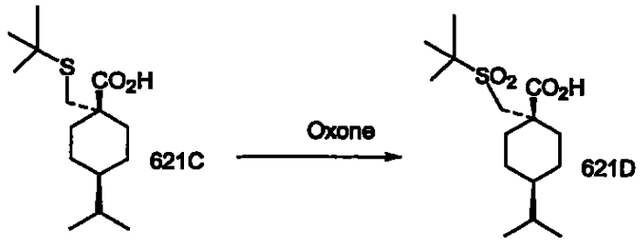
Step 4

The alcohol (621B; 0.32g) was dissolved in dichloromethane (5ml) and methane sulfonyl chloride (0.166ml) followed by triethylamine (0.37ml) were added and the resulting reaction was stirred for 0.5h before partitioning between EtOAc and 10% aq. HCl. The organic phase was separated washed with sat. aq. sodium bicarbonate, water, dried (MgSO4) and the volatiles removed under reduced pressure to yield a residue which was used in step 5 without purification.

Step 5

The residue from step 4 was dissolved in DMF (10ml) and sodium tert-butyl thiolate was added and the resulting reaction mixture was stirred at room temperature under an atmosphere of nitrogen overnight. The reaction mixture was partitioned between EtOAc and aq. 10% HCl. The organic phase was separated, washed with water (X4), dried ($MgSO_4$) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-Hexanes (3:7) as eluent to give the carboxylic acid (621C;0.214g).

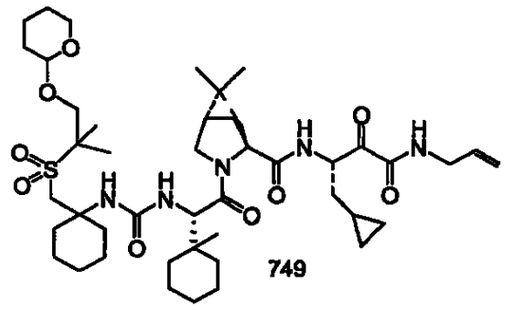
Step 6



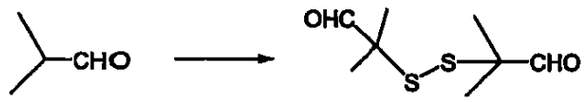
Using the sulfide (621C; 0.090g), oxone (0.61g), methanol (2ml), water (2ml) and the procedure set forth in example 792 (Step 2), the sulfone (621D; 0.091g) was obtained as a white solid.

As described above (Example 792; Steps 6 through 8), the sulfone-carboxylic acid was converted to compound 621.

Example 749:



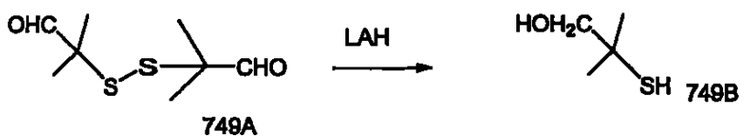
Step 1



749A

Procedure: To Isobutyraldehyde (59g, 0.69mol) in CCl4 was added sulfur monochloride (27.6mL, 0.345mol, 0.5eq.) dropwise at 50°C. After a short lag (10min), evolution of HCl gas began. After HCl evolution ceased, the mixture was stirred at 55°C for 2.5hrs, which TLC indicated the reaction almost completed. Then cooled to room temperature. Crude was concentrated it to dryness. The oily residue, the disulfide (749A), was used without purification.

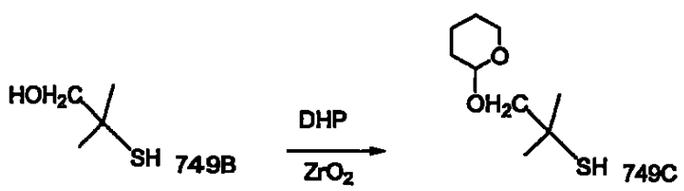
Step 2



749A 749B

To the disulfide (749A; 7.5g, 36mmol) in THF was added $LiAlH_4$ (2.76g, 72.7mmol, 2eq.) at 0°C very slowly. The mixture was stirred at RT for 3hrs then Sat. Na2SO4 was added dropwise until white grey solid appeared. Stirred at RT for 10min. Diltued it with CH_2Cl_2. Dried over $MgSO_4$. Filtered and concentrated to dryness. Purified it by HPFC with 2~20% EtOAc in hexane to give the alcohol (749B; 6.81g). Yield 89%.

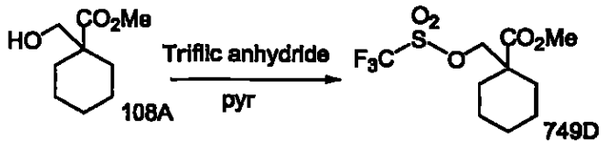
Step 3



749B 749C

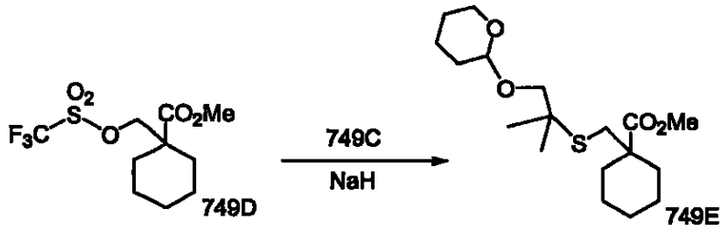
To the alcohol (749B; 10g, 94.2mmol) was added 3,4-dihydro-2H-pyran (8.8mL, 94.2mmol, 1equiv) and ZrO_2. (2.0g, 20% w/w). The mixture was stirred at 80°C for 2hrs. reaction was diluted it with CH_2Cl_2 and filtered. The filtrate was concentrated to dryness and purified by HPFC with 2~10% EtOAc in hexane to give 14.3g of product (749C). Yield 80%.

Step 4



To the alcohol (108A; 3.0g, 17.4mmol, 1equiv) in CH_2Cl_2 was added pyridine (2.4mL, 29.6mmol, 1.7equiv) and triflic anhydride (3.8mL, 22.6mmol, 1.3equiv) at -20°C. The reaction was stirred at -20~10°C for 2hr which MS and TLC indicated the reaction completed. Diluted it with EtOAc, Washed with sat. NH4Cl and brine. Dried over MgSO4. Concentrated it to dryness to give the sulfonate (749D; 5.21g). Yield 98%.

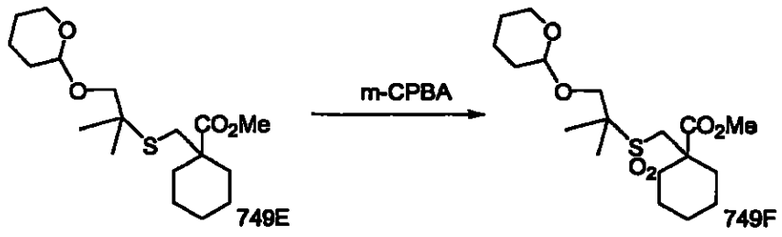
Step 5



To THF at 0°C was added NaH(1.02g, 25.6mmol, 1.5eq.), then (749C; 4.88g, 25.6mmol, 1.5eq.) . The mixture was stirred at 0°C for 10min, then (749D; 5.21g, 17.1mmol) was added at 0°C. The reaction was stirred at RT for 1hr, which TLC indicated no starting materials. Diluted it with EtOAc and water. Extracted aqueous layer with EtOAc. Combined organic layer was

washed with H_2O and brine. Organic layer was dried over $MgSO_4$. Concentrated it to dryness. Purified it by HPFC with 2~8% EtOAc in hexane to give (749E;5.89g) of product. Yield 100%.

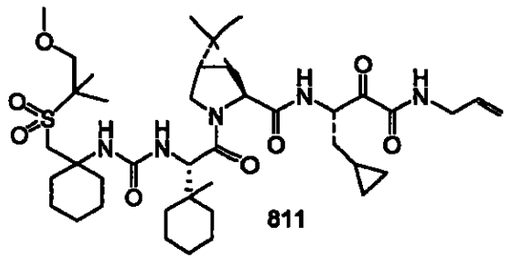
Step 6



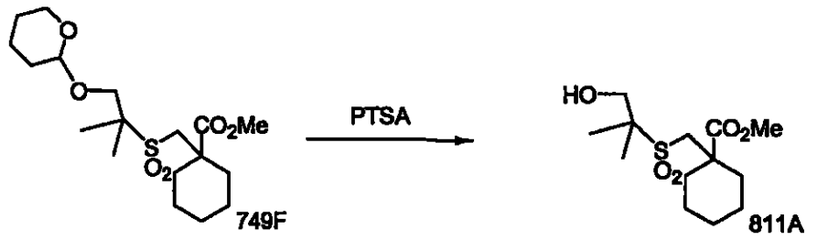
To the sulfide (749E; 0.17g, 0.49mmol) in CH_2Cl_2 was added $NaHCO_3$ (0.205g, 2.45mmol, 5equiv) , mCPBA(0.304g, 1.23mmol, 2.5eq.) at 0°C . The reaction was stirred at RT for 2hrs, which TLC and MS showed the reaction completed. Diluted with CH2Cl2. Washed with sat. NaHCO3 and brine. Dried over MgSO4. Purified it by HPFC with 5~20% EtOAc in hexane to give 0.14g of the sulfone (749F). Yield 76%.

The methyl ester (749F) can be converted to the corresponding carboxylic acid and subsequently the isocyanate (Example 108; Steps 5 and 6) and converted to 749 (Example 792; Steps 7 and 8).

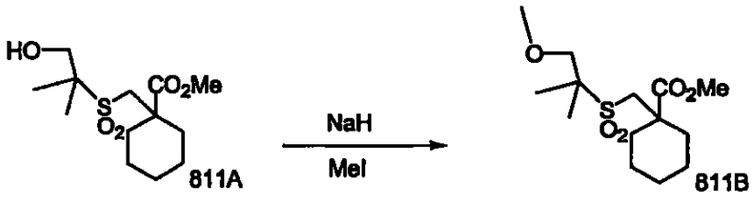
Example 811:



Step 1



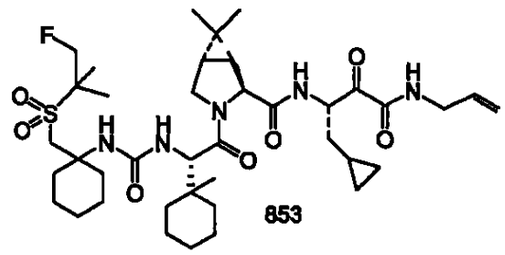
To 749F (70mg,0.18mmol) in MeOH was added pTsOH. The reaction was stirred at RT for overnight. MS showed the reaction almost completed. Concentrated it to dryness. Diluted with EtOAc. Washed with sat $NaHCO_3$, brine. Purified by HPFC with 10 ~40% EtOAc in hexane to give 52mg of the alcohol (811A) Yield 99%.



To NaH (88mg, 2.21mmol, 1.3equiv) in DMF at 0°C was added the alcohol(811A; 0.5g, 1.7mmol) and MeI (0.16mL, 2.56mmol, 1.5equiv) . The reaction was stirred at RT for 2hrs which TLC indicated the reaction didn't completed. 1 equiv MeI was added again. The reaction was stirred at RT for overnight. Diluted it with EtOAc. Washed with water, brine. Dried over MgSO4. Purified it by HPFC with 2~10~40% EtOAc in hexane to give the ether (811B; 0.283g) Yield 54%.

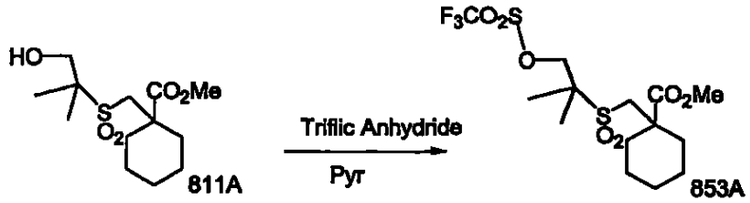
The methyl ester (811B) can be converted to the corresponding carboxylic acid and subsequently the isocyanate (Example 108; Steps 5 and 6) and converted to 749 (Example 792; Steps 7 and 8).

Example 853:



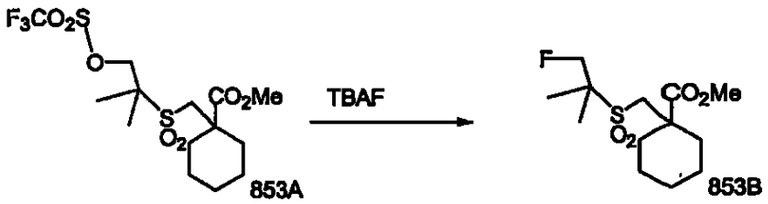
853

Step 1



To the alcohol (811A; 56mg, 0.19mmol, 1equiv) in CH_2Cl_2 was added pyridine (0.026mL, 0.32mmol, 1.7equiv) and triflic anhydride (0.042mL, 0.25mmol, 1.3equiv) at -20°C. The reaction was stirred at -20~10°C for 2hr which MS and TLC indicated the reaction completed. Diluted it with EtOAc, Washed with sat. NH4Cl and brine. Dried over MgSO4. Concentrated it to dryness to give 75.9 mg of crude product (853A)

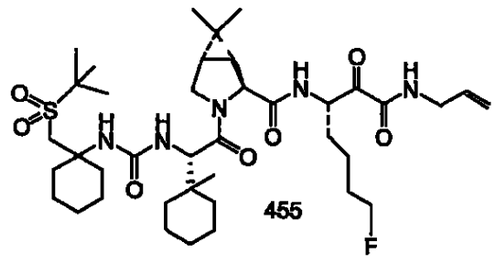
Step2



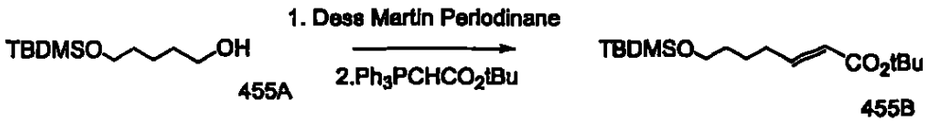
To 853A (75.9mg, 0.18mmol, 1equiv) in ether was added tetra-n-butyl ammonium fluoride (0.23mL, 0.23mmol, 1.3equiv) dropwise at -15°C. The reaction was stirred at RT for over night. Diluted it with ether, washed with sat. NH4Cl and brine. Dried over $MgSO_4$. Purified it with 2~10% EtOAc in hexane to give 32mg of the fluoride (853B). Yield 60%.

The methyl ester (853B) can be converted to the corresponding carboxylic acid and subsequently the isocyanate (Example 108; Steps 5 and 6) and converted to 749 (Example 792; Steps 7 and 8).

Example 455:



Steps 1 and 2



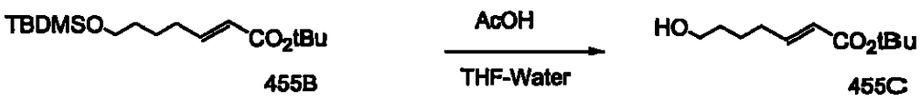
455A 455B

Steps 1 and 2 ('one-pot')

Dess-Martin Periodinane (21.35g) was added to a solution of the alcohol (455A; 10.00g) in dichloromethane (100ml) and stirred for 45 min., before the addition of the phosphorane (17.42g) and stirred overnight. The reaction mixture was partitioned between 5% aq. sodium thiosulfate and EtOAc and the organic phase was separated, washed with sat. aq. sodium bicarbonate,

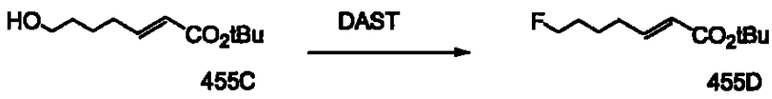
water, dried ($MgSO_4$) and concentrated under reduced pressure. Hexanes was added to the residue and the resulting suspension was stirred vigorously for 2h and filtered. The filtrate was concentrated under reduced pressure and purified by silica gel ciolumn chromatography using EtOAc-hexanes (1:99) as eluent to give the desired alkene (455B; 7.33g) as a yellow oil.

Step 3



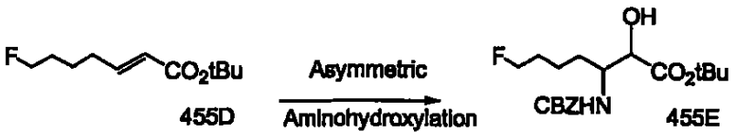
Acetic acid (26ml) was added to a solution of the silyl ether in THF (6ml) and water (14ml) and the resulting mixture was stirred at room temperature overnight. The reaction was partitioned between EtOAc and sat. aq. sodium bicarbonate. The organic phase was separated, washed with water, dried ($MgSO_4$) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-hexanes (1:5) as eluent to give the alcohol (455C; 4.46g) as a colorless oil.

Step 4



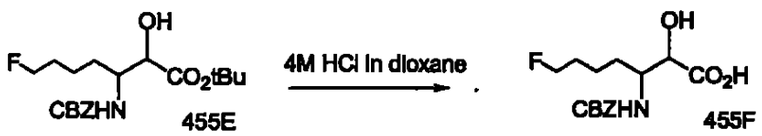
DAST (1.32ml) was added to a stirred solution of the alcohol (455C; 2.00g) in dichloromethane (50ml) at -78C, under an atmosphere of nitrogen. When the addition was complete the cooling bath was removed and the reaction allowed to stir at room temperature for 2h., before partitioning between EtOAc and water. The organic phase was separated, dried ($MgSO_4$) and the volatiles removed under reduced pressure before purification by column chromatography. Gave the fluoride (455D; 0.758g).

Step 5



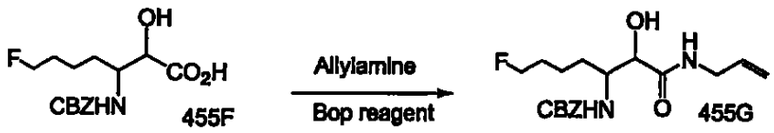
Using benzylcarbamate (2.06g) in n-PrOH (18ml), the alkene (455D; 0.881g), NaOH (0.537g), freshly prepared tBuOCl (1.54ml), $(DHQ)_2PHAL$ (0.176g) in nPrOH (16ml), potassium osmate (0.065g) and the procedure set for in Angewandte Int. Ed. (Engl), 1996, 35, 2813 a crude product was formed which was purified by silica gel column chromatography using EtOAc-Hexanes (1:5) as eluent to give the desired hydroxyamide (455E; 0.892g).

Step 6



4M HCl in dioxane (25ml) (ex. Aldrich) was added to the t-Bu ester (455E; 0.69g) and the resulting solution was allowed to stand at room temperature for 2h. The volatiles were removed under reduced pressure to yield the carboxylic acid (455F; 0.613g), used in subsequent reactions without purification.

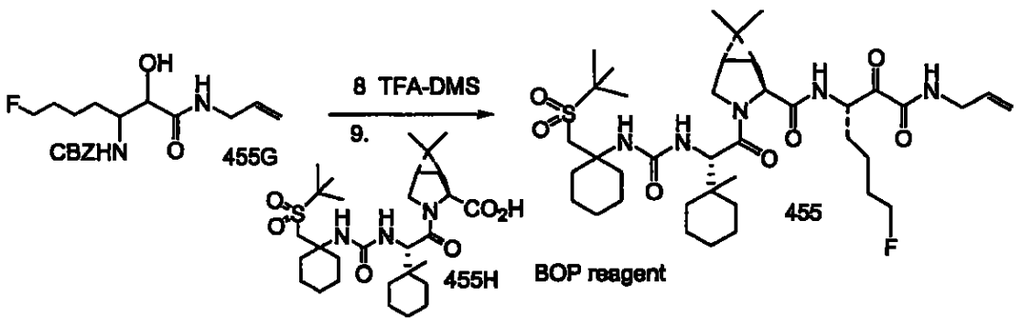
Step 7



Bop reagent (0.254g) followed by triethylamine (0.240ml) were added to a mixture of the carboxylic acid (455F; 0.15g) and allylamine (0.043ml) in

dichloromethane (5ml) and the resulting reaction mixture was stirred at room temperature overnight. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, waster , dried ($MgSO_4$) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography on silica gel using EtOAc:Hexanes (7:3) as eluent to give the amide (455G; 0.151g) as a white solid.

Steps 8, 9 and 10



Step 8

To the benzylcarbamate (455G; 0.037g) was added TFA (2ml) followed by methylsulfide (0.5ml) and the resulting solution was allowed to stand at room temperature for 3h., before removal of the volatiles. The crude reaction product was used in step 9, below, without purification.

Step 9

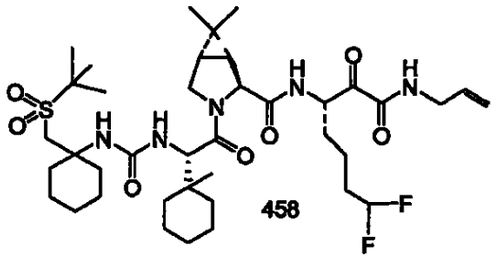
To the residue from step 8 was added dichloromethane (3ml), the carboxylic acid (455H; 0.050g), Bop reagent (0.047g) and finally triethylamine (0.044ml) and the resulting mixture was stirred at room temperature overnight. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, dried

($MgSO_4$) and the volatiles removed under reduced pressure to yield a residue which was used, in step 10, below, without purification.

Step 10

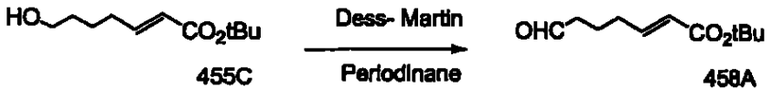
To the residue from step 9, was added dichloromethane (3ml) followed by Dess-Martin periodinane (0.075g) and the suspension was stirred at room temperature for 2h., before partitioning between EtOAc and 5% aq. sodium thiosulfate. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried ($MgSO_4$) and the volatiles removed under reduced pressure. The crude reaction product was purified by silica gel column chromatography to give the desired keto-amide (455; 0.0467g) as a white solid.

Example 458:



458

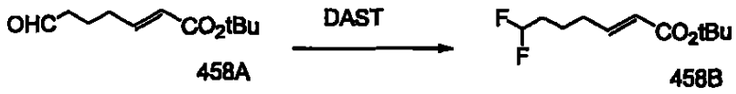
Step 1



455C 458A

To a solution of the alcohol (455C; 1.66g) in dichloromethane (20ml) was added Dess-Martin periodinane (4.22g) and the resulting mixture stirred at room temperature for a period of 1h., before partitioning between EtOAc and 5% aq. sodium thiosulfate. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried ($MgSO_4$) and the volatiles removed under reduced to yield the aldehyde (458A; 0.775g) used with purification.

Step 2

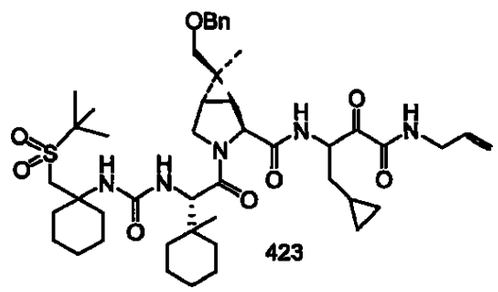


458A 458B

DAST (1.11ml) was added dropwise to a stirred solution of the aldehyde (458A; 0.755g) in dichloromethane (50 ml) while cooled in an ice bath, under an atmosphere of nitrogen. After completion of the addition the resulting mixture was stirred at room temperature for a period of 2h., before partitioning between EtOAc and water. The organic phase was separated, dried ($MgSO_4$) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography to give the desired difluoride (458B; 0.758g).

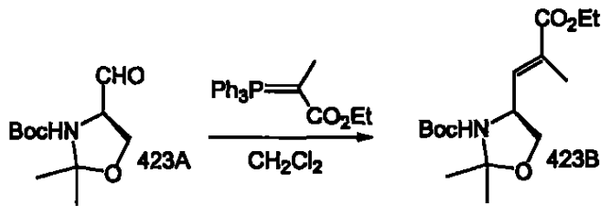
Using 458B and the procedures outlined in example 455 (Steps 5 through 10) target 458 was produced.

Example 423:



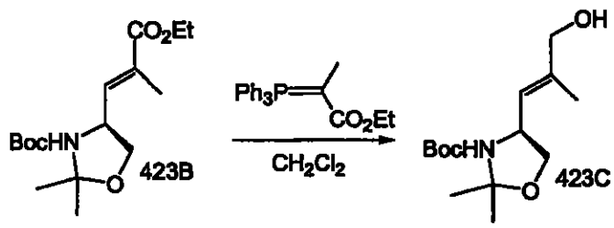
423

Step 1



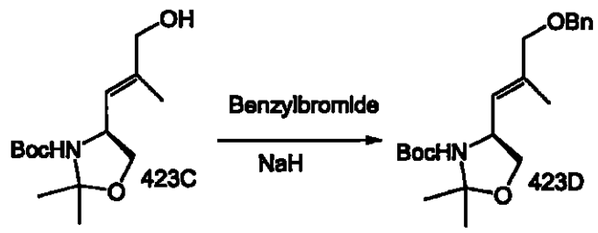
To a solution of Garner aldehyde (423A; 10.7g) in dichloromethane (110ml) was added (carbethoxyethylidene)triphenylphosphorane (28.75g) the resulting solution was stirred at room temperature overnight. The volatiles were removed under reduced pressure and the residue purified by silica gel column chromatography using 4-10% EtOAc in hexanes to give the desired alkene (423B; 12.7g), as a colorless oil.

Step 2



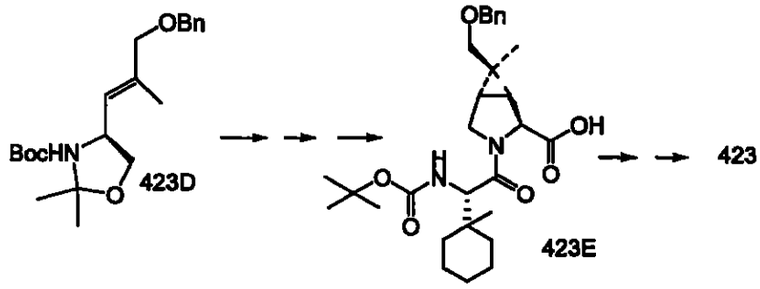
To a solution of the ethyl ester (423B;12.72g) in dichloromethane (20ml) was added DIBAL-H (90ml of a 1M solution in dichloromethane) at -78C, under an atmosphere of nitrogen. When the addition was complete the reaction was maintained at this temperature for a further 30 min the at room temperature for 1h., before the addition of MeOH (3ml) and sat aq. potassium sodium tartrate (3ml) and EtOAc. The organic phase was separated, washed with 1M aq HCl, brine, dried ($MgSO_4$). The volatiles were removed under reduced pressure and the residue purified by silica gel column chromatography using 6-35% EtOAc in hexanes to give the alcohol (9.06g), as a colorless oil.

Step 3

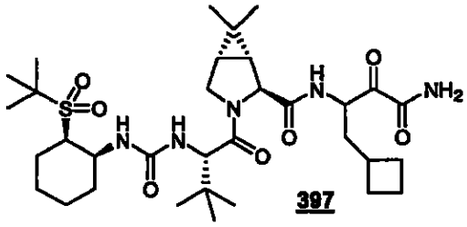


To a solution of the alcohol (423C; 8.66g) in anhydrous DMF (30ml), while cooled in an ice bath, was added NaH (1.38g) and the resulting mixture was maintained at that temperatuefor 45 min., before the addition of benzyl bromide (5ml). The reaction was allowed to warm to room temperature overnight befor the addition of ether followed bt 10% aq. HCl. The organic phase was separated, washed with sat aq. sodium bicarbonate, brine, dried (Na_2SO_4). The volatiles were removed under reduced pressure to yield a residue which was purified by silica gel column chromatography using 8% EtOAc in hexanes to yield the benzyl ether (8.10g) as a yellow oil.

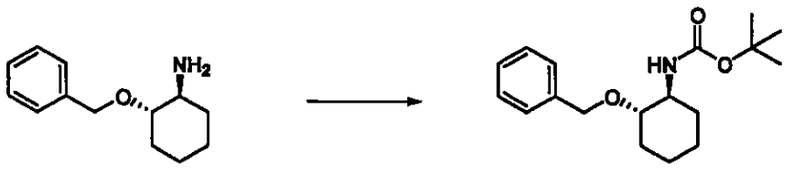
Using analogous procedures described above for the conversion of 22.03 to 22.01, 423D was transformed into 423E



Example 397:



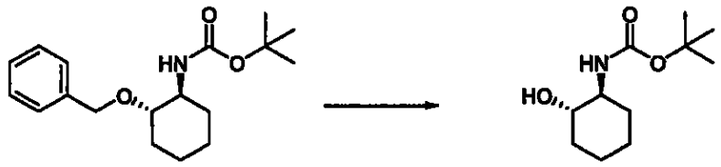
Step A



397a 397b

A solution of benzyloxycyclohexyl amine **397a** (10.6 g, Lancaster) and N-methylmorpholine (8.5 mL, d 0.920) in 200 mL of dry dichloromethane was cooled to -78 °C. Boc-anhydride in 100 mL of dry dichloromethane was added over 15 min using an addition funnel. After addition was completed, the cooling bath was removed and the mixture was stirred of further 30 min. The reaction mixture was partitioned between 300 mL of ether and 100 mL of aqueous 1N HCl. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the product **397b** (15.7 g; 99 %) as a white solid which was used without further purification.

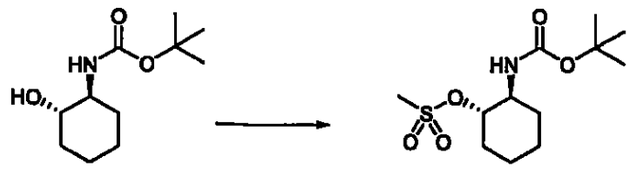
Step B



397b 397c

20% palladium dihydroxide on carbon (30 mol%; 10.8 g) was added to a solution of benzyl ether **397b** (15.7 g) in 300 mL of methanol. The heterogeneous mixture was subjected to hydrogenation at 40 psi until no more starting material was detected by TLC (ethyl acetate/hexanes; 2:8). The mixture was filtered thru celite and the filtrate was concentrated under reduced pressure. No further purification was carried out for the product **397c** (11.1 g; 99%).

Step C



397c 397d

Pyridine (25.0 mL) was added to a solution of cyclohexanol **397c** in 300 mL of dry dichloromethane at 0 °C. Methanesulfonyl chloride (8.0 mL) in 100 mL of dry dichloromethane was added over 15 min. The reaction mixture turned to a homogeneous yellow solution. The reaction mixture was stirred at 0 °C for 15 min and then the cooling bath was removed. Reaction was stirred at room temp for about 3 h. The mixture was partitioned between ether (500 mL) and aqueous 1N HCl (100 mL). The organic layer was washed with aqueous saturated sodium bicarbonate (100 mL), brine (100 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: ethyl acetate/(hexanes-dichloromethane, 1:1); 0:10 to 2:8) to afford the product **397d** (9.7 g; 64 %) as a white solid.

Step D



397d 397e

A 250 mL-flask was charged with mesylate **397d** (3.0 g) and t-butylthiol sodium salt (3.44 g). The flask was flushed with nitrogen and 100 mL of dry DMF were added. The resulting solution was degassed (vacuum/nitrogen-flush) and heated to 70 °C. The flow of the reaction was monitored by TLC (ethyl acetate/hexanes; 2:8). All the starting material was consumed in about

3 h. The reaction mixture was dissolved in 300 mL of ethyl acetate and washed with water (3 x 50 mL) and brine (1 x 50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. No further purification was done for the product **397e** (2.78 g; 95 %).

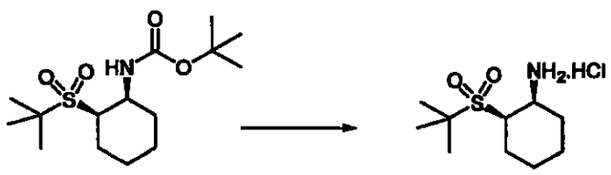
Step E



397e **397f**

A solution of sulfide **397e** (10.22 mmol) in dry dichloromethane (60 mL) was treated with m-CPBA (5.28 g; 60%). The homogeneous mixture was heated at 45 °C for about 3 h. TLC analysis (ethyl acetate/hexanes; 1:9) showed that all the starting material had been consumed. The mixture was concentrated under reduced pressure and the residue was dissolved in 20 mL of ether and treated with aqueous sodium thiosulfate solution at 0 °C. The mixture was diluted with ether (350 mL) and washed with aqueous saturated sodium bicarbonate (5 x 30 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexane; 3:97 to 2:8) to afford the product **397f** (2.45 g; 75 %) as a white solid.

Step F

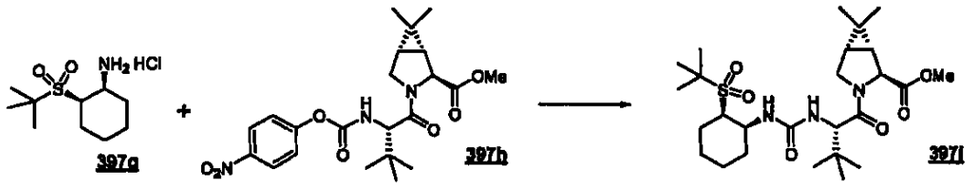


397f **397g**

The N-Boc protected amine **397f** (2.43 g) was dissolved in 20 mL of 4M HCl in dioxanes. The mixture was stirred at room temperature until all the starting

material had been consumed as determined by TLC analysis (ethyl acetate/hexanes; 2:8). After 3 h, all the volatiles were removed under reduced pressure to afford the product **397g** (1.90 g; 98 %) as a white solid.

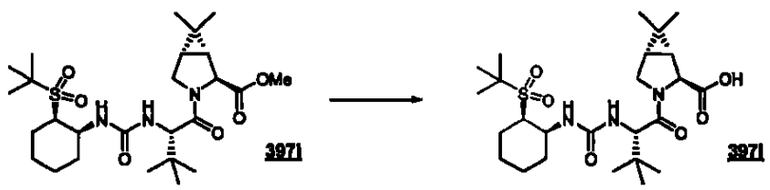
Step G



397g 397h 397i

A solution of the p-nitrophenylcarbamate **397h** (640 mg) in 10 mL of acetonitrile was treated with amine hydrochloride **397g** (350 mg). N-methylmorpholine (0.37 mL, d 0.920) was added to the heterogeneous mixture and the reaction mixture was stirred at room temperature. The reaction was completed after 7 h as determined by TLC analysis (acetone/hexanes; 2:8). The reaction mixture was concentrated under reduced pressure. The residue was dissolved in 150 mL of dichloromethane and washed with aqueous 1N HCl (1 x 30 mL), and aqueous saturated sodium bicarbonate (2 x 30 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The product was purified on silica gel (gradient: acetone/hexanes; 1:9 to 4:6) to afford the product **397i** (625 mg; 87 %) as a white solid.

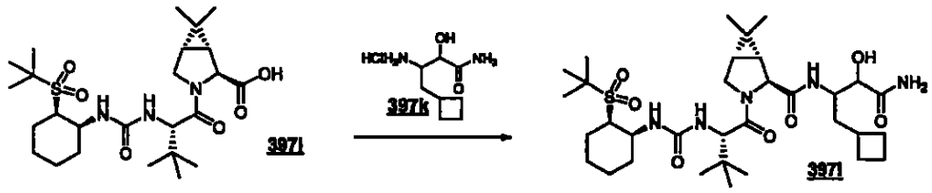
Step H



397i 397j

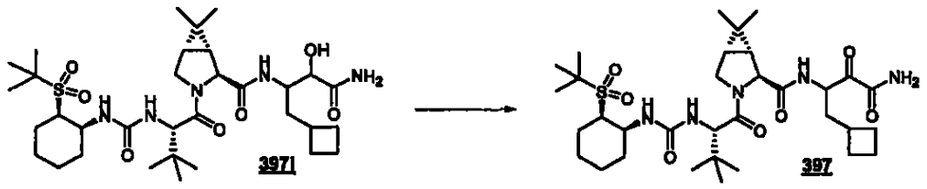
A solution of methyl ester **397I** (610 mg) in 15 mL of a mixture of THF/MeOH/water (1:1:1) was treated with lithium hydroxyde monohydrate (121 mg). Reaction was stirred at room temperature and monitored by TLC (acetone/hexanes; 3:7). After 3 h, all the volatiles were removed under reduced pressure. The residue was partitioned between 30 mL of aqueous 1N HCl and 100 mL of dichloromethane. The aqueous layer was back extracted with dichloromethane (2 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the product **397J** (570 mg; 96 %) as a white solid.

Step I



A solution of acid **397J** (120 mg) in 2 mL of dry dichloromethane and 2 mL of dry DMF was stirred at 0 °C and treated with HATU (124 mg). The amine hydrochloride **397k** (63 mg) was added followed by addition of N-methyl morpholine (0.10 mL, d 0.920). The reaction mixture was gradually warmed to room temperature and stirred overnight. All the volatiles were removed under vacuum and the residue was taken into 100 mL of ethyl acetate. The organic layer was washed with aqueous 1N HCl (15 mL), aqueous saturated sodium bicarbonate (15 mL), and brine (15 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the desired product **397l** (150 mg; 96 %) which was used without further purification.

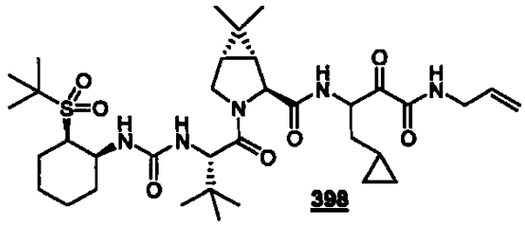
Step J



397I 397

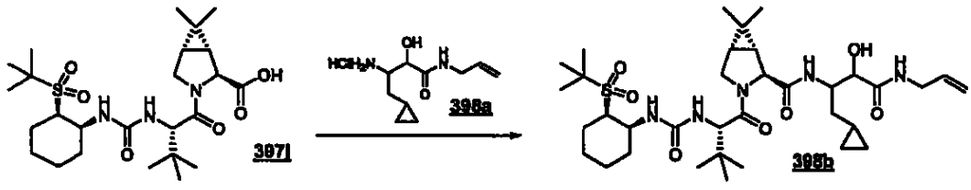
A solution of **397I** (150 mg) in 6 mL of a 1:1 mixture of toluene/DMSO was treated with EDCI (430 mg) and dichloroacetic acid (0.09 mL, d 1.563). Reaction mixture was stirred at room temperature for about 2 h. The reaction mixture was diluted with dichloromethane (100 mL) and washed with aqueous saturated sodium bicarboante (15 mL), aqueous 1N HCl (15 mL), and brine (15 mL). The organic layer was dried over magnesium sulfate, filtrated, and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 5:5) to afford the product **397** (94 mg; 64 %) as a white solid. HRMS calcd for $C_{33}H_{58}N_5O_7S$ $[M+H]^+$: 666.3900, found 666.3883.

Example 398:



398

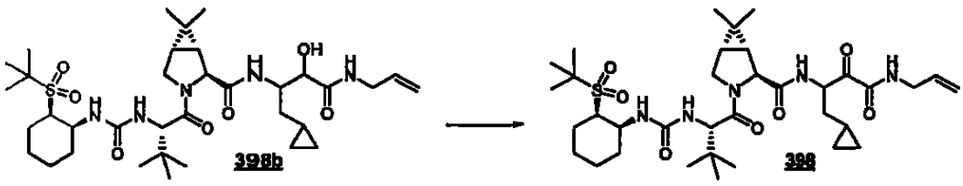
Step A



397I 398a 398b

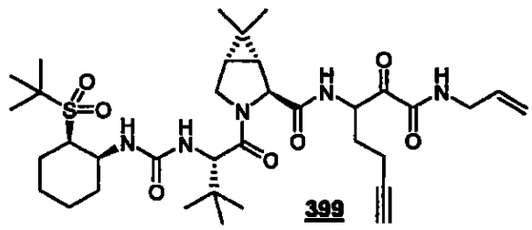
A solution of acid **397J** (100 mg) in 2 mL of dry dichloromethane and 2 mL of dry DMF was stirred at 0 °C and treated with HATU (103 mg). The amine hydrochlonde **398a** (60 mg) was added followed by addition of N-methyl morpholine (0.09 mL, d 0.920). The reaction mixture was gradually warmed to room temperature and stirred overnight. All the volatiles were removed under vacuum and the residue was taken into 100 mL of ethyl acetate. The organic layer was washed with aqueous 1N HCl (15 mL), aqueous saturated sodium bicarbonate (15 mL), and brine (15 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the desired product **398b** (115 mg; 86 %).

Step B



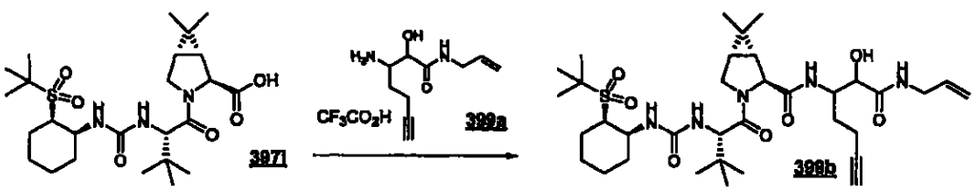
A solution of hydroxyamide **398b** (115 mg) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (210 mg). Reaction mixture was stirred at room temperature for 1 h. The mixture was treated with aqueous 1M sodium sulfite solution (10 mL) and aqueous saturated sodium bicarbonate (10 mL) and stirred for 15 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 5:5) to afford the product **398** (60 mg; 53 %) as a white solid. HRMS calcd for $C_{35}H_{58}N_5O_7S$ $[M+H]^+$: 692.4057, found 692.4081.

Example 399:



399

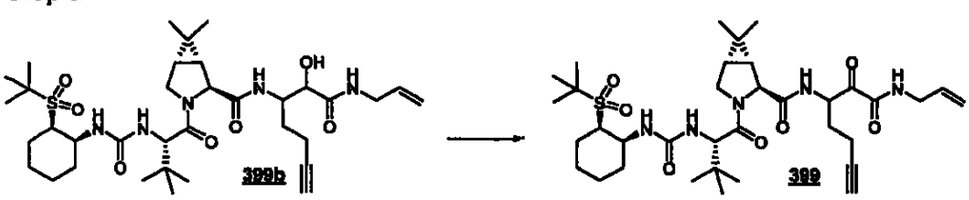
Step A



397j 399a 399b

A solution of acid **397j** (100 mg) in 2 mL of dry dichloromethane and 2 mL of dry DMF was stirred at 0 °C and treated with HATU (106 mg). A solution of the amine salt **399a** (0.252 mmol) and N-methyl morpholine (0.09 mL, d 0.920) in 1 mL of dichloromethane was added dropwise. The reaction mixture was gradually warmed to room temperature and stirred overnight. All the volatiles were removed under vacuum and the residue was taken into 100 mL of ethyl acetate. The organic layer was washed with aqueous 1N HCl (15 mL), aqueous saturated sodium bicarbonate (15 mL), and brine (15 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the desired product **399b** (85 mg; 63 %).

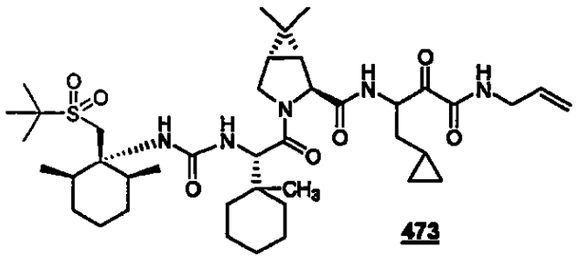
Step B



399b 399

A solution of hydroxyamide **399b** (85 mg) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (157 mg). Reaction mixture was stirred at room temperature for 1 h. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and aqueous saturated sodium bicarbonate (10 mL) and stirred for 15 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 4:6) to afford the product **399** (50 mg; 60 %) as a white solid. HRMS calcd for $C_{33}H_{55}N_6O_7S$ $[M+H]^+$: 679.3853, found 679.3834.

Example 473:



473

Step A

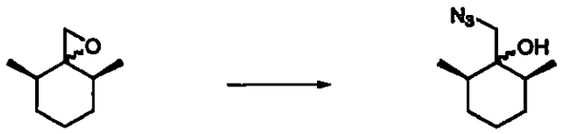


473a **473b**

Cis-2,6-dimethyl-1-methylene cyclohexane (3.0 g, ChemSamp Co.) was added to a stirred suspension of solid sodium bicarbonate (6 eq, 12.19 g) in 150 mL of dichloromethane. The mixture was cooled to 0 °C and a slurry of 70% m-CPBA (3 eq, 17.4 g) in 150 mL of dichloromethane was added in small portions. After addition was completed, the cooling bath was removed and the mixture was stirred for about 2h. The excess m-CPBA was quenched at 0 °C by careful addition of aqueous saturated sodium thiosulfate solution.

The mixture was washed with aqueous saturated sodium bicarbonate solution (100 mL). The organic layer was concentrated in the rotavap (ice-water bath was used). The residue was dissolved in ether (80 mL) and hexanes (120 mL) and washed several times with aqueous saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure (ice-water bath). The residue was chromatographed on silica gel (gradient: ether/hexanes; 0:10 to 8:92) to afford the product **473b** (3.0 g; 90 %) as a colorless oil.

Step B



473b **473b**

A heterogeneous mixture of epoxide **473b** (3 g) and ammonium chloride (5 eq, 5.72 g) in 80 mL of methanol was treated with sodium azide (5 eq, 7.17 g) and heated at 65 °C for 3 h. TLC analysis showed some starting material left and more ammonium chloride (1.5 eq, 1.71 g) and sodium azide (1.5 eq, 2.15 g) were added. The mixture was heated (65 °C) overnight. The reaction mixture was diluted with 30 mL of water and extracted with ether (3 x 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: ether/hexanes; 0:10 to 2:8) to afford the corresponding diastereomeric product **473b** (2.73 g; 71 %) as a colorless oil.

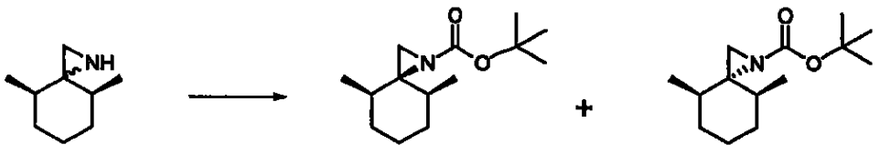
Step C



473b 473c

A solution of azidoalcohol **473b** (1.73 g) in 50 mL of acetonitrile was treated with triphenylphosphine (1.1 eq, 2.69 g) and refluxed for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was chromatographed on silica gel (gradient: ether/hexanes; 5:5 to 9:1) to afford the desired aziridine product **473c** (2.0 g; 98 %).

Step D



473c 473d 473e

A solution of aziridine **473c** (aprox 1.5 g) in dry dichloromethane (50 mL) was cooled to 0 °C and treated with di-tert-butyldicarbonate (1.3 eq, 3.0 g) in 50 mL of dry dichloromethane. N-methylmorpholine (2.5 eq, 2.9 mL, d 0.920) was added dropwise and the mixture was stirred overnight (temp: 0 to 25 °C). The mixture was diluted with ether (300 mL) and washed with aqueous 1M HCl (100 mL), aqueous saturated sodium bicarbonate (80 mL) and brine (80 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: ether/hexanes; 0:10 to 1:9) to afford the products **473d** and **473e** as clear oils (970 mg).

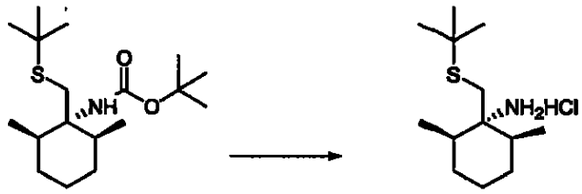
Step E



473e 473f

A 20 mL vial was charged with a solution of N-Boc-aziridine **473e** (469 mg) in 20 mL of dry DMF and sodium tert-butylthiolate (2 eq, 438 mg). The reaction was carried out in a microwave oven at 130 °C for 30 min. The reaction mixture was diluted with 100 mL of ether and washed with water (3 x 30 mL) and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: hexanes to ether/hexanes, 4:96) to afford the product **473e** (140 mg) as a white solid and unreacted starting material (120 mg).

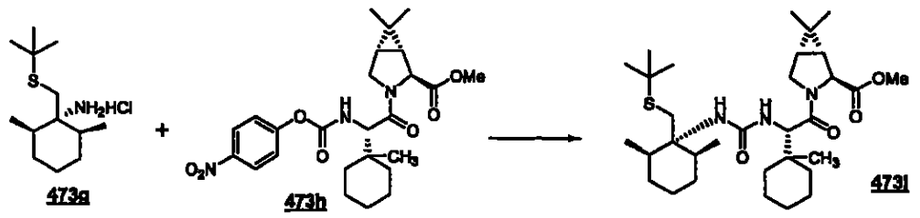
Step F



473f 473g

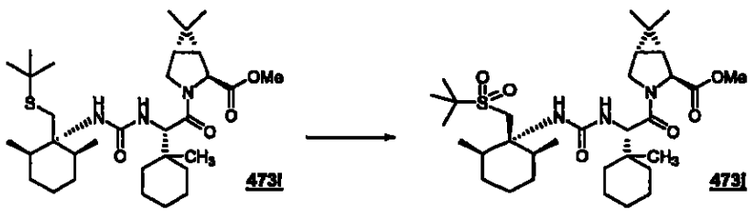
The N-Boc protected amine **473f** (140 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min until all the starting material had been consumed as determined by TLC analysis (ether/hexanes; 5:95). All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h to afford the product **473g** (112 mg; 98 %) as a white solid.

Step G



A solution of the p-nitrophenylcarbamate **473h** (1.05 eq, 212 mg) in 3 mL of acetonitrile was treated with amine hydrochloride **473g** (110 mg) in 2 mL of acetonitrile. N-methylmorpholine (2.5 eq, 0.11 mL, d 0.920) was added and the resulting yellow solution was stirred at room temperature for 8 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in 100 mL of dichloromethane and washed with aqueous 1N HCl (1 x 20 mL), and aqueous saturated sodium bicarbonate solution (2 x 20 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The product was purified on silica gel (gradient: hexanes to acetone/hexanes, 2:8) to afford the product **473l** (150 mg; 63 %).

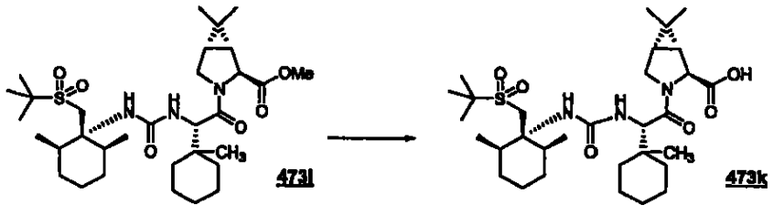
Step H



A solution of sulfide **473l** (150 mg) in dry dichloromethane (15 mL) was treated with 60% m-CPBA (3 eq, 134 mg). The homogeneous mixture was heated at 45 °C for about 1.5 h. Excess m-CPBA was quenched by addition of aqueous sodium thiosulfate solution (20 mL) and stirring was continued for 10 min. Aqueous saturated sodium bicarbonate solution (20 mL) was added and the product was taken into ethyl acetate (100 mL). The organic layer was

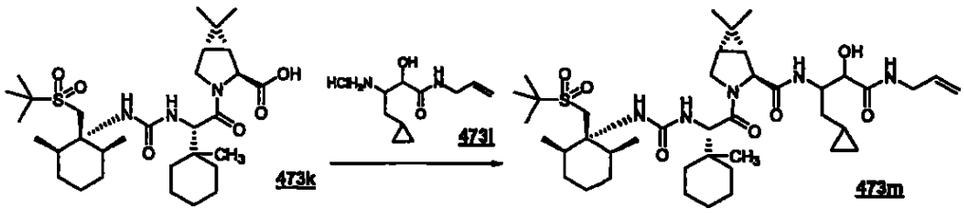
concentrated and the residue was dissolved in ethyl acetate (80 mL). The organic layer was washed with aqueous saturated sodium bicarbonate solution (3 x 10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel (gradient: ethyl acetate/hexanes; 1:3 to 5:5) to afford the product **473j** (120 mg; 76%) as a colorless oil.

Step I



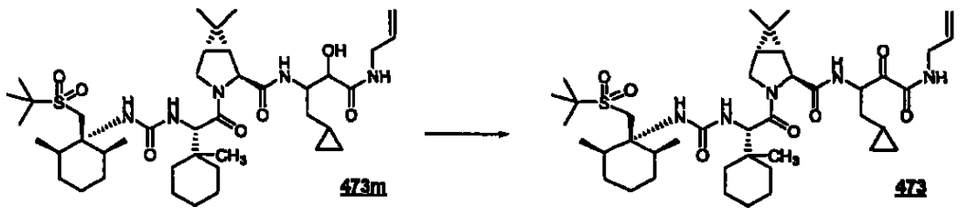
A solution of methyl ester **473j** (110 mg) in 10 mL of a 1:1:1 mixture of THF/water/MeOH was cooled to 0 °C and treated with lithium hydroxide monohydrate (2.5 eq, 19 mg). The cooling bath was removed after 30 min and the mixture was stirred at room temp for further 2 h until all the starting material had been consumed as determined by TLC analysis (ethyl acetate/hexanes; 3:7). The reaction mixture was treated with 20 mL of aqueous 1M HCl (pH of mixture = 1) and the organic solvents were removed under reduced pressure. The aqueous residue was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the product **473k** (105 mg; 98 %) as a clear oil.

Step J



A solution of acid **473k** (50 mg) in 2 mL of dry dichloromethane and 1 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 44 mg). The amine salt (1.3 eq, 25 mg) was added followed by N-methylmorpholine (4 eq, 0.036 mL, d 0.920). The reaction mixture was stirred overnight (temp 0 to 25 °C). All the volatiles were removed under vacuum and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (20 mL), aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **473m** (64 mg) was used without further purification.

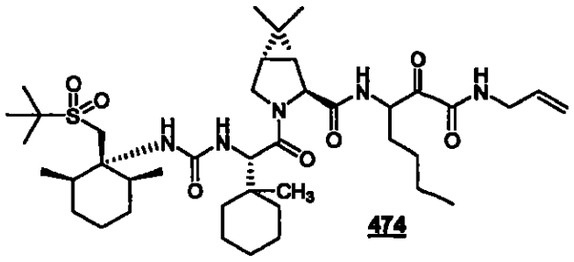
Step K



A solution of hydroxyamide **473m** (0.083 mmol) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 70 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (20 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers

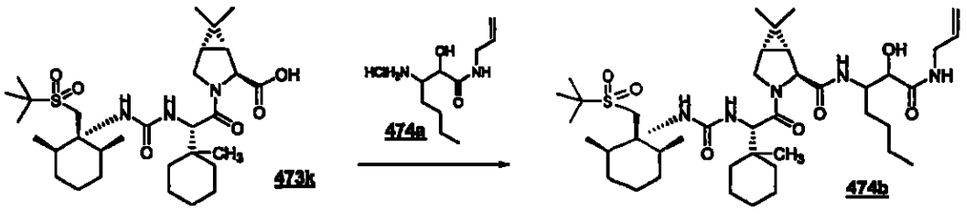
were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 4:6) to afford the product **473** (40 mg; 62% for two steps) as white solid. HRMS calcd for $C_{41}H_{68}N_5O_7S$ $[M+H]^+$: 774.4839, found 774.4834.

Example 474:



474

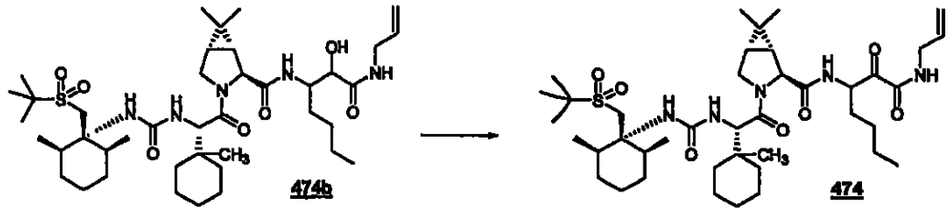
Step A



473k **474a** **474b**

A solution of acid **473k** (50 mg) in 2 mL of dry dichloromethane and 1 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 44 mg). The amine salt **474a** (1.3 eq, 25 mg) was added followed by N-methylmorpholine (4 eq, 0.036 mL, d 0.920). The reaction mixture was stirred overnight (temp 0 to 25 °C). All the volatiles were removed under vacuum and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (20 mL), aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **474b** (65 mg) was used without further purification.

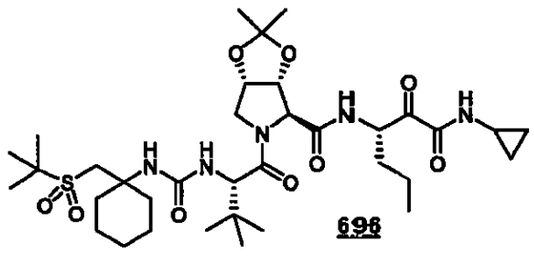
Step B



474b 474

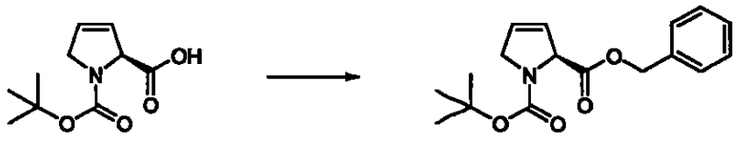
A solution of hydroxyamide **474b** (0.083 mmol) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 70 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (20 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 4:6) to afford the product **474** (40 mg; 62% for two steps) as white solid. HRMS calcd for $C_{41}H_{70}N_5O_7S$ $[M+H]^+$: 776.4995, found 776.5005.

Example 696:



696

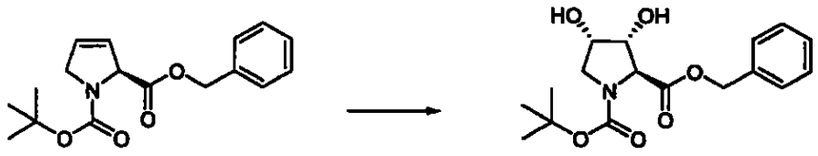
Step A



696a 696b

A solution of acid **696a** (3.0 g) in 140 mL of dry DMF was cooled to 0 °C and treated with cesium carbonate (1.1 eq, 5.04 g) followed by addition of benzyl bromide (1.2 eq, 2.00 mL, d 1.438). The reaction mixture was stirred for 24 h (temp: 0 to 25 °C). The mixture was diluted with ethyl acetate (350 mL) and washed with water (3 x 50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: hexanes to ethyl acetate/hexanes 25:75) to afford the product **696b** (3.82 g; 90 %) as a clear oil.

Step B



696b **696c**

A solution of N-methylmorpholine-N-oxide (1.3 eq, 1.9 g) in tert-butanol (20 mL), THF (7 mL) and water (3.5 mL) under argon atmosphere was treated with osmium tetroxide (0.1 eq, 318 mg). The resulting pale yellow solution was stirred for 5 min followed by dropwise addition of benzylester **696b** (3.8 g) in 30 mL of THF. The reaction mixture was stirred at room temperature for 20 h. The mixture was filtered thru a short path of silica gel and the solids were washed with ethyl acetate (500 mL). The organic layer was washed with brine (80 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 55:45) to afford the product **696c** (3.5 g; 83 %) as a paste.

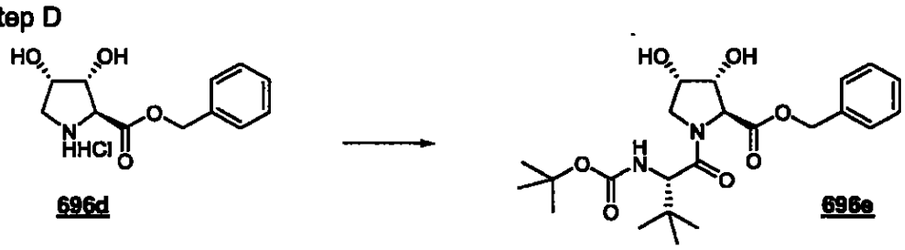
Step C



696c 696d

The N-Boc amine **696c** (3.5 g) was dissolved in 60 mL of 4M HCl in dioxane. The resulting solution was stirred at room temperature for about 2 h. All the volatiles were removed under reduced pressure to afford the product **696d** (2.8 g; 98 %) which was used without further purification.

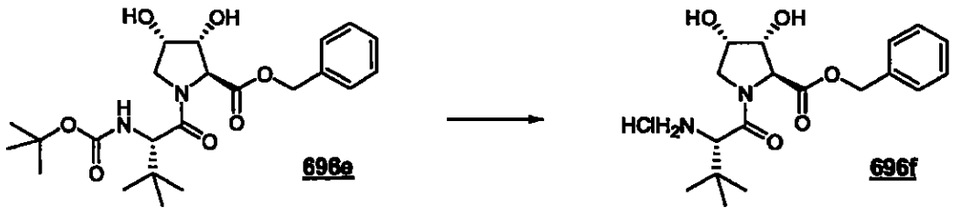
Step D



696d 696e

A solution of N-Boc-tert-butyl glycine (2.15 g) in 100 mL of dry dichloromethane and 20 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 4.96 g). The amine salt **696d** (1.1 eq, 2.8 g) was added in 30 mL of DMF followed by addition of N-methyl morpholine (4 eq, 4.08 mL, d 0.920). The reaction mixture was stirred at 0 °C overnight. All the volatiles were removed under vacuum and the residue was dissolved in 300 mL of ethyl acetate. The organic layer was washed with water (1 x 100 mL), aqueous 1M HCl (100 mL), aqueous saturated sodium bicarbonate solution (100 mL), and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate/hexanes; 6:4) to afford the product **696e** (3.29 g; 79 %) as a colorless oil.

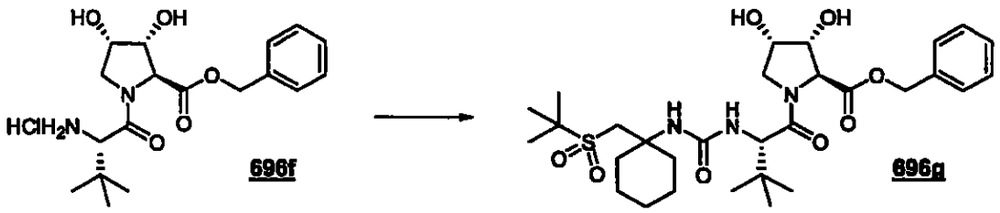
Step E



696e 696f

The N-Boc amine **696e** (1.24 g) was dissolved in 30 mL of 4M HCl in dioxane. The resulting solution was stirred at room temperature for about 2h. All the volatiles were removed under reduced pressure to afford the product **696f** (1.06 g; 98 %) as a white solid.

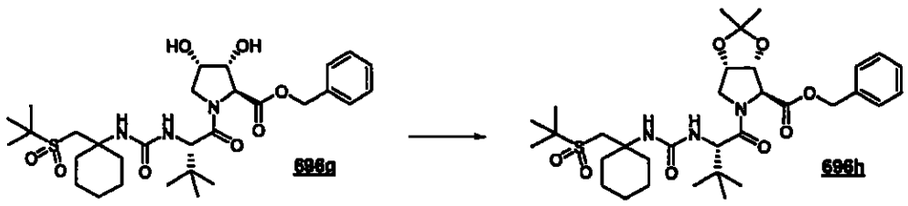
Step F



696f 696g

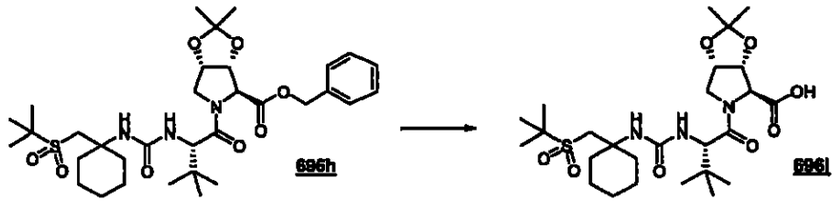
N-methyl morpholine (1.3 eq, 0.39 mL, d 0.920) was added to a heterogeneous mixture of amine-diol **696f** (1.06 g) in 50 mL of dichloromethane. After 5 min, a solution of isocyanate (1.05 eq, 9.63 mL of a 0.3M soln in toluene) was added. DMF (5 mL) was also added and the slurry was stirred at room temperature. The mixture gradually converted (over 4 h) to a clear homogeneous solution. The mixture was diluted with ethyl acetate (300 mL) and washed with aqueous 1M HCl. The aqueous layer was back extracted with 100 mL of ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 3:7 to 6:4) to give the product **696g** (1.6 g; 98 %) as a colorless oil.

Step G



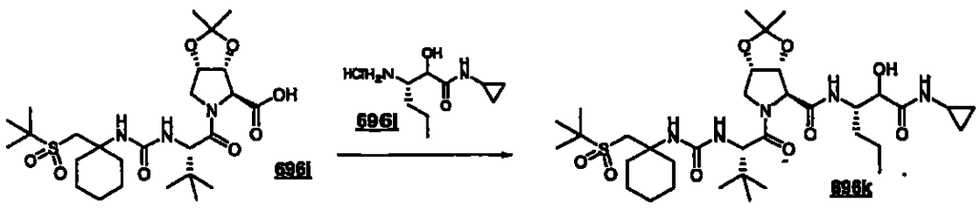
A solution of diol **696g** (1.5 g) was treated with 2,2-dimethoxypropane (2 eq, 0.6 mL, d 0.847) and a catalytic amount of pyridinium p-toluenesulfonic acid (0.1 eq, 62 mg). The mixture was stirred overnight at 50 °C. The mixture was diluted with 200 mL of ethyl acetate and washed with 50 mL of aqueous saturated sodium bicarbonate soln. The aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 5:95 to 35:65) to afford the product **696h** (1.33 g; 83 %) as a white solid.

Step H



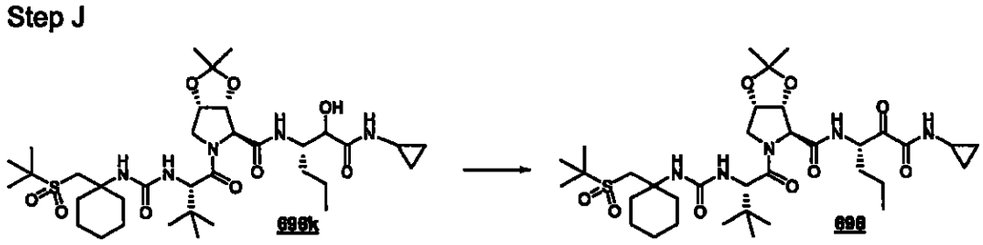
The benzyl ester **696h** (1.33 g) was dissolved in 70 mL of ethyl acetate and treated with 20% palladium dihydroxide on carbon (0.1 mol%; 144 mg). The heterogeneous mixture was hydrogenated at 50 psi for 3 h. The mixture was diluted with 200 mL of dichloromethane and filtered thru a short path of celite. The filtrate was concentrated under reduced pressure to afford the product **696l** (1.14 g; 98 %) as a white solid.

Step I



A solution of acid **696i** (100 mg) in 3 mL of dry dichloromethane and 3 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 93 mg). The amine salt **696j** (1.2 eq, 47 mg) was added followed by N-methylmorpholine (4 eq, 0.08 mL, d 0.920). The reaction mixture was stirred overnight (temp 0 to 25 °C). All the volatiles were removed under vacuum and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (10 mL), aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **696k** was used without further purification.

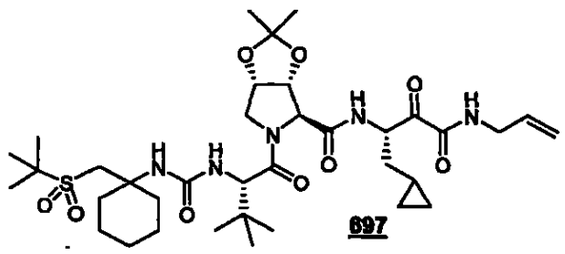
Step J



A solution of hydroxyamide **696k** (0.178 mmol) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 150 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (10 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers

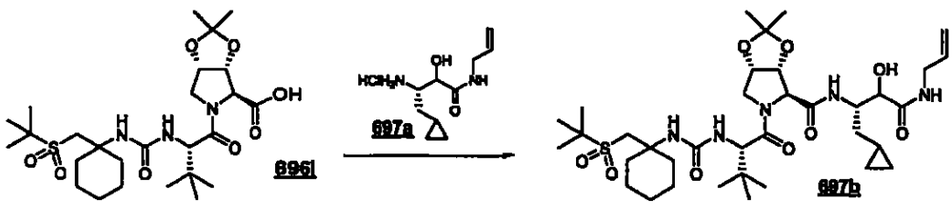
were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 15:85 to 1:1) to afford the product **696** (120 mg; 93 %) as white solid. HRMS calcd for $C_{35}H_{60}N_5O_9S$ $[M+H]^+$: 726.4112, found 726.4128.

Example 697:



697

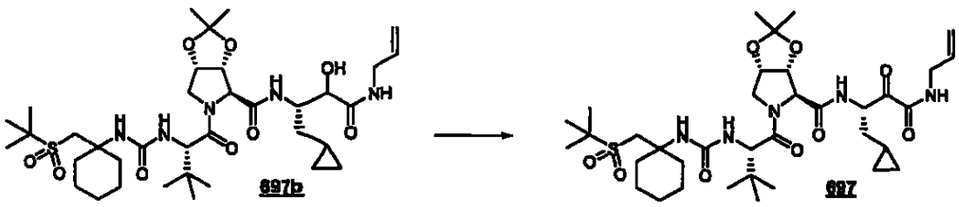
Step A



696i 697a 697b

A solution of acid **696i** (100 mg) in 3 mL of dry dichloromethane and 3 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 93 mg). The amine salt **697a** (1.2 eq, 50 mg) was added followed by N-methylmorpholine (4 eq, 0.08 mL, d 0.920). The reaction mixture was stirred overnight (temp 0 to 25 °C). All the volatiles were removed under vacuum and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (10 mL), aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **697b** was used without further purification.

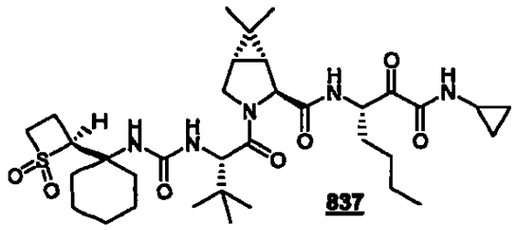
Step B



697b 697

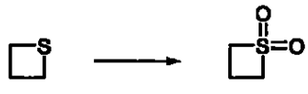
A solution of hydroxyamide **697b** (0.178 mmol) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 150 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (10 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 15:85 to 1:1) to afford the product **697** (120 mg; 91 %) as white solid. HRMS calcd for $C_{36}H_{60}N_5O_8S$ $[M+H]^+$: 738.4112, found 738.4092.

Example 837:



837

Step A

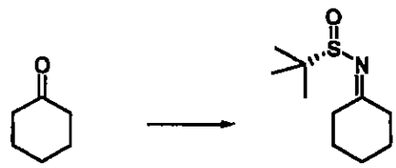


837a 837b

A solution of thietane (10 g, 9.727 mL, d 1.028, Aldrich) in 200 mL of dichloromethane was treated with a slurry of m-chloroperoxybenzoic acid (2.3

eq, 76 g of 70% m-CPBA) in dichloromethane (400 mL) at 0 °C. The cooling bath was removed and the mixture was stirred for 3 h. The solids were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (400 mL) and the solution was extensively washed with aqueous saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography to afford the product **837b** as a white solid.

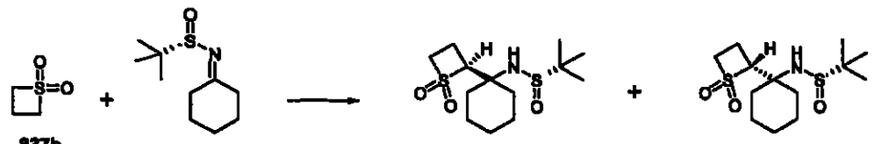
Step B



837c **837d**

Titanium tetraethoxide (2 eq, 24.2 mL, d 1.088) was added to a solution of cyclohexanone (1.2 eq, 7.18 mL, d 0.947) in 150 mL of dry THF under nitrogen atmosphere. After 5 min, t-butanesulfinamide (7.0 g, Aldrich) in 50 mL of THF was added dropwise. The mixture was heated to 60 °C overnight. The reaction mixture was poured into an equal volume of aqueous saturated sodium bicarbonate solution with rapid stirring and immediately filtered through filter paper whatman #1. The filter cake was washed with ethyl acetate (100 mL). The layers in the filtrate were separated and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were washed with aqueous saturated sodium bicarbonate solution (100 mL), dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel (ethyl acetate/hexanes; 3:7) to afford the product **837d** (7.5 g; 55 %) as a colorless oil. The product is kept under inert atmosphere at -20 °C.

Step C



837b 837d 837e 837f

n-Butyl lithium (1.1 eq, 7.6 mL of a 1.6M soln in cyclohexane) was added dropwise to a cooled (-78 °C) solution of sulfone **837b** (1.15 eq, 1.35 g) in 100 mL of dry THF under anhydrous atmosphere. The mixture was stirred for 1 h at that temperature and then transferred via cannula to a pre-cooled (-78 °C) solution of sulfinylimine **837d** (2.23 g) in 100 mL of dry THF. The resulting mixture was stirred at -78 °C and monitored by TLC (acetone/hexanes; 3:7). All the sulfinylimine **837d** starting material was consumed in 2 h. The reaction was quenched by addition of aqueous saturated ammonium chloride solution (5 mL). The mixture was allowed to reach room temperature and partitioned between ethyl acetate (200 mL) and aqueous saturated sodium bicarbonate (80 mL). The aqueous layer was back extracted with ethyl acetate (2 x 60 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: dichloromethane to acetone/dichloromethane; 3:7) to afford the corresponding diastereomeric products **837e** and **837f** as a 1.4:1 mixture (1.64 g; 50 % comb.yield).

Step D



837e 837g

The sulfinamide **837e** (910 mg) was dissolved in 50 mL of methanol and treated with 20 mL of 4M HCl solution in dioxane. The mixture was stirred for

about 1 h until all the starting material had been consumed as determined by TLC (acetone/hexanes; 1:9). The mixture was concentrated to dryness. Dichloromethane (10 mL) was added to make a homogeneous solution then ether was added (80 mL) and a white precipitate was formed. The amine hydrochloride product **837g** (700 mg; 98 %) was recovered by filtration as a white solid.

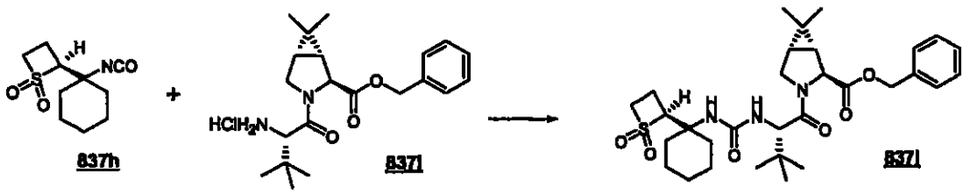
Step E



837g **837h**

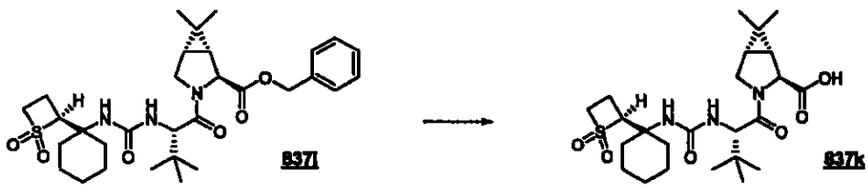
A solution of amine hydrochloride **837g** (2.960 mmol) in 40 mL of dichloromethane was treated with 20 mL of aqueous saturated sodium bicarbonate solution and stirred vigorously for 10 min at 0 °C. Stirring was stopped and layers were allowed to separate. Phosgene (10 mL of 20% soln in toluene) was added through a needle to the organic layer (lower layer) in one portion. The mixture was vigorously stirred immediately after addition for 10 min at 0 °C and further stirred at room temp for 3 h. The mixture was diluted with 100 mL of dichloromethane and layers were separated. The organic layer was washed with 50 mL of cold aqueous saturated sodium bicarbonate solution and dried over magnesium sulfate. The organic layer was filtered and diluted with 50 mL of toluene. The resulting solution was concentrated and kept as a 0.118M solution in toluene.

Step F



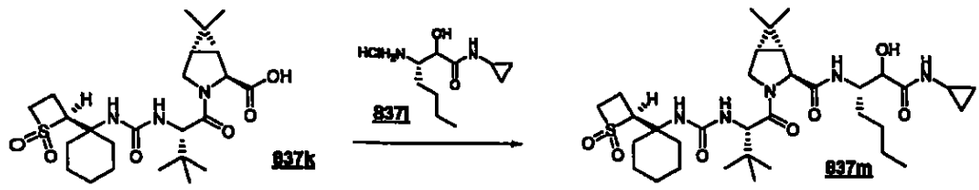
A solution of amine hydrochloride **837i** (1.5 mmol) in 30 mL of dichloromethane was treated with 5 mL of aqueous saturated sodium bicarbonate. The mixture was stirred for 10 min followed by addition of the isocyanate **837h** (1.03 eq, 13.1 mL of a 0.118M solution in toluene. The reaction mixture was stirred overnight. The reaction mixture was diluted with dichloromethane (200 mL) and washed with aqueous saturated sodium bicarbonate solution (40 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 1:1) to afford the product **837j** (740 mg; 84 %) as a white solid.

Step G



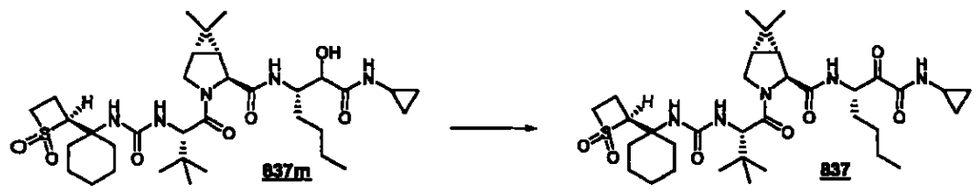
The benzyl ester **837j** (740 mg) was dissolved in 20 mL of methanol and treated with 20% palladium dihydroxide on carbon (0.1 mol%; 90 mg). The heterogeneous mixture was hydrogenated at 50 psi for 2 h. TLC (acetone/hexanes; 35:65) showed that all the starting material had been consumed. The mixture was diluted with 100 mL of dichloromethane and filtered thru a short path of celite. The filtrate was concentrated under reduced pressure to afford the product **837k** (620 mg; 98 %) as a white solid.

Step H



A solution of acid **837k** (69 mg) in 2 mL of dry dichloromethane and 2 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 74 mg). The amine salt **837l** (1.2 eq, 39 mg) was added followed by N-methylmorpholine (4 eq, 0.06 mL, d 0.920). The reaction mixture was stirred overnight (temp 0 to 25 °C). All the volatiles were removed under vacuum and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (10 mL), aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **837m** was used without further purification.

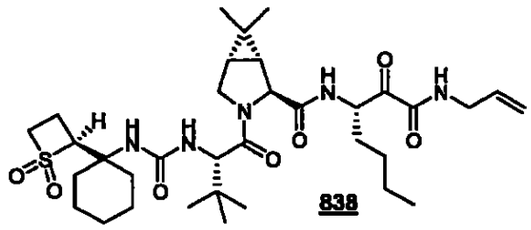
Step I



A solution of hydroxyamide **837m** (0.138 mmol) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 117 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (10 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers

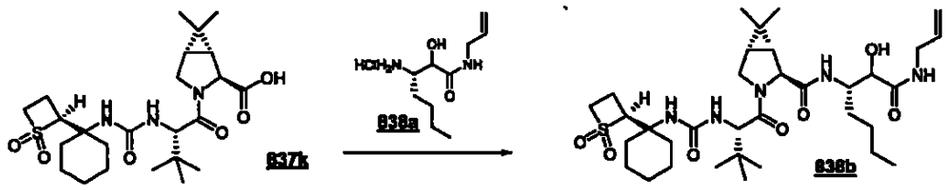
were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 1:1) to afford the product **837** (66 mg; 70 %) as white solid. HRMS calcd for $C_{34}H_{58}N_5O_7S$ $[M+H]^+$: 678.3900, found 678.3883.

Example 838:



838

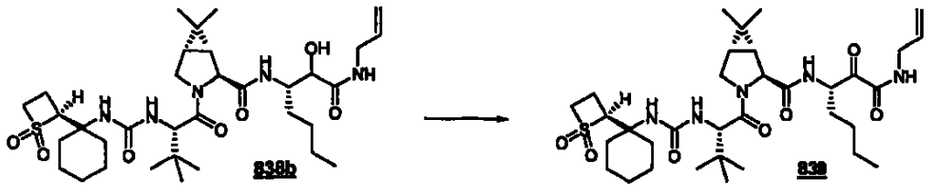
Step A



837k **838a** **838b**

A solution of acid **837k** (69 mg) in 2 mL of dry dichloromethane and 2 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 74 mg). The amine salt **838a** (1.2 eq, 39 mg) was added followed by N-methylmorpholine (4 eq, 0.06 mL, d 0.920). The reaction mixture was stirred overnight (temp 0 to 25 °C). All the volatiles were removed under vacuum and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (10 mL), aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **838b** was used without further purification.

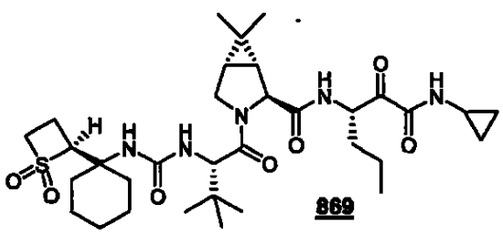
Step B



838b 838

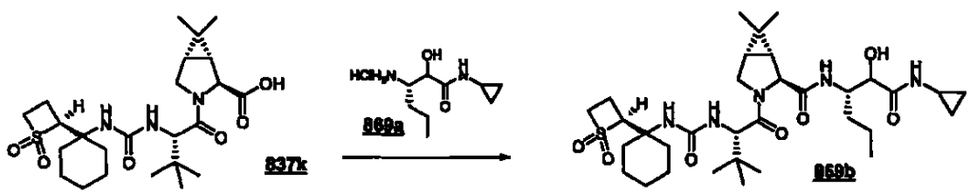
A solution of hydroxyamide **838b** (0.138 mmol) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 117 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (10 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 4:6) to afford the product **838** (71 mg; 76 %) as white solid. HRMS calcd for $C_{34}H_{58}N_5O_7S$ $[M+H]^+$: 678.3900, found 678.3883.

Example 869:



869

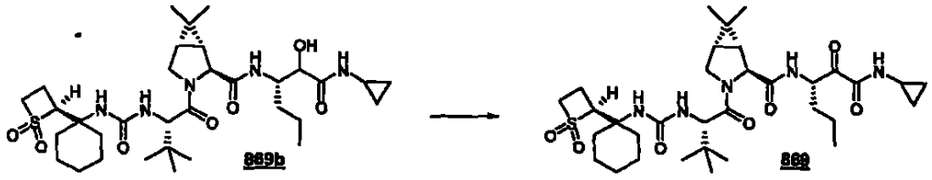
Step A



837k 869a 869b

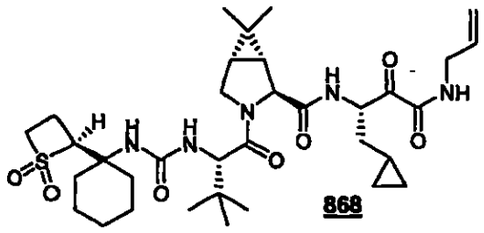
A solution of acid **837k** (69 mg) in 2 mL of dry dichloromethane and 2 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 74 mg). The amine salt **869a** (1.2 eq, 37 mg) was added followed by N-methylmorpholine (4 eq, 0.06 mL, d 0.920). The reaction mixture was stirred overnight (temp 0 to 25 °C). All the volatiles were removed under vacuum and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (10 mL), aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **869b** was used without further purification.

Step B



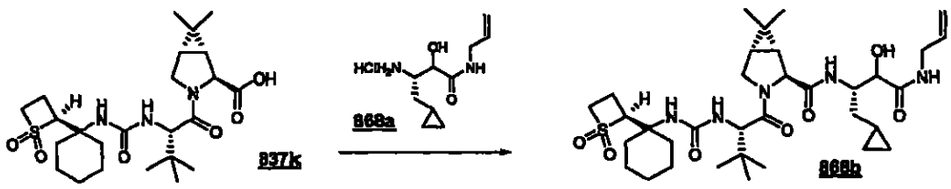
A solution of hydroxyamide **869b** (0.138 mmol) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 117 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (10 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 18:85 to 45:55) to afford the product **869** (69 mg; 75 %) as white solid.

Preparative Example 868:



868

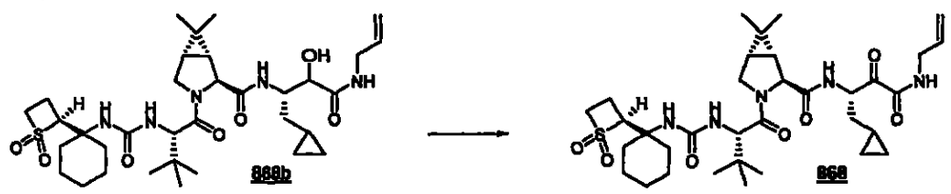
Step A



837k 868a 868b

A solution of acid **837k** (69 mg) in 2 mL of dry dichloromethane and 2 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 74 mg). The amine salt **868a** (1.2 eq, 39 mg) was added followed by N-methylmorpholine (4 eq, 0.06 mL, d 0.920). The reaction mixture was stirred overnight (temp 0 to 25 °C). All the volatiles were removed under vacuum and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (10 mL), aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **868b** was used without further purification.

Step B

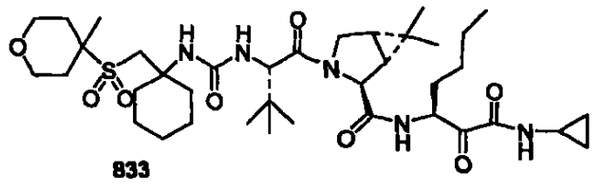


868b 868

A solution of hydroxyamide **868b** (0.138 mmol) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 117 mg).

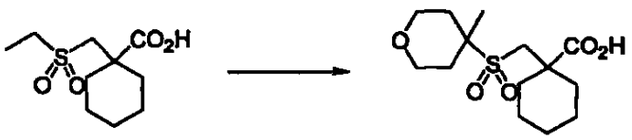
The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (10 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 4:6) to afford the product **868** (73 mg; 78 %) as white solid.

Example **833**:



833

Step 1

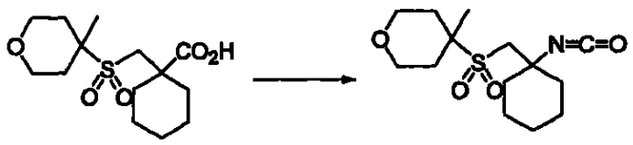


833a **833b**

To a solution of ethylsulfone acid **833a** (2.06 g, 8.79 mmol) in anhydrous THF at -78°C under N_2 was added LiHMDS solution (19.3 mL, 1.0 Min THF). The mixture was stirred at -78°C for 30 min before it was allowed to warmed to 0°C along with a cold acetone bath. It was then re-cooled to -78°C and to it was added 2-bromoethyl ether (1.8 mL, 13.2 mmol). After stirred at -78°C for 30 min, the mixture was warmed to rt and stirred for 2 h. It was again re-cooled to -78°C and to it was added LiHMDS solution (10.6 mL, 10.6 mmol). After stirred at -78°C for 30 min, the mixture was warmed to rt and stirred for 3 h before it was quenched with 1 N aqueous HCl solution until the pH is about 1-2. The solution was extracted with CH_2Cl_2 (2x450 mL).

Combined organic solution was dried ($MgSO_4$), filtered and concentrated. The crude product was dissolved in 1 N NaOH solution (300 mL) and extracted with EtOAc (100 mL). After layers were separated, the organic solution was washed with 1 N NaOH (2x150 mL). The combined aqueous solution was acidified to pH~1 using 6 N HCl solution. It was extracted with EtOAc (3 x 300 mL). The organic solutions were combined, dried ($MgSO_4$), filtered and concentrated to give 2.3 g product (**833b**; 7.56 mmol, 89%).

Step 2

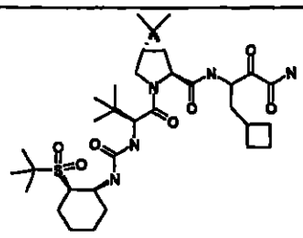
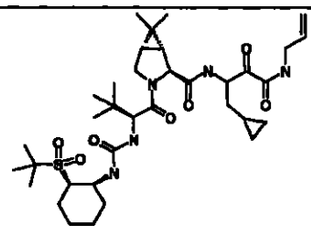
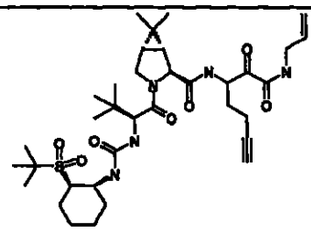


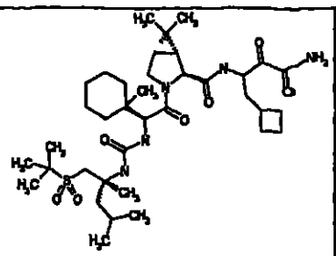
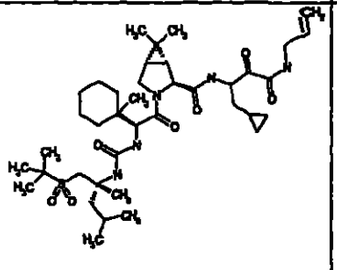
833b **833c**

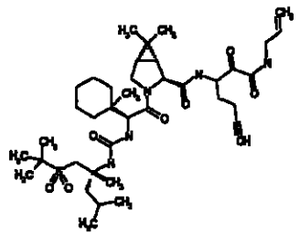
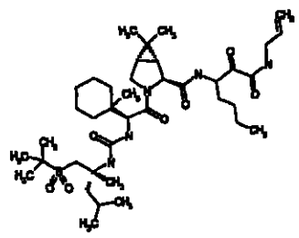
To the acid **833b** (2.30 g, 7.56 mmol) in toluene at rt under N_2 was added triethylamine (1.15 mL, 8.32 mmol) and diphenylphosphoryl azide (1.79 mL, 8.32 mmol). The resulting mixture was stirred at rt for 30 min and heated to reflux for 5.5 h. After it was cooled to rt, more toluene was added to make up a 0.19 M solution of the isocyanate **833c**, which was used without further purification.

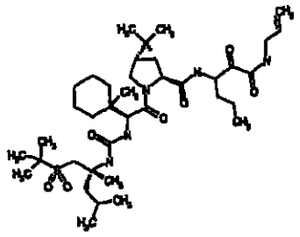
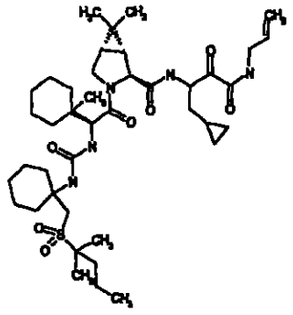
Using the aforementioned procedures **833c** was transformed into **833**.

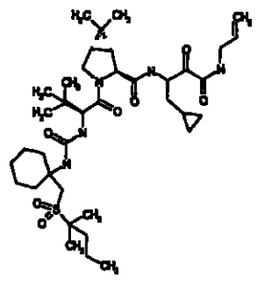
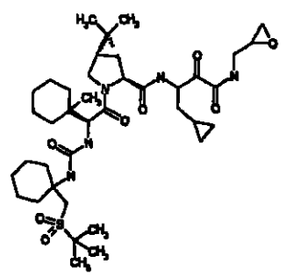
Table 3A

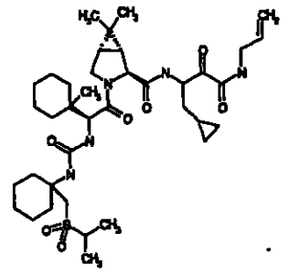
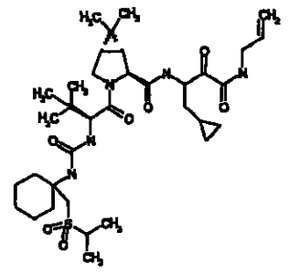
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398		691.925	692.4	C
399		689.909	690.3	B

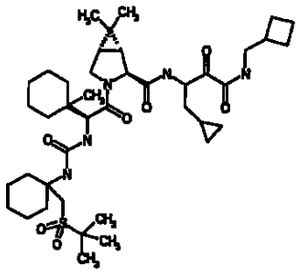
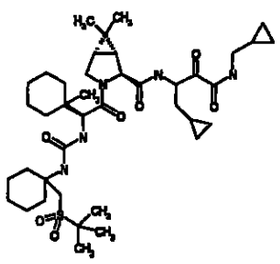
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401		748.0462	748.4	A

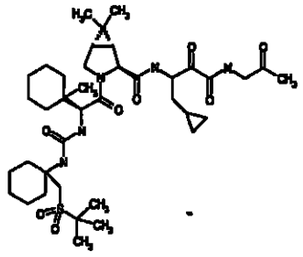
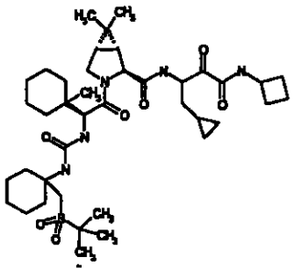
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403		750.0621	750.4	A

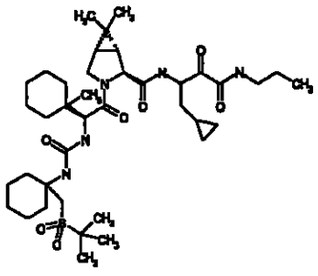
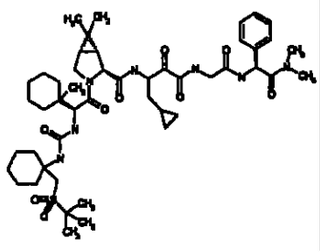
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405		774 0844		A

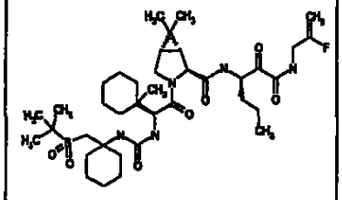
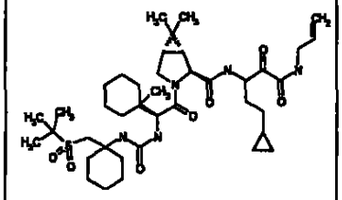
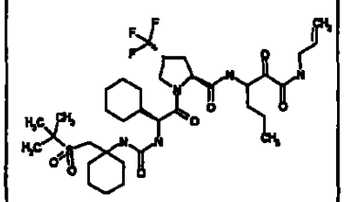
406		734.0191		A
407		762.0297		A

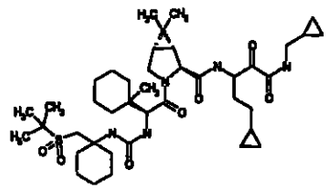
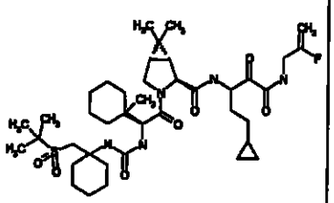
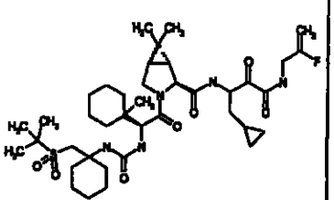
408		732.0032		A
409		691.9378		A

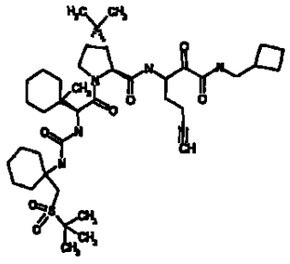
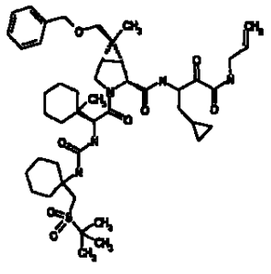
410		774.0844		A
411		760.0574		A

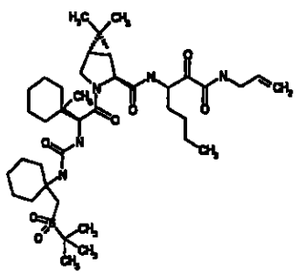
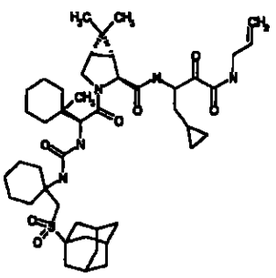
412		762.0297		A
413		760.0574		A

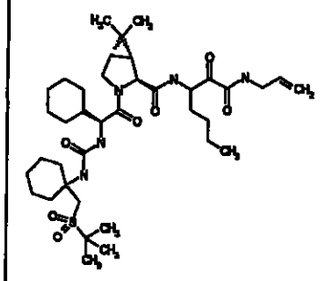
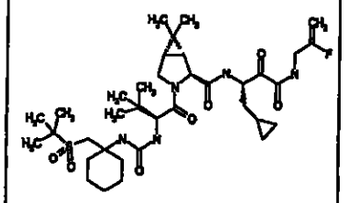
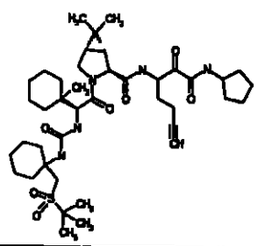
414		748.0462		A
415		924.2225		B

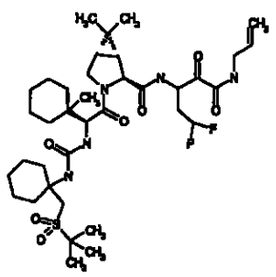
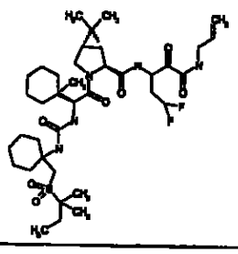
416		752.0095		A
417		760.0574		A
418		747.9251		A

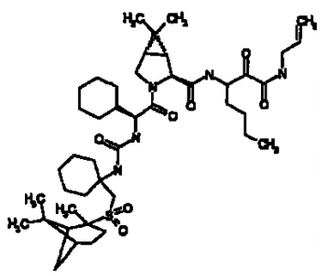
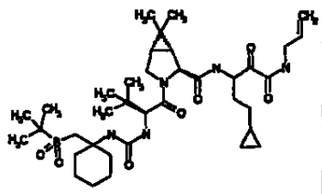
419		774.0844		A
420		778.0478		A
421		764.0207		A

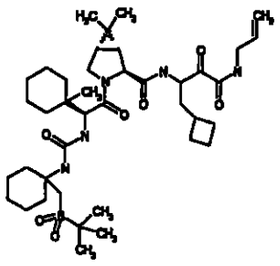
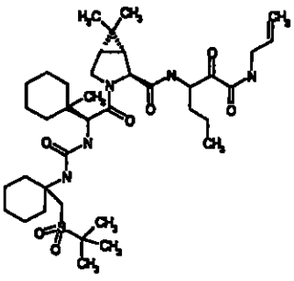
422		772.0685		A
423		852.1555	852.5	A

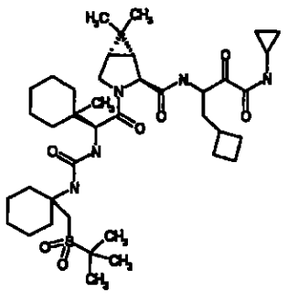
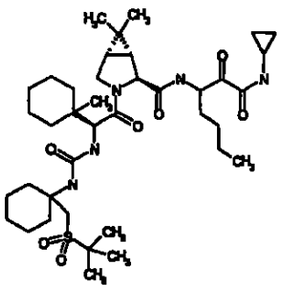
424		748 0462		A
425		824.145		A

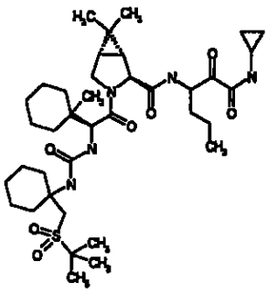
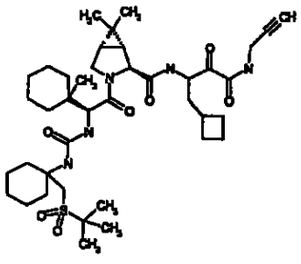
426		734.0191		A
427		723 9554		A
428		772.0685		A

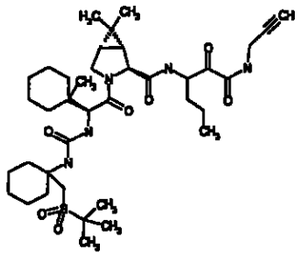
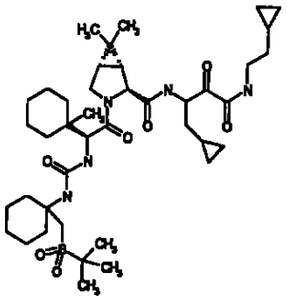
429		755.9729		A
430		770		A

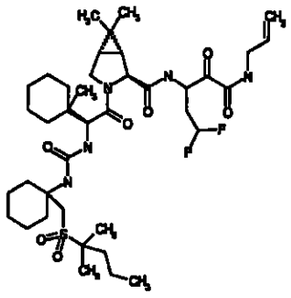
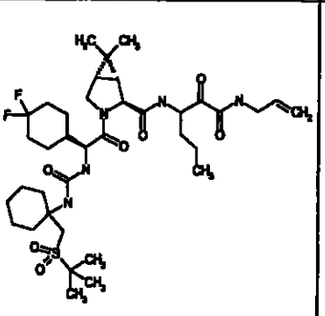
431		814.1498		A
432		719.992		A

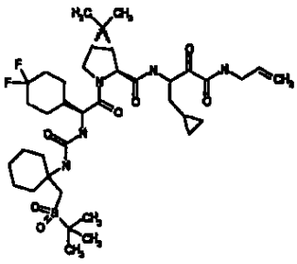
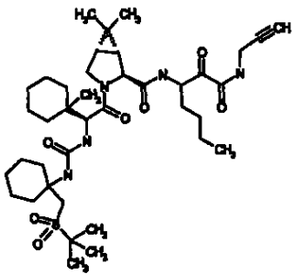
433		760.0574		A
434		734.0191		A

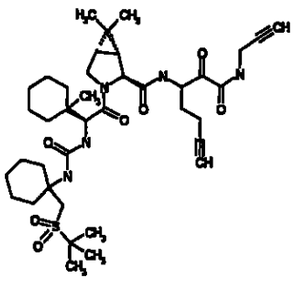
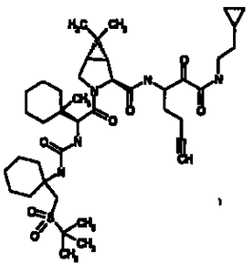
435		760.0574		A
436		748.0462		A

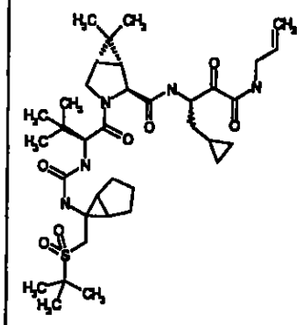
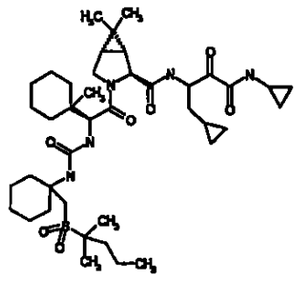
437		734.0191		A
438		758.0414		A

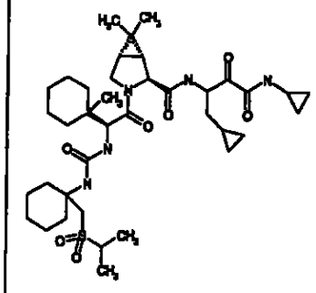
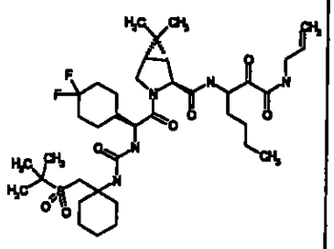
439		732.0032		A
440		774 0844	774.2	A

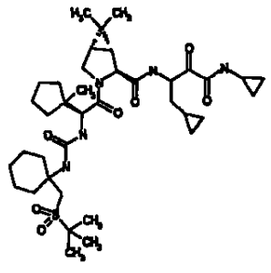
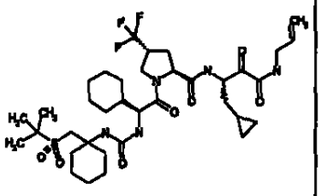
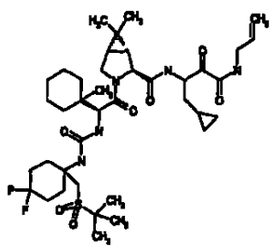
441		784.0271	784.2	A
442		755.9729	756.2	A

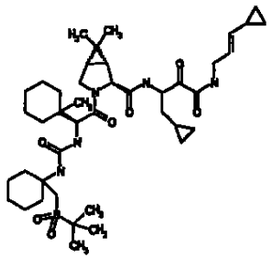
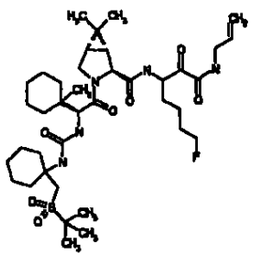
443		767.984	768.4	A
444		746.0303		A

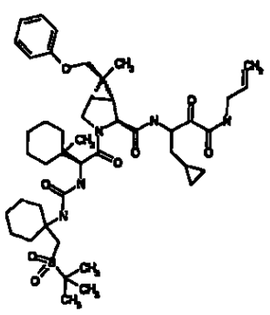
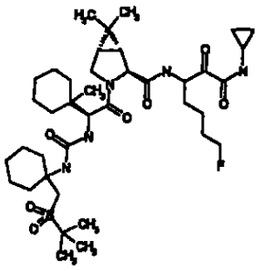
445		741.9984		A
446		772.0685		A

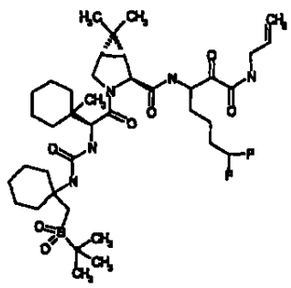
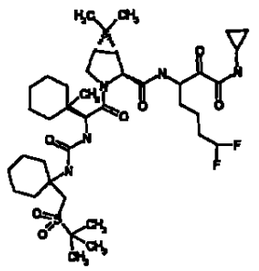
447		703.949	704.4	A
448		774.0844		A

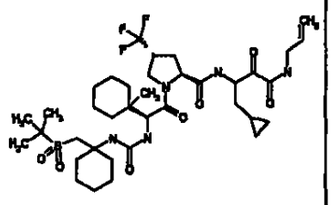
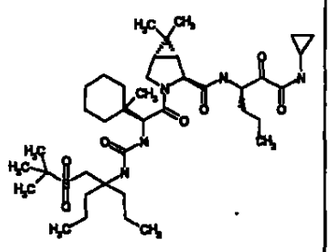
449		732.0032		A
450		770	770.2	A

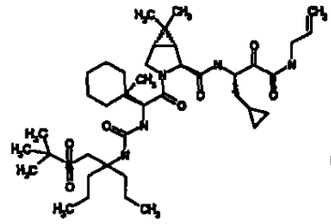
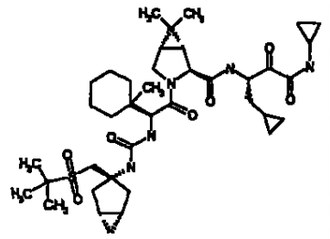
451		732.0032	732 2	A
452		759.9362		A
453		782.0111		A

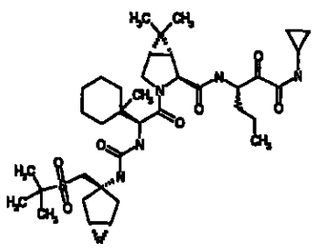
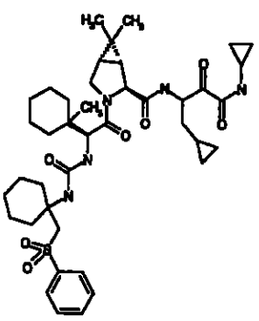
454		786 0956		A
455		766.0366		A

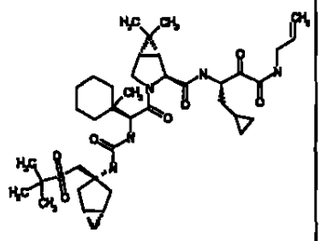
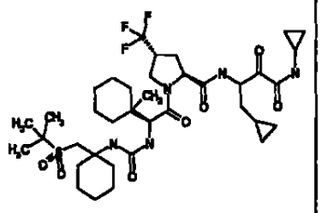
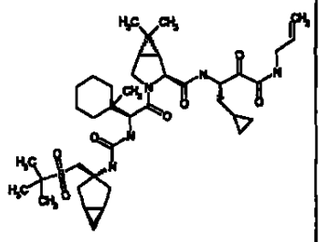
456		838.1284		B
457		766.0366	766.4	A

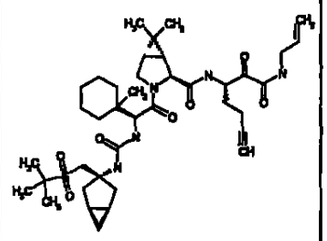
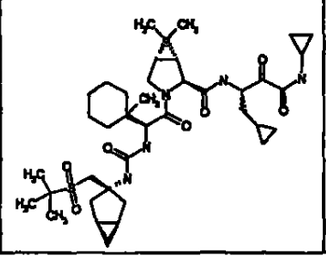
458		784.0271	784.4	A
459		784.0271	784.2	A

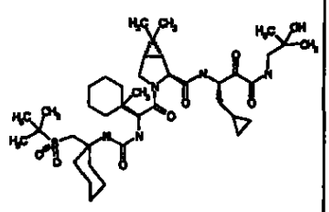
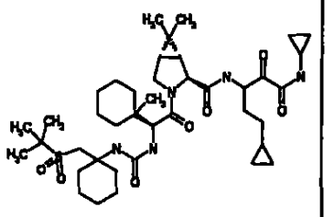
460		773.9633		A
461		750.0621	750.9	B

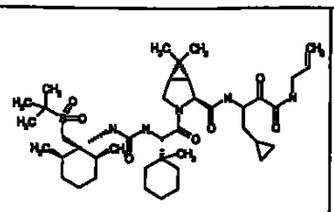
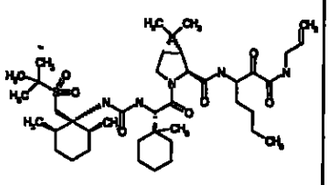
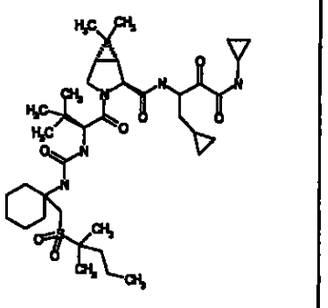
462		762.0733	762.41	C
463		744.0143	744.2	B

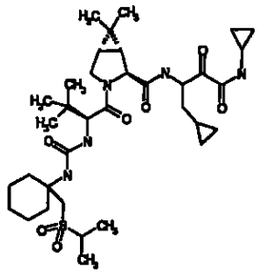
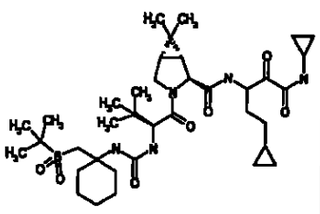
464		732.0032	732.4	A
465		766.0207		B

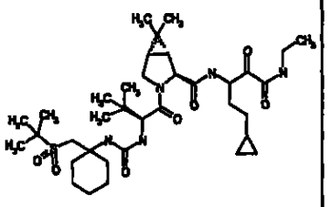
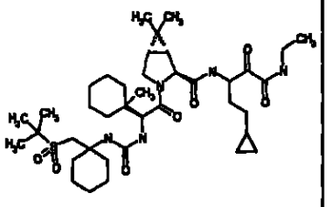
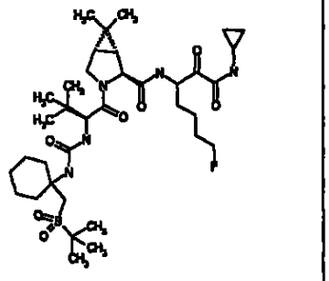
466		744.0143	744.4	A
467		773.9633		B
468		744.0143	744.70	B

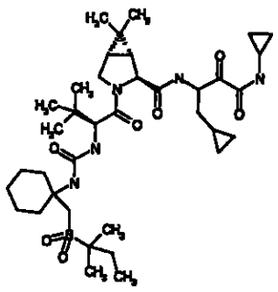
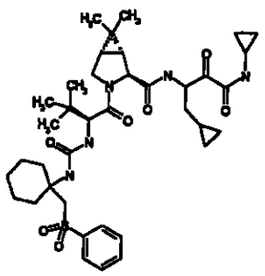
469		741.9984	742.40	A
470		744.0143	744.38	B

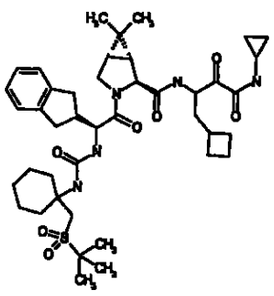
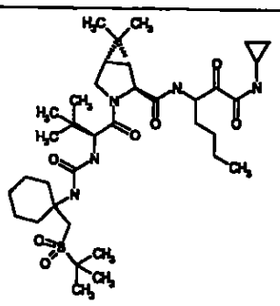
471		778.0727	778.7	B
472		760.0574		A

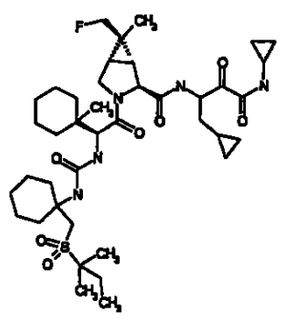
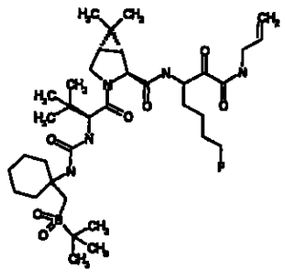
473		774.0844	774.4	A
474		776.1004	776 5	A
475		734.0191		A

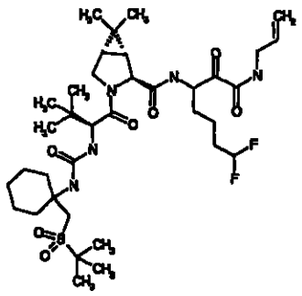
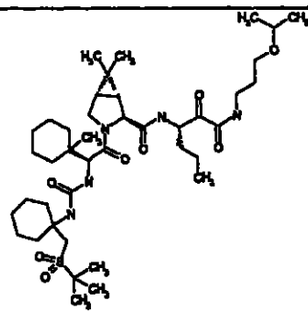
476		691.9378		B
477		719.992		A

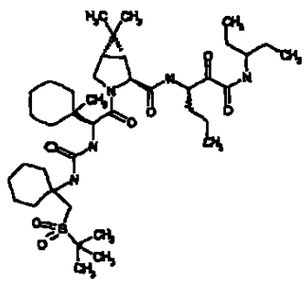
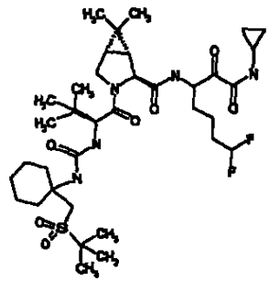
478		707.9809		A
479		748.0462		A
480		725.9713	726.4	A

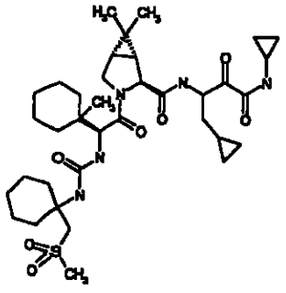
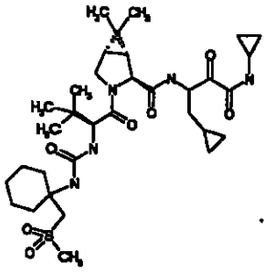
481		719.992		A
482		725 9554		B

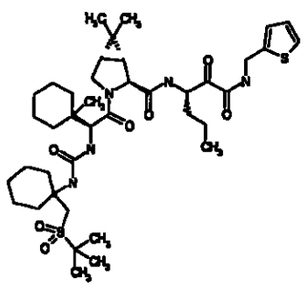
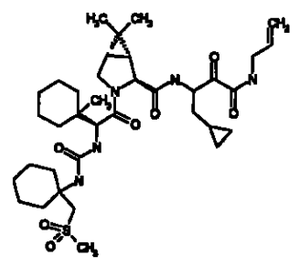
483		780.0478		B
484		707.9809		A

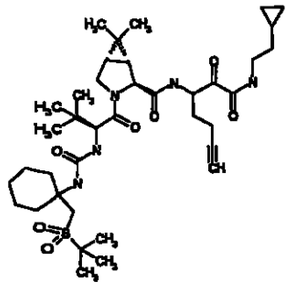
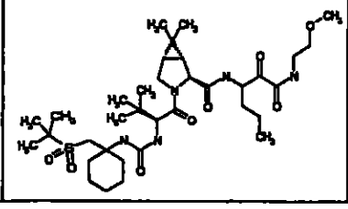
485		778.0478		B
486		725.9713		A

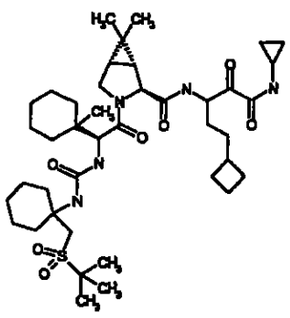
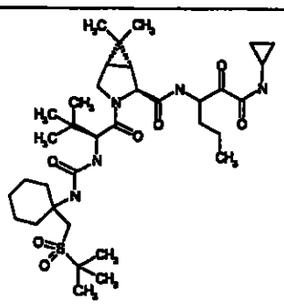
487		743.9617		A
488		794.1157	794.2	B

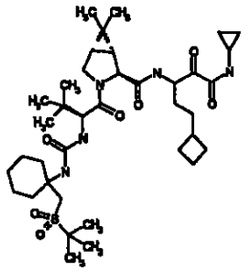
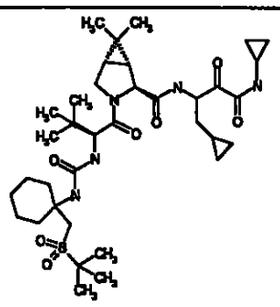
489		764.0892	764.1	B
490		743.9617	744.4	A

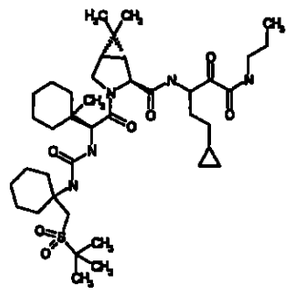
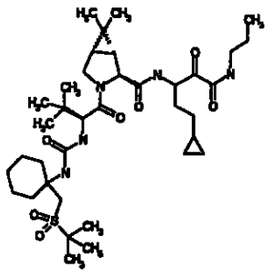
491		703.949		A
492		663.8837		A

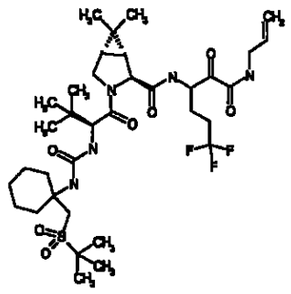
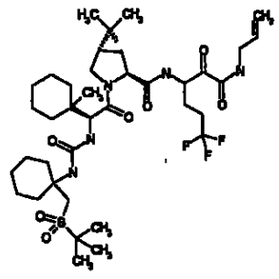
493		790.1054	791.4	A
494		703.949		A

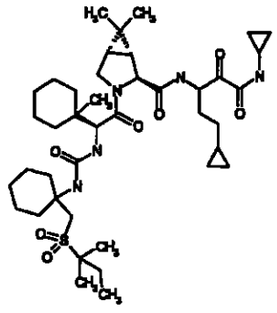
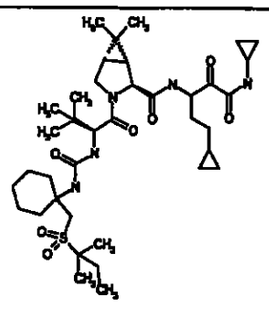
495		732.0032		A
496		712		A

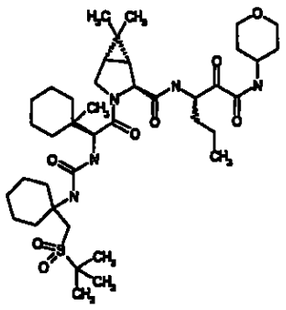
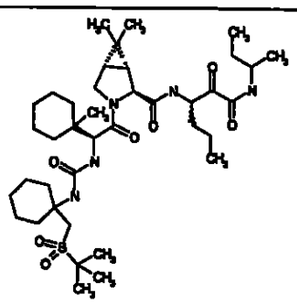
497		774	774.2	A
498		693.9538		A

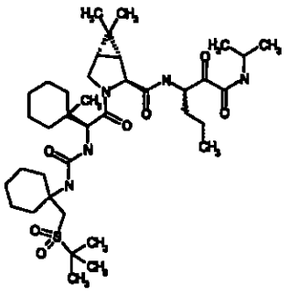
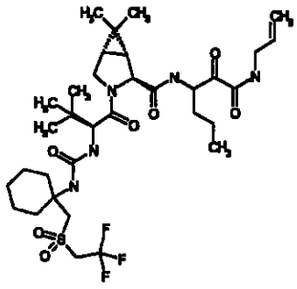
499		734	735.2	A
500		706		A

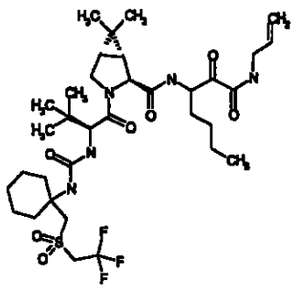
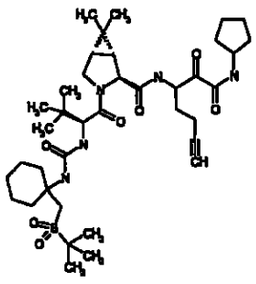
501		762		A
502		722		A

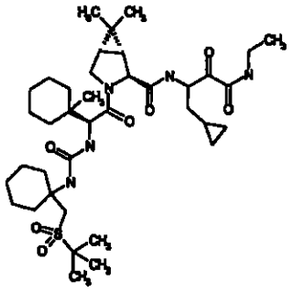
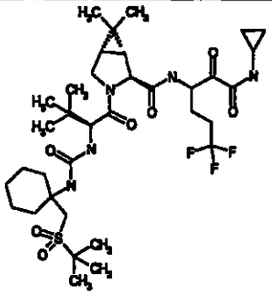
503		748		A
504		788		A

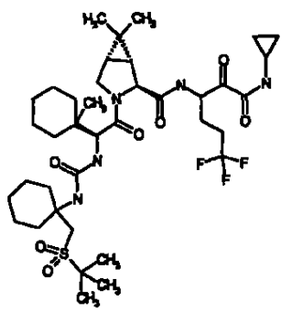
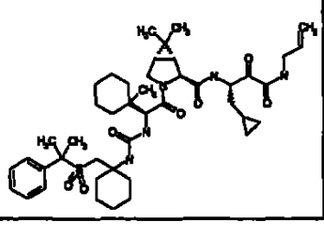
505		774		A
506		734		A

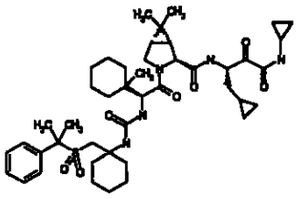
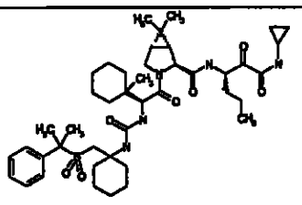
507		778	778.2	C
508		750	750.5	B

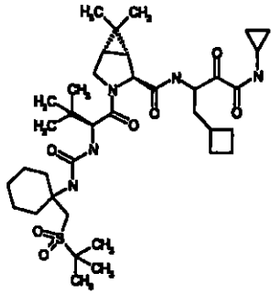
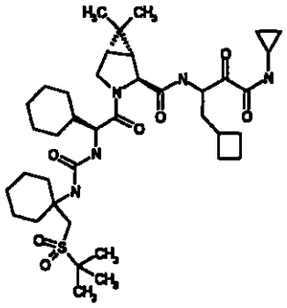
509		736	736.2	A
510		720		A

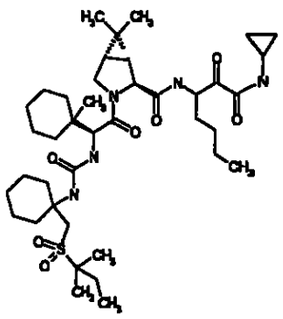
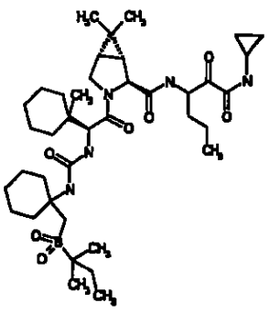
511		734		A
512		732	733.4	A

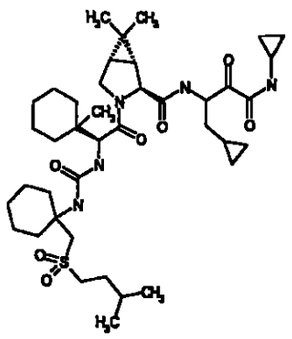
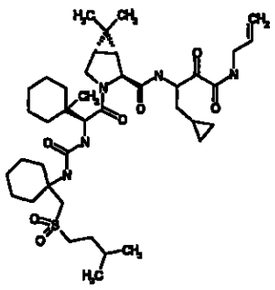
513		734	734.4	A
514		748		A

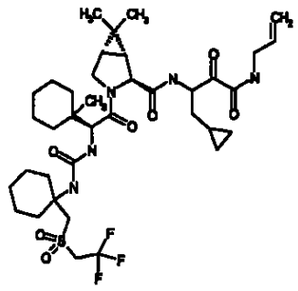
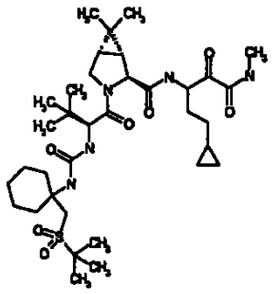
515		788		A
516		808.102	809.1	A

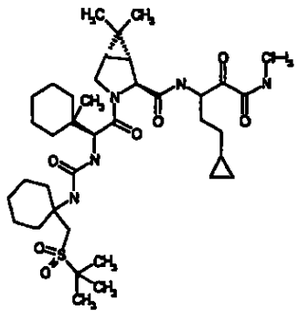
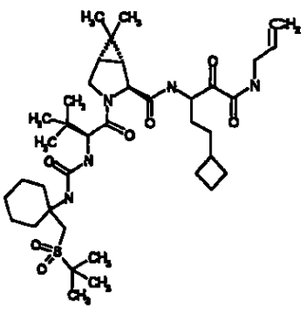
517		808.102	809.1	B
518		796.0908	797.1	A

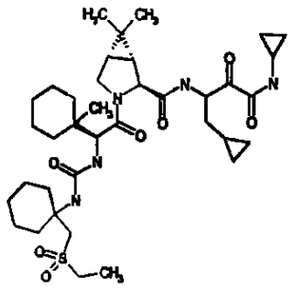
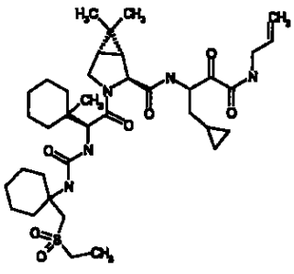
519		719.992		A
520		746.0303		B

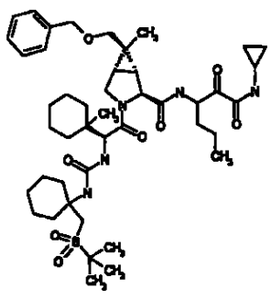
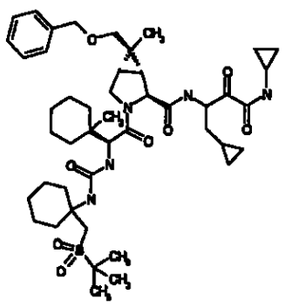
521		762.0733		A
522		748.0462		A

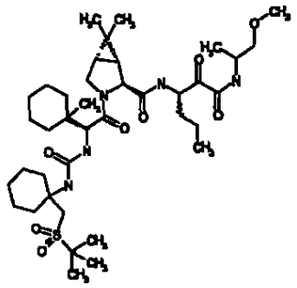
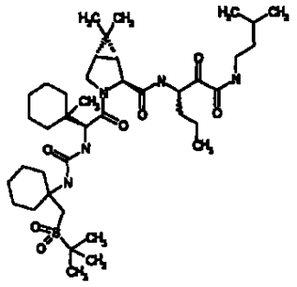
523		760.0574		A
524		760.0574		A

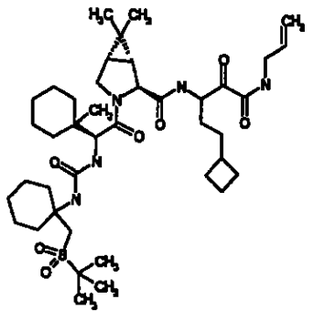
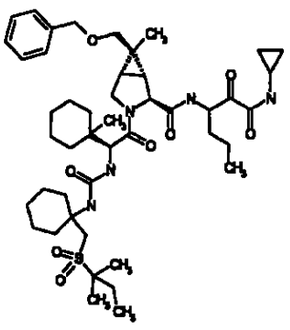
525		771.9474		A
526		693.9538		A

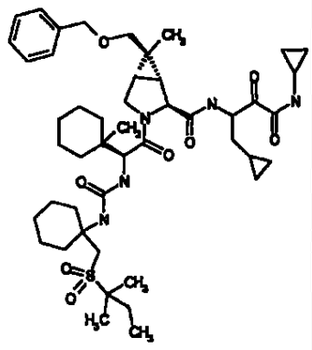
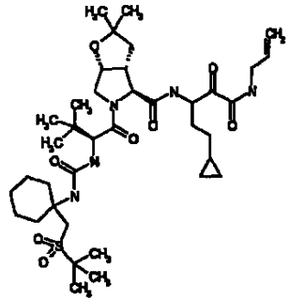
527		734.0191		A
528		734.0191		A

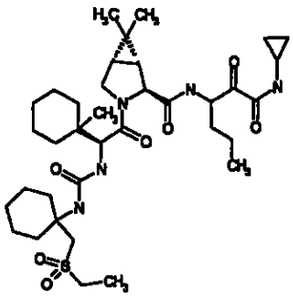
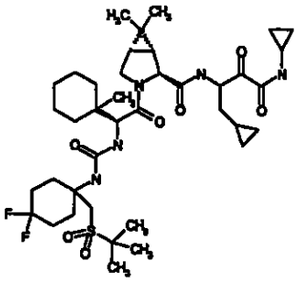
529		717.9761		A
530		717.9761		A

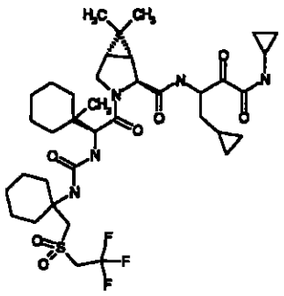
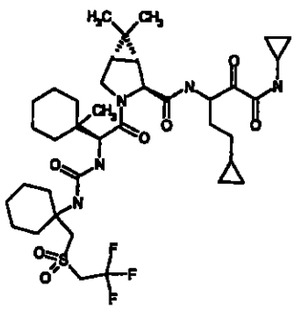
531		840.1444		A
532		852.1555		A

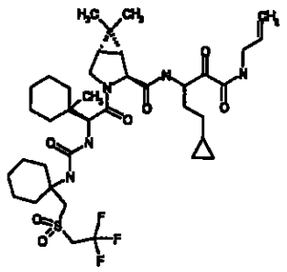
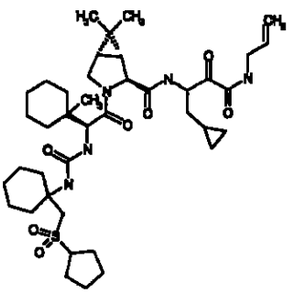
533		766.0615	766.4	B
534		764.0892	764.4	C

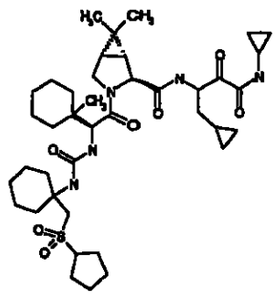
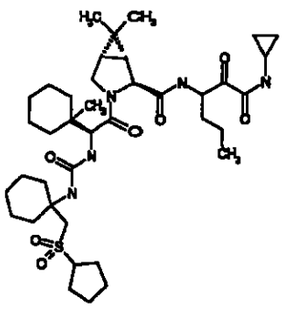
535		774.0844		A
536		854.1715		A

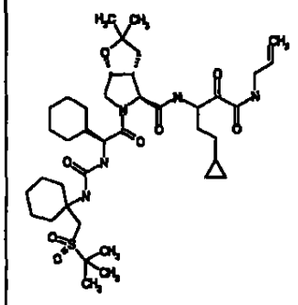
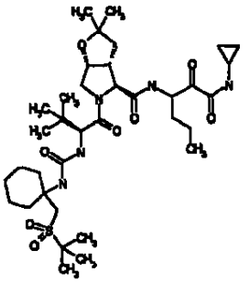
537		866.1826		A
538		750.0185	750.4	A

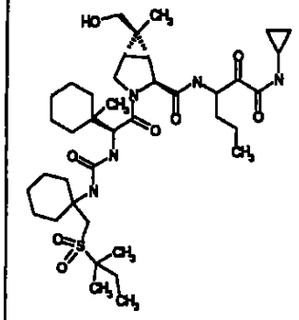
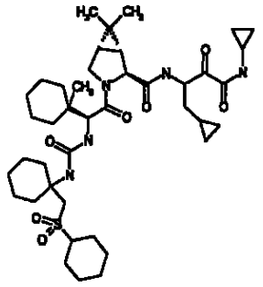
539		705.9649		A
540		782.0111		A

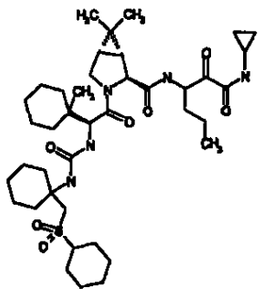
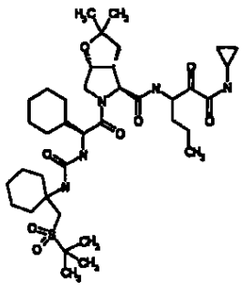
541		771.9474		A
542		785.9745		A

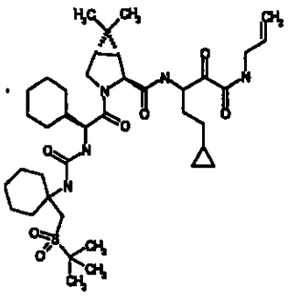
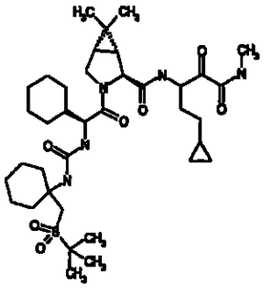
543		785.9745		A
544		758.0414		A

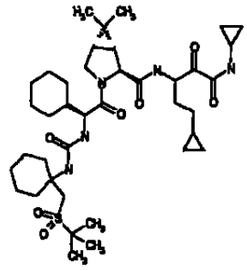
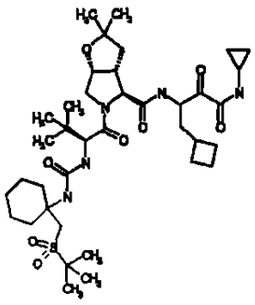
545		758.0414		A
546		746.0303		A

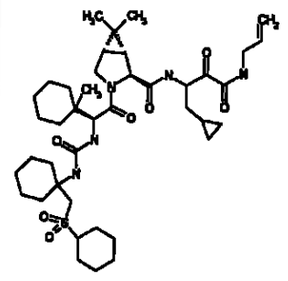
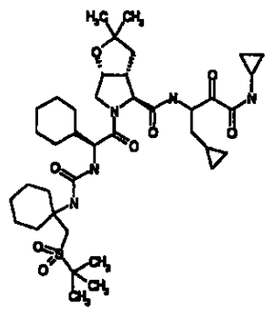
547		776.0568	776 4	A
548		723 9803	724.4	B

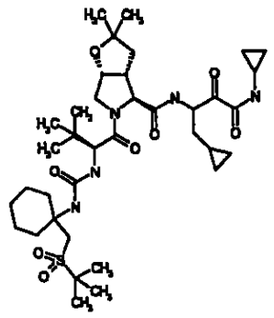
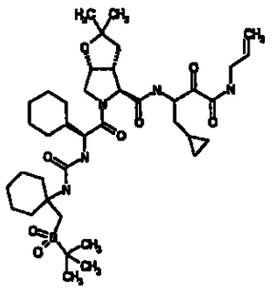
549		764.0456		A
550		772.0685		A

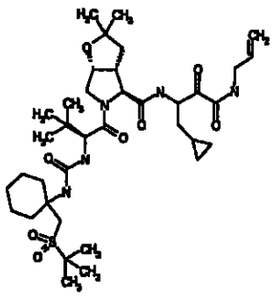
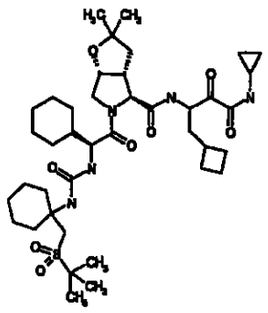
551		760.0574		A
552		750.0185	750.1	B

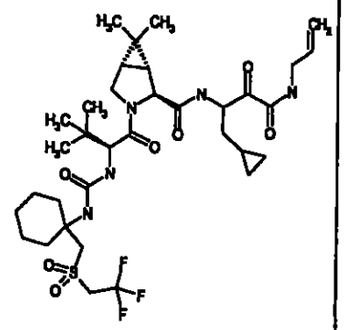
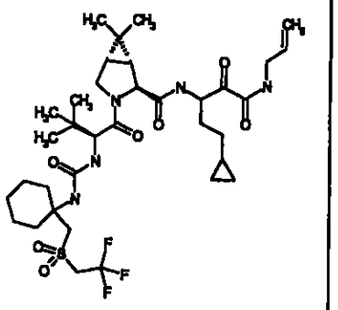
553		746.0303		A
554		719.992		A

555		746.0303		A
556		750.0185	750.1	B

557		772.0685		A
558		762.0297		B

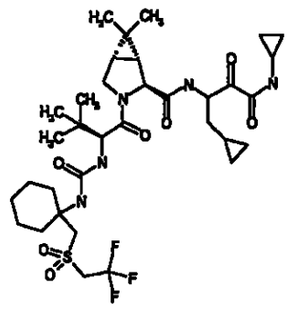
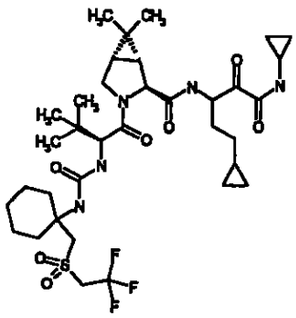
559		735.9914		B
560		762.0297		A

561		735.9914		A
562		776.0568		B

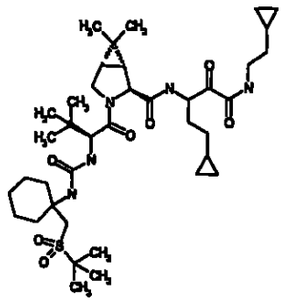
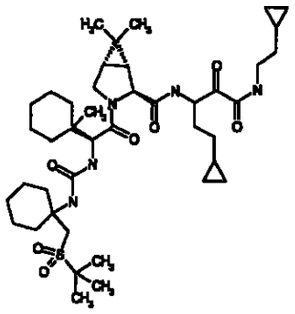
563		731.882		A
564		745.9091		A

446

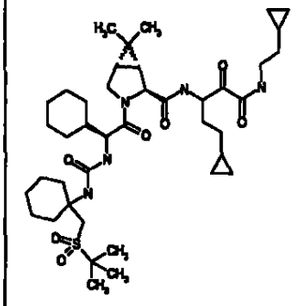
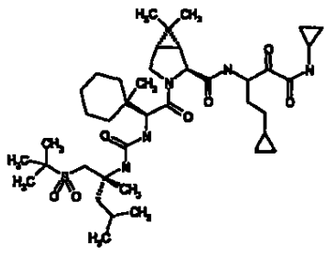
447

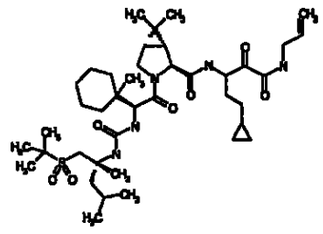
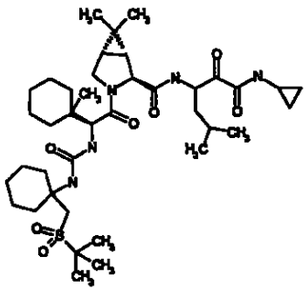
565		731.882		A
566		745.9091		1A

448

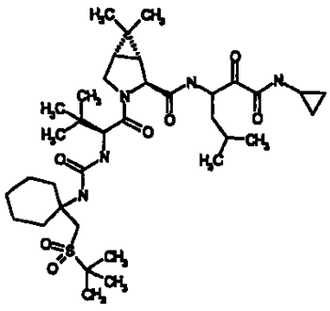
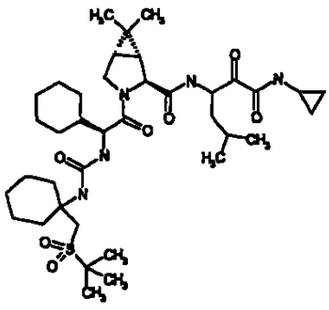
567		748.0462		A
568		788.1115		A

449

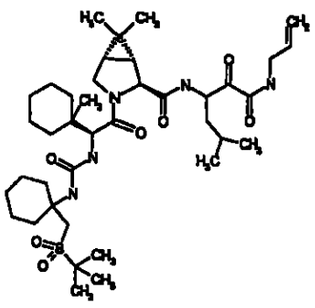
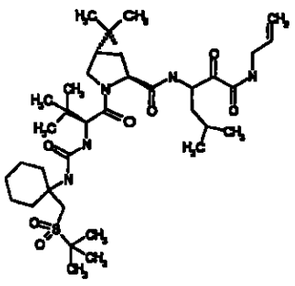
569		774.0844		A
570		762.0733	763.1	A

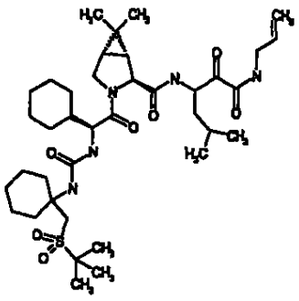
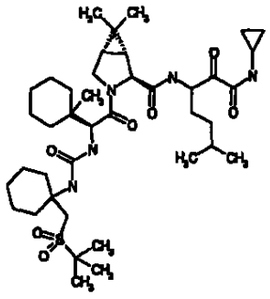
571		762.0733	763.1	A
572		748.0462		B

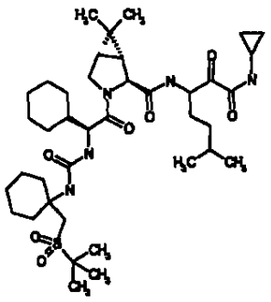
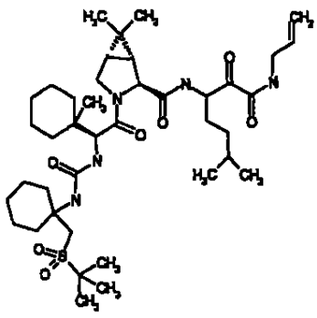
451

573		707.9809		B
574		734.0191		B

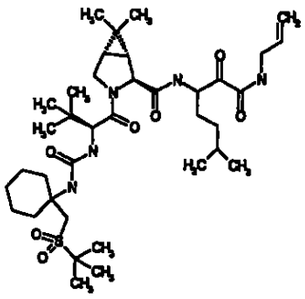
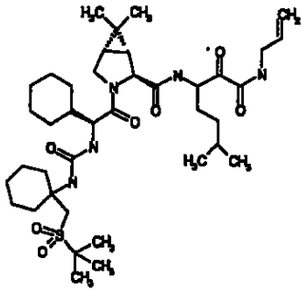
452

575		748.0462		B
576		707.9809		B

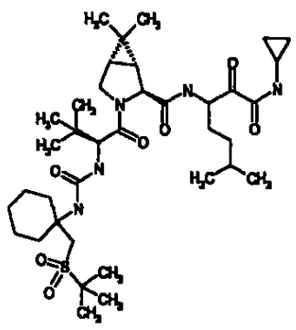
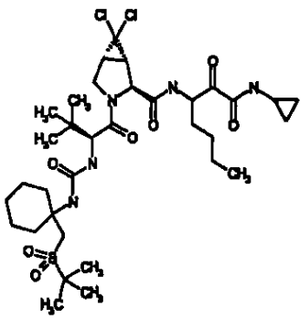
577		734.0191		C
578		762.0733	762.4	B

579		748 0462	748.4	A
580		762.0733		A

455

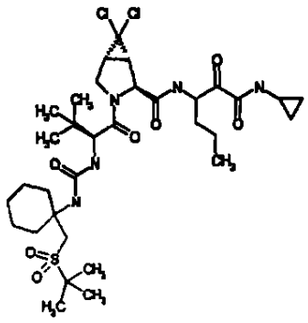
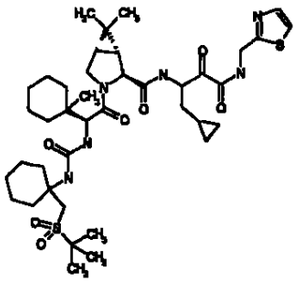
581		722.008		A
582		748.0462		A

456

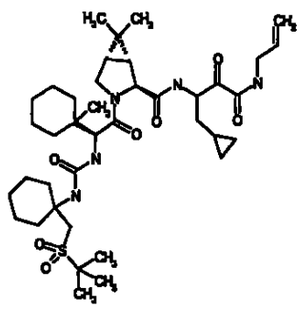
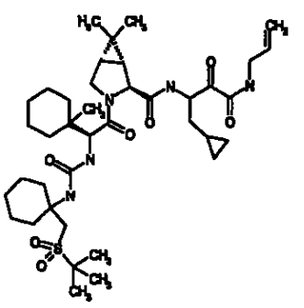
583		722.008	722.4	A
584		748.8168	748.4	A

454

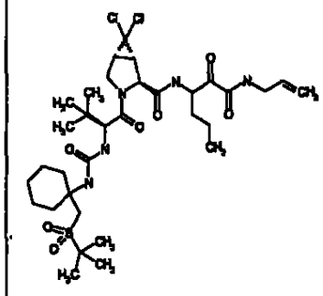
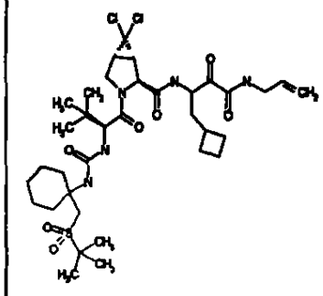
457

585		734.7897	734.4	A
586		803.1041	803.4	A

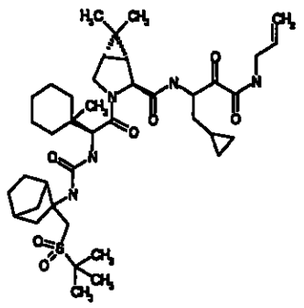
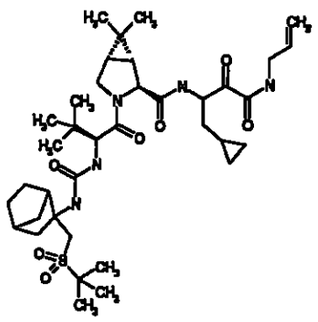
458

587		746.0303		C
588		746.0303		B

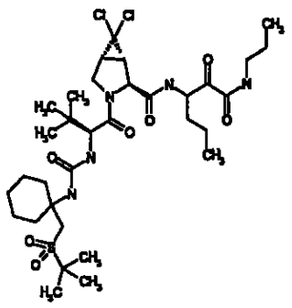
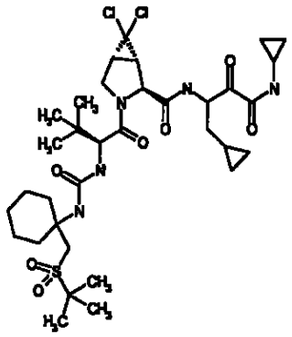
459

589		734.7897	734.1	A
590		760.8279	760.1	A

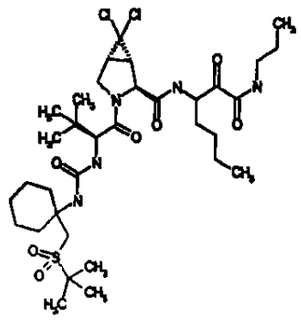
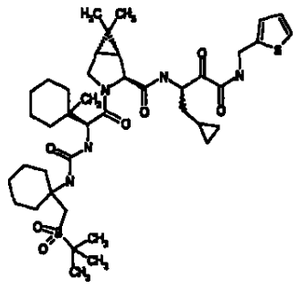
460

591		758.0414		A
592		717.9761		A

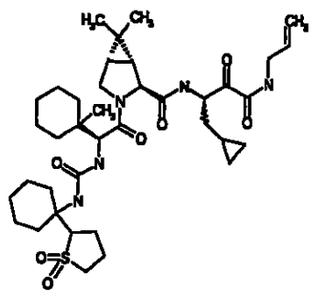
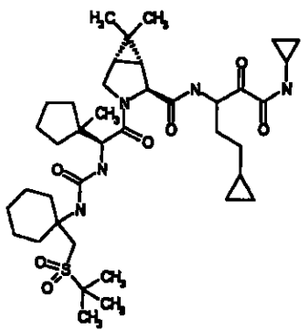
461

593		736.8056	736.1	A
594		746.8008	746.1	A

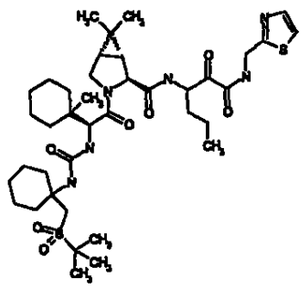
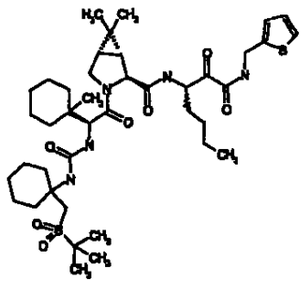
462

595		750.8327	750.4	A
596		802.1166	802.5	A

463

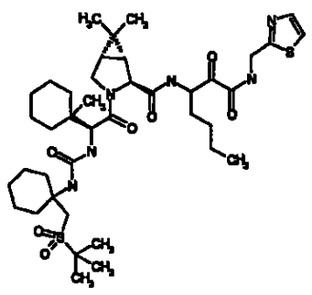
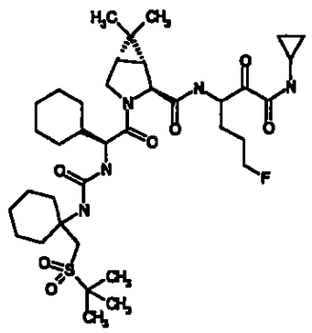
597		729.9872	731.4	A
598		746.0303	746.4	A

464

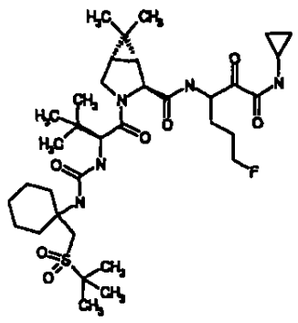
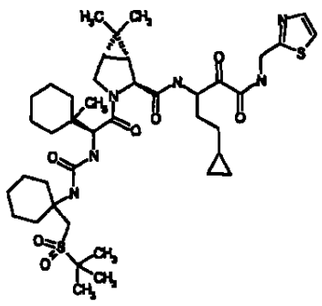
599		791.093	791.4	A
600		804.1325	804.5	A

462

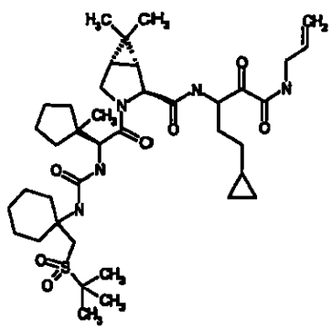
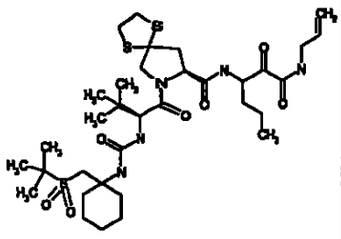
465

601		805.1201	805.4	A
602		737.9825		A

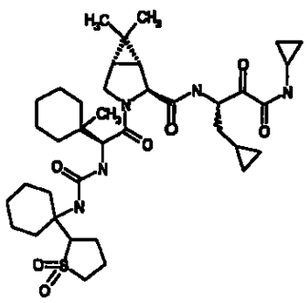
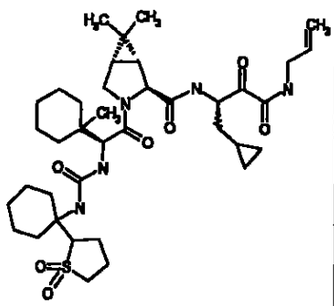
466

603		711.9442		A
604		817.1312	817.4	A

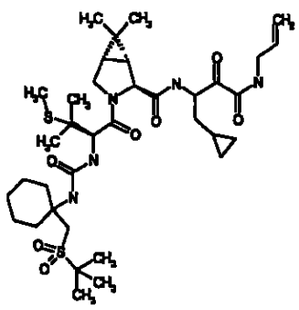
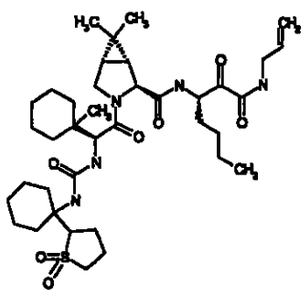
467

605		746.0303	746.4	A
606		744.0547	745.1	A

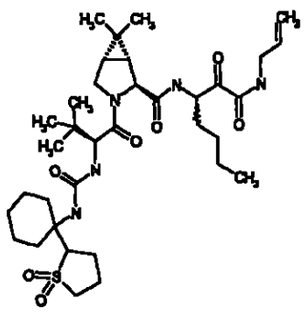
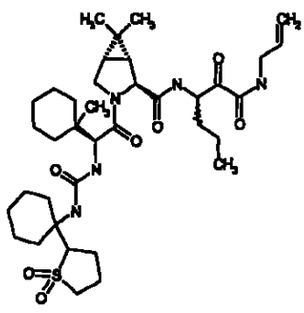
468

607		729.9872		A
608		729.9872	730.4	A

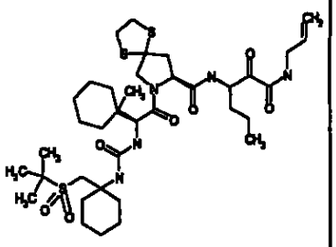
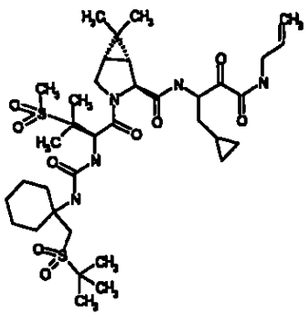
469

609		738.0289	738.1	A
610		732.0032	732.1	A

470

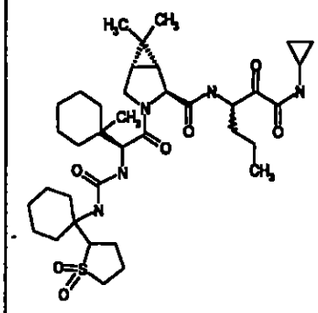
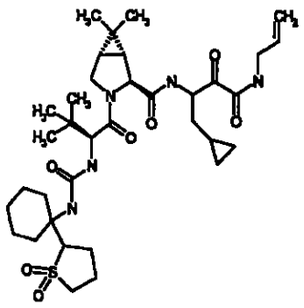
611		691.9378	692.1	3.8
612		717.9761	718.1	A

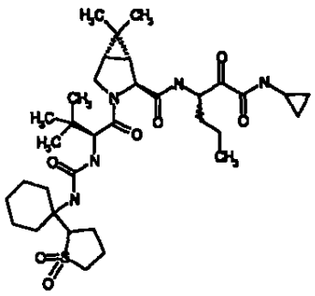
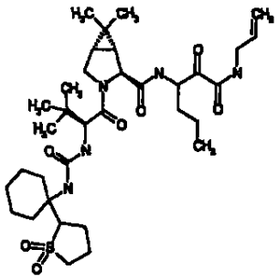
471

613		784.12	784.2	A
614		770.0277	770 2	B

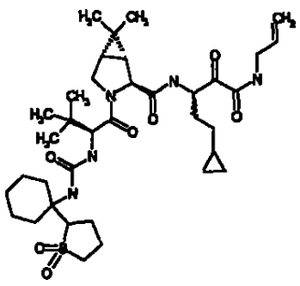
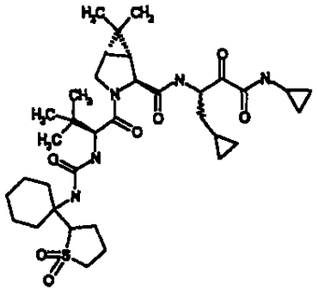
469

472

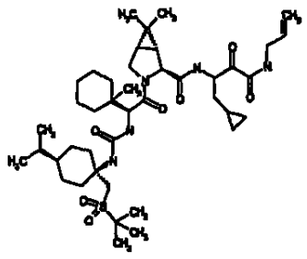
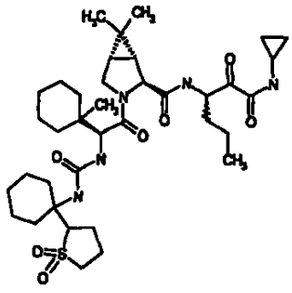
615		717.9761		A
616		689.9219		A

617		677.9108	678.4	A
618		677.9108	678.4	A

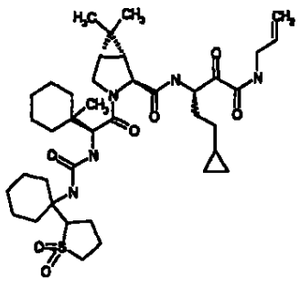
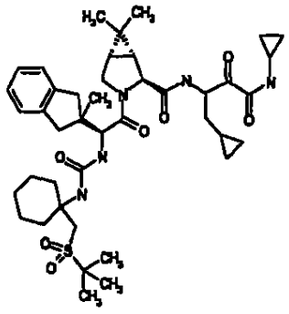
474

619		703.949	704.4	A
620		689.9219	690.4	A

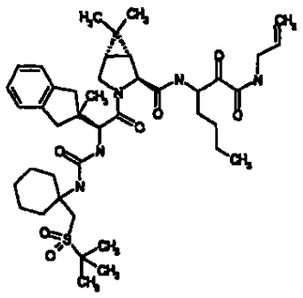
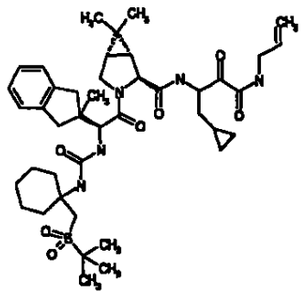
475

621		788.1115	789.4	C
622		717.9761	718.1	A

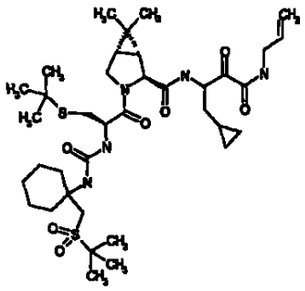
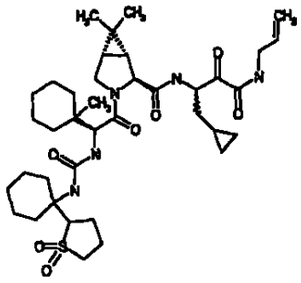
476

623		744.0143	744.1	A
624		780.0478	780.5	B

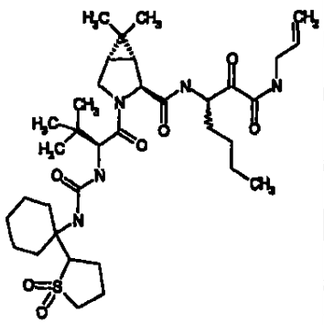
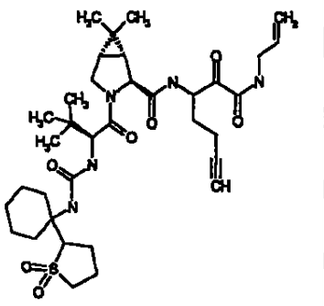
477

625		782 0637	782.5	A
626		780.0478	780.5	A

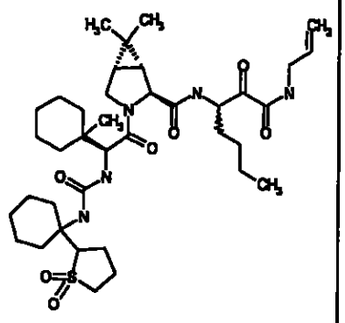
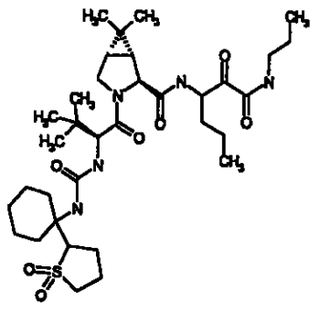
478

627		752.056	752.1	C
628		729.9872	730.4	A

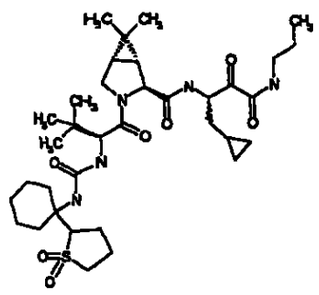
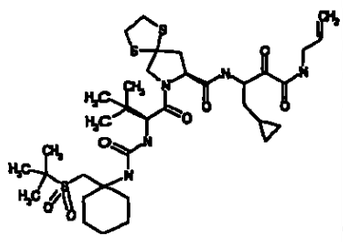
479

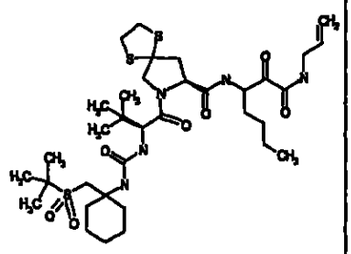
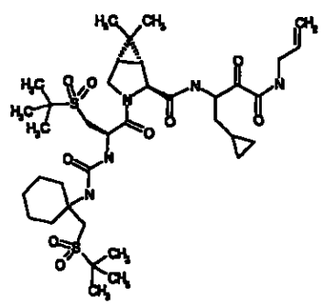
629		691.9378	692.4	A
630		687.906	688.4	A

480

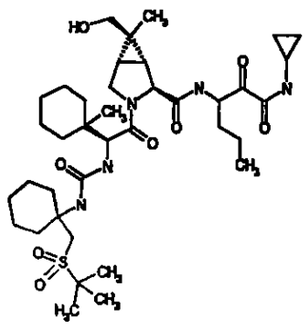
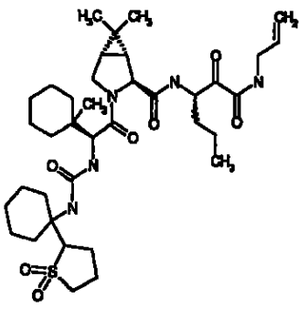
631		732.0032	732.4	A
632		679.9267	680.4	A

481

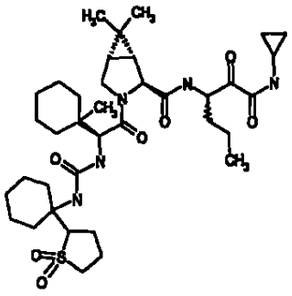
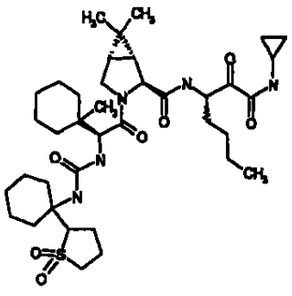
633		691 9378	692.4	A
634		756.0658	756.1	A

635		758.0818	758.1	A
636		784.0548	784.2	C

483

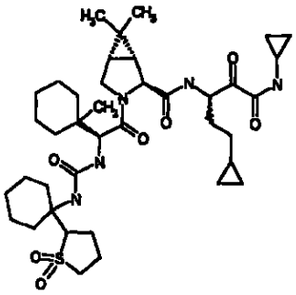
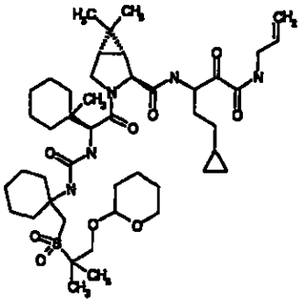
637		750.0185		B
638		717.9761	718.4	A

484

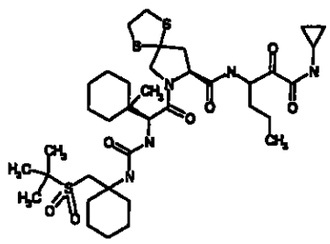
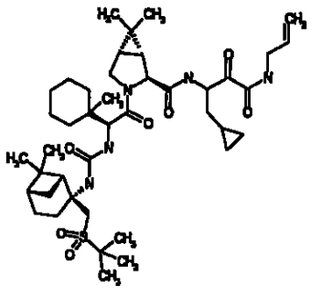
639		717.9761	718.4	A
640		732.0032	732.4	A

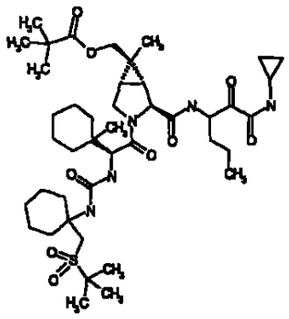
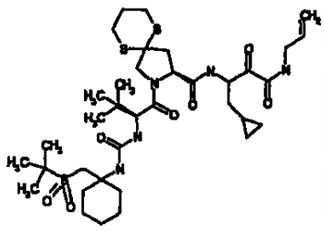
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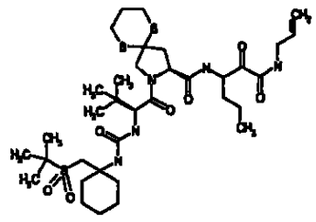
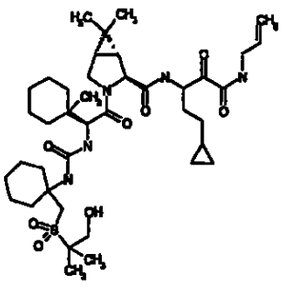
641		744.0143	744 4	A
642		860.1757		A

486

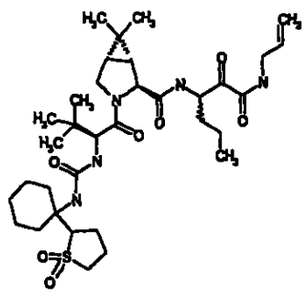
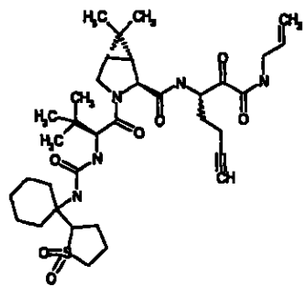
643		784.12		B
644		786.0956		B

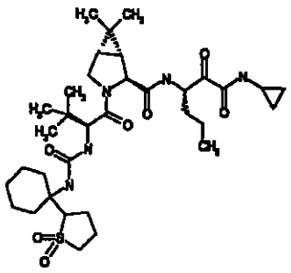
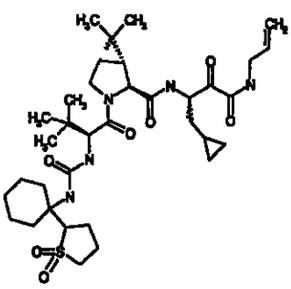
645		834.1374		B
646		770.0929	770.2	A

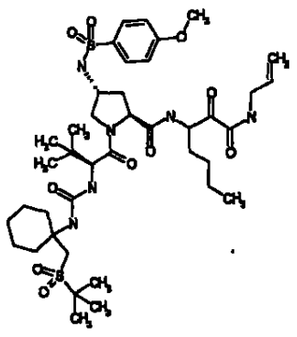
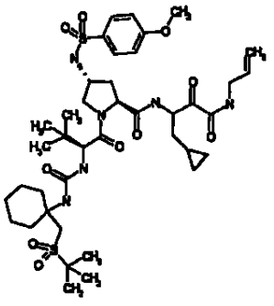
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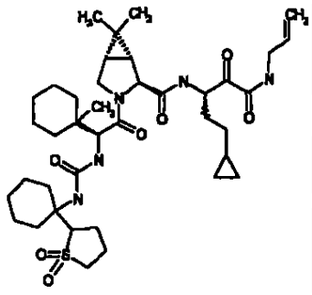
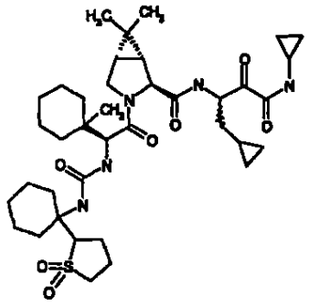
647		758.0818	758 2	A
648		776.0568		A

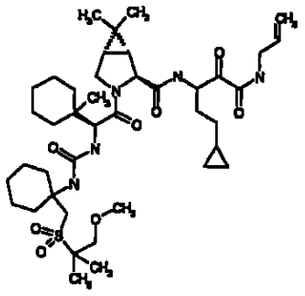
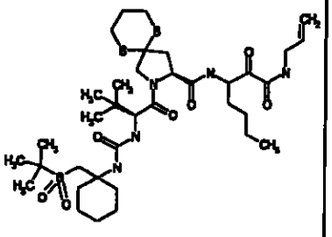
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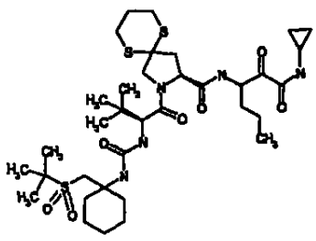
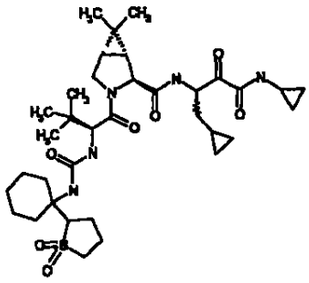
649		677.9108	678.2	A
650		687.906	688.2	A

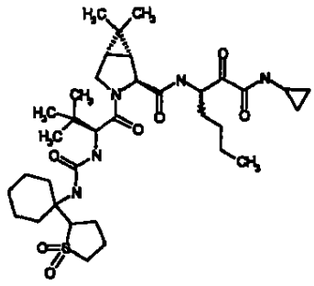
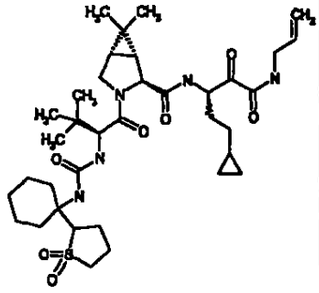
651		677.9108	678.2	A
652		689.9219	690.2	A

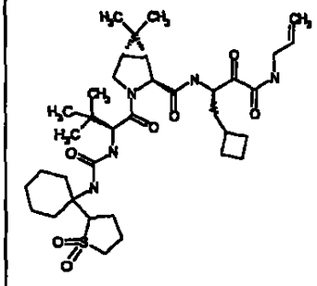
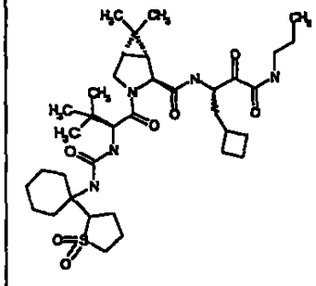
653		853 1183	853.4	C
654		851.1023	851.4	C

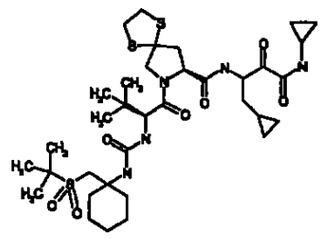
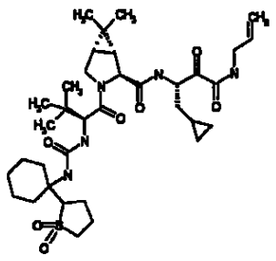
655		744.0143	744.1	A
656		729.9872	730.1	A

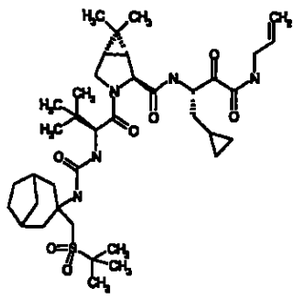
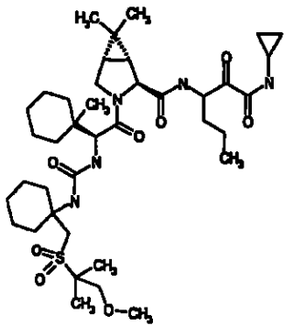
657		790.0838		A
658		772.1089	772.2	A

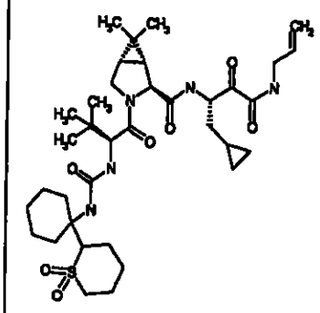
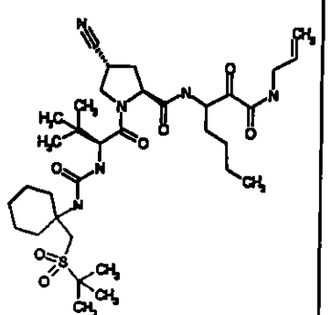
659		758.0818	758.2	A
660		689 9219	690.1	A

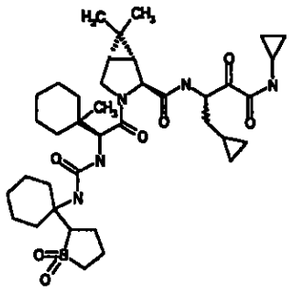
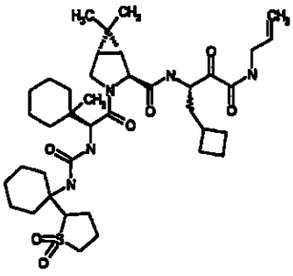
661		691.9378	692.1	A
662		703.949	704.1	A

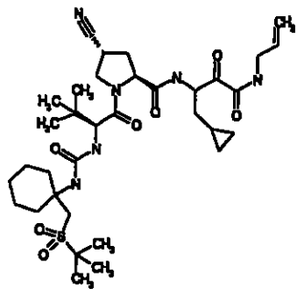
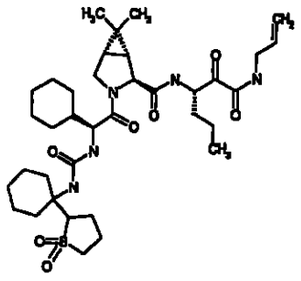
663		703 949	704.1	A
664		705.9649	706.2	A

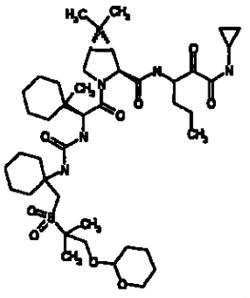
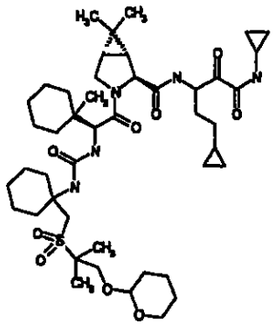
665		756.0658		B
666		689.9219		A

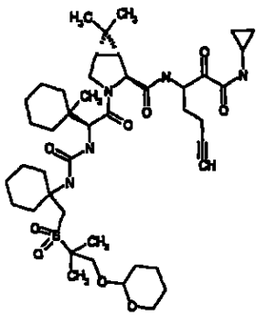
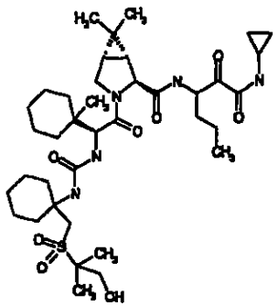
667		732.0032		A
668		764.0456		A

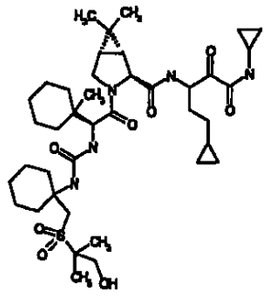
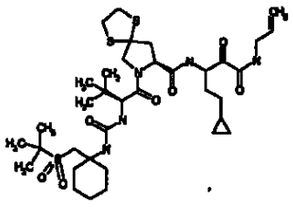
669		703.949		A
670		692 9254	693.3	C

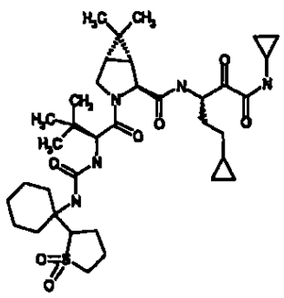
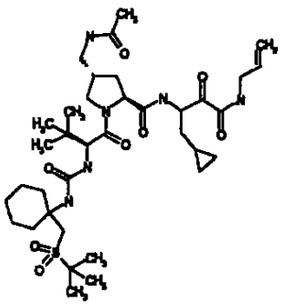
671		729.9872	730.1	A
672		744 0143	744.1	A

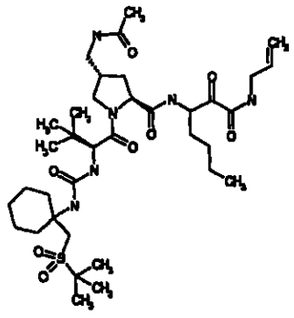
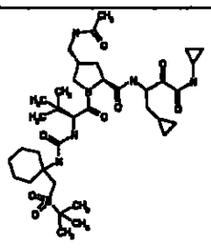
673		690.9095	691.35	C
674		703.949		A

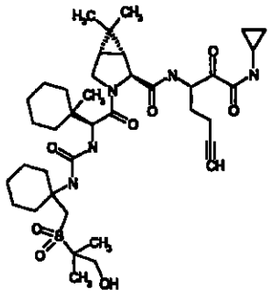
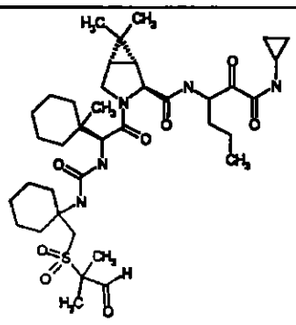
675		834.1374		A
676		860.1757		A

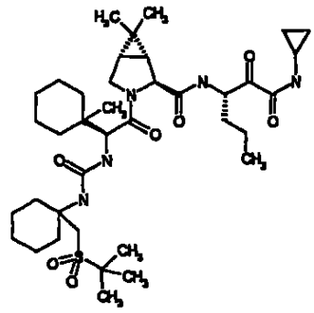
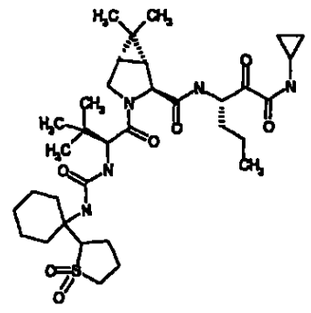
677		844.1326		A
678		750.0185		A

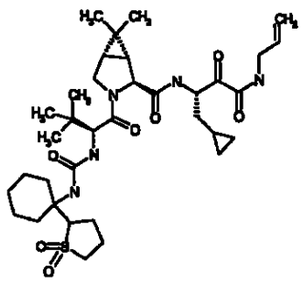
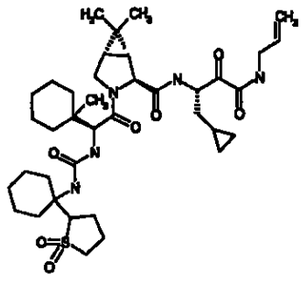
679		776.0568		A
680		770.0929	770.4	A

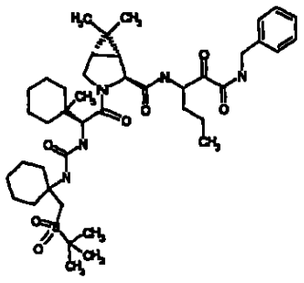
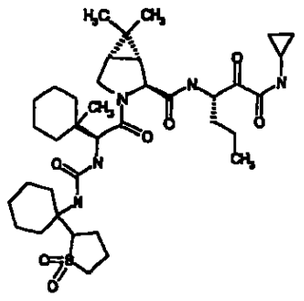
681		703.949	704.2	A
682		736.979	737.5	C

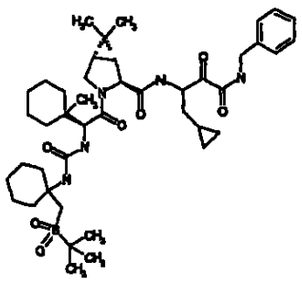
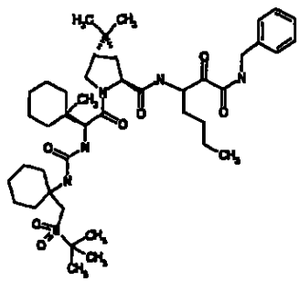
683		738.9949	739.4	C
684		736.979	737.4	C

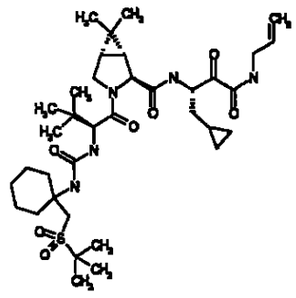
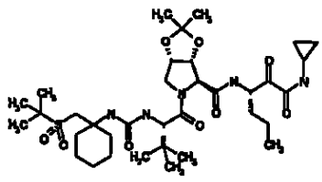
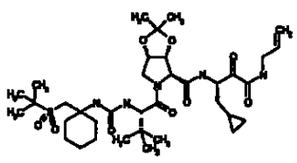
685		760.0137		A
686		748.0026		A

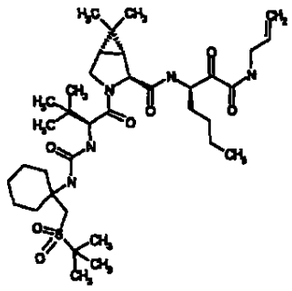
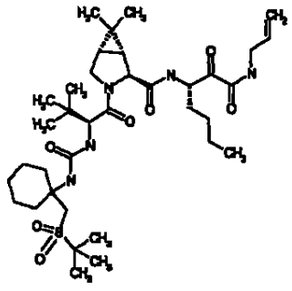
687		734.0191		A
688		677.9108	678.2	A

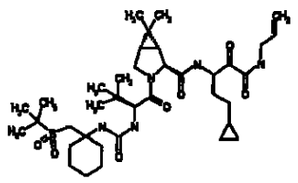
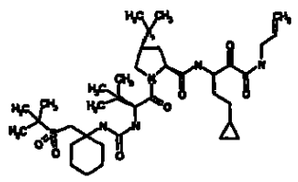
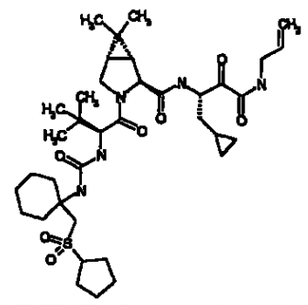
689		689.9219	690.2	A
690		729.9872	730.2	A

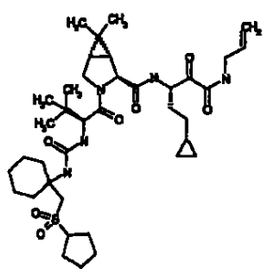
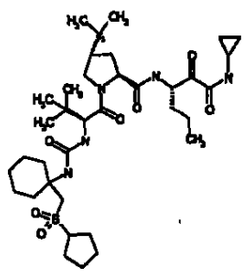
691		784.0797	784.2	A
692		717.9761		A

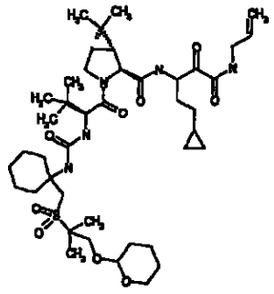
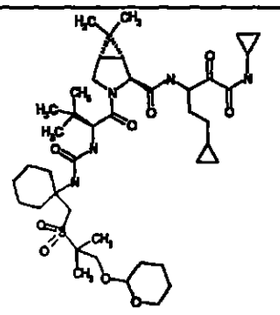
693		796.0908	796.2	A
694		798.1067	798.2	A

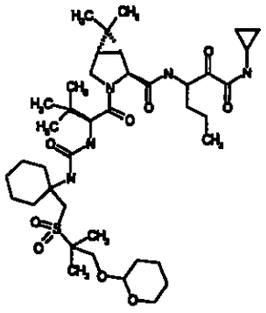
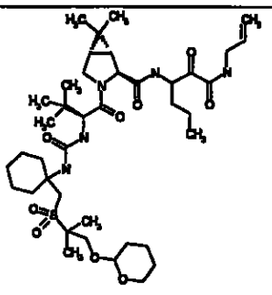
695		705.9649		5
696		725.9526	726 4	A
697		737.9637	738.4	A

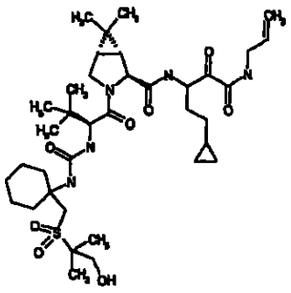
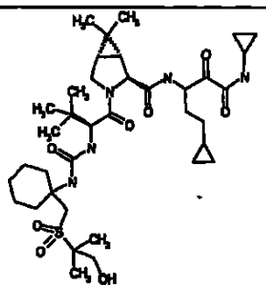
698		707.9809	708.4	B
699		707.9809	708.4	A

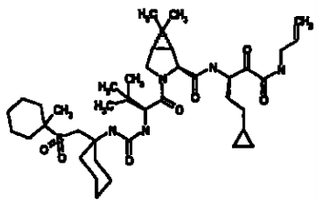
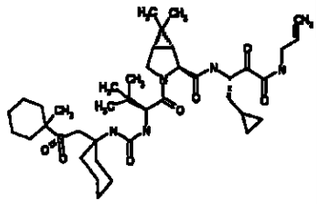
700		719.992		A
701		719.992		6
702		717 9761	718.60	A

703		732.0032	732.6	A
704		705.9649	706.6	A

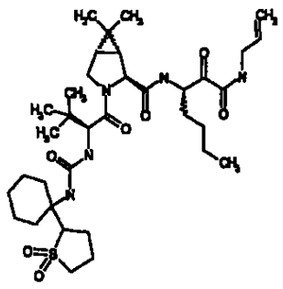
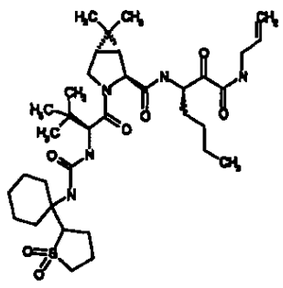
705		820.1103		A
706		820.1103		A

707		794.0721		A
708		794.0721		A

709		735.9914		A
710		735.9914		A

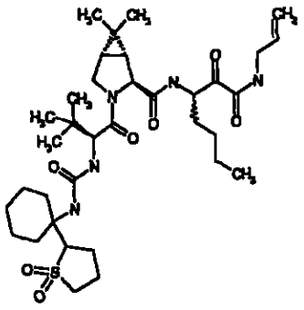
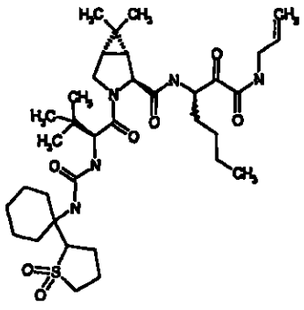
711		760.0574		A
712		746 0303		A

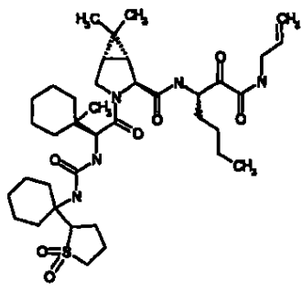
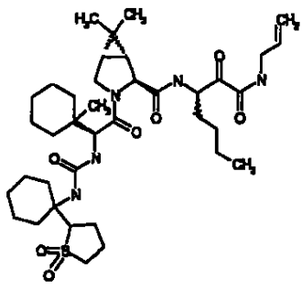
520

713		691.9378	692.2	B
714		691.9378	692.2	A

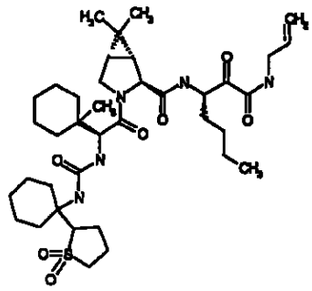
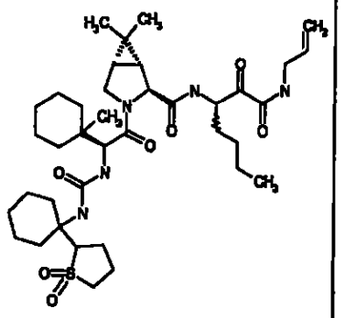
800

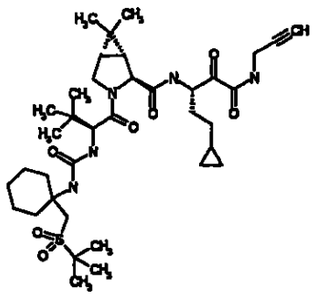
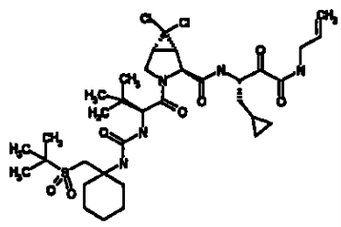
521

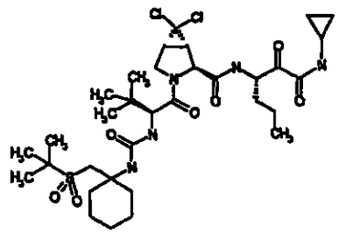
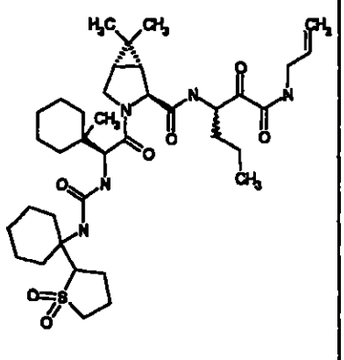
715		691.9378	692.2	A
716		691.9378	692.2	A

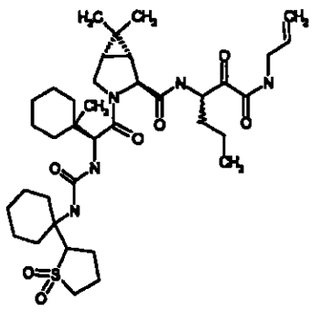
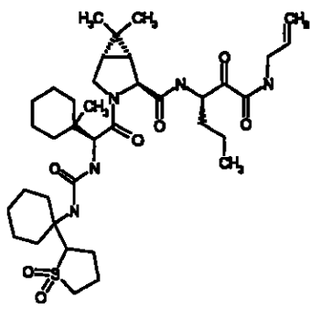
717		732.0032	732.2	B
718		732.0032	732.2	B

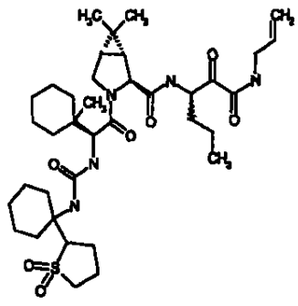
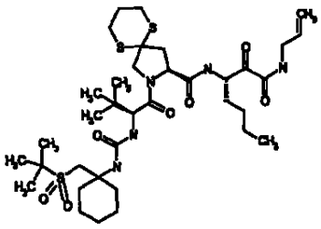
523

719		732.0032	732.2	A
720		732.0032	732.2	A

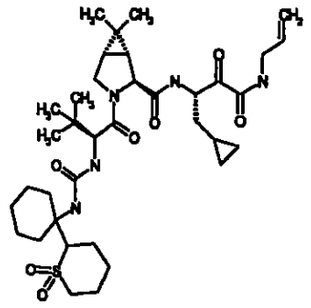
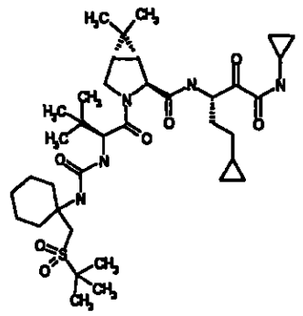
721		717.9761	718.1	A
722		746.8008		A

723		734.7897		A
724		717.9761	718.2	B

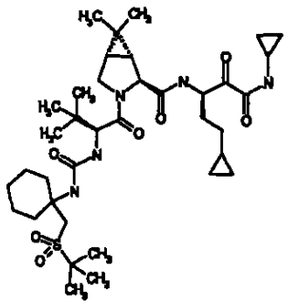
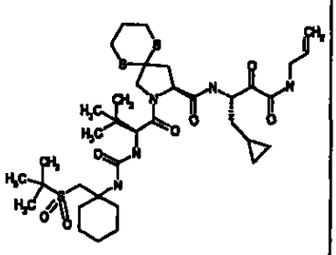
725		717.9761	718.2	A
726		717.9761	718.2	A

727		717.9761	718.2	A
728		772.1089		A

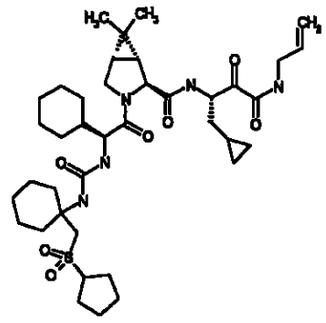
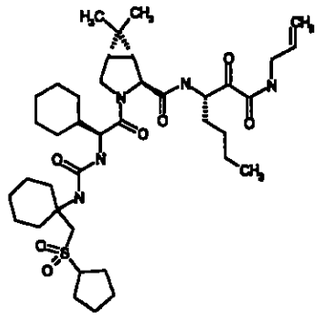
528

729		703.949	704.2	A
730		719.992		5.6

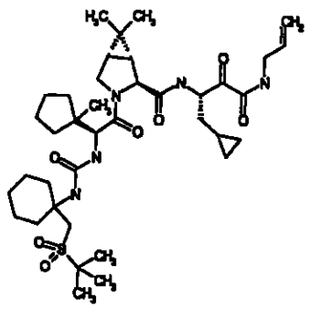
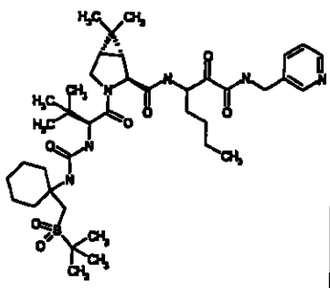
529

731		719.992		64
732		770.0929	770.2	A

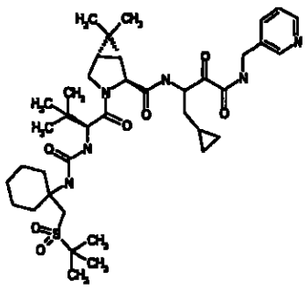
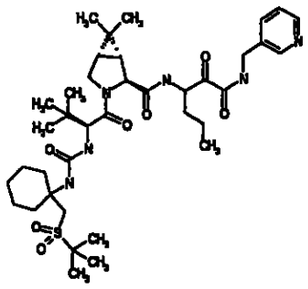
530

733		744.0143	744.3	A
734		746.0303	746.2	A

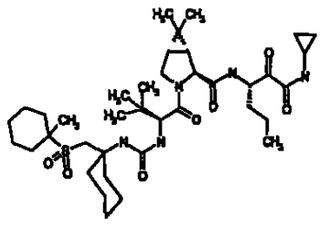
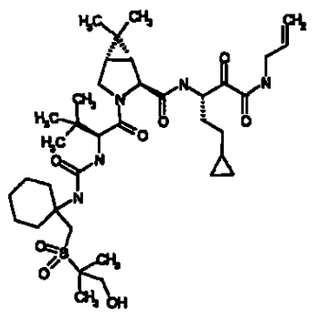
531

735		732.0032	732.4	A
736		759.029	759.4	A

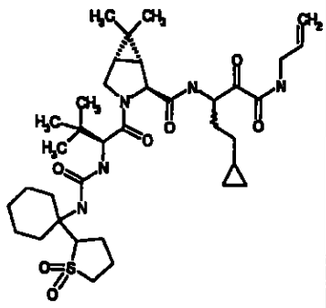
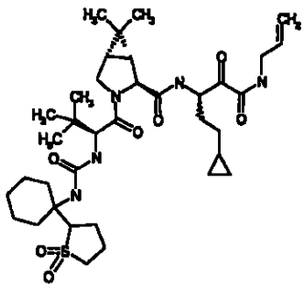
532

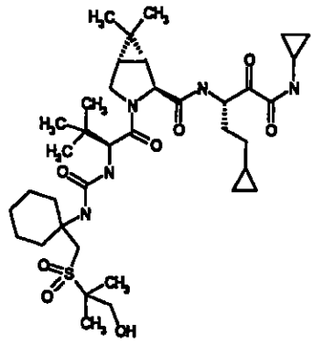
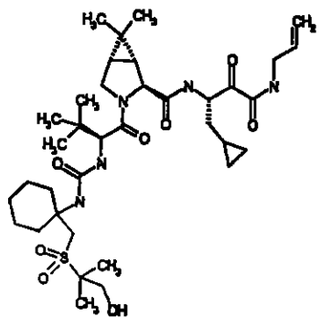
737		757.0131	757.4	A
738		745.0019	745.4	A

533

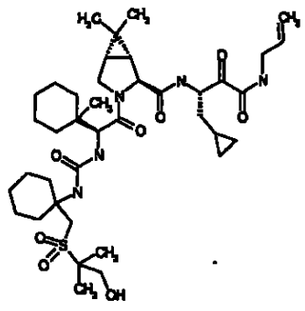
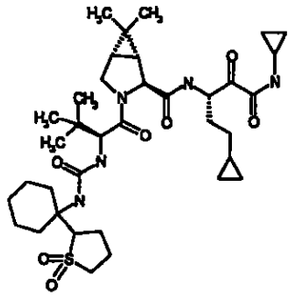
739		734.0191	734.3	18
740		735.9914		A

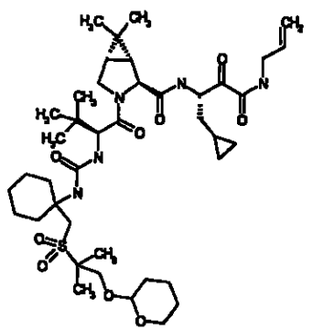
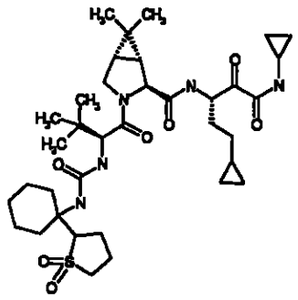
534

741		703.949	704.2	A
742		703.949	704.2	A

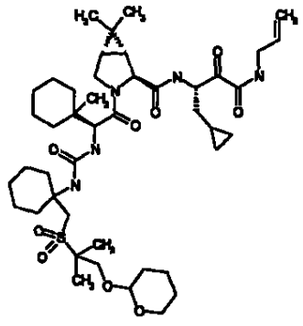
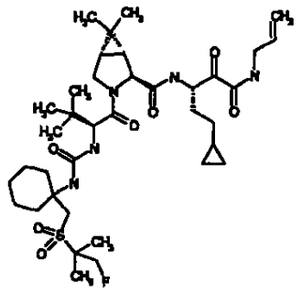
743		735.9914		A
744		721.9643		A

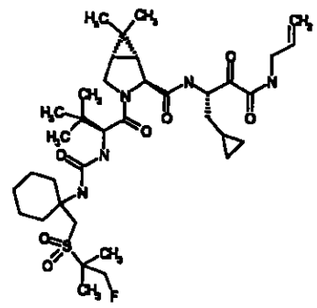
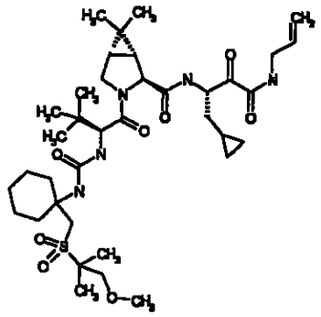
536

745		762.0297		A
746		703.949	704.2	A

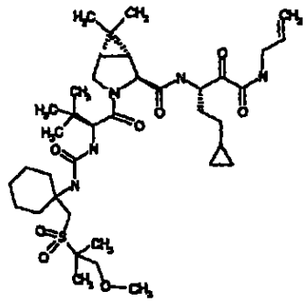
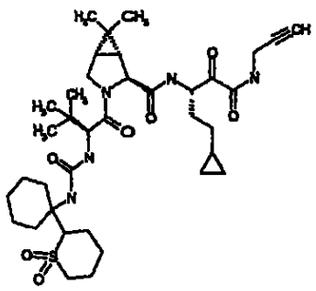
747		806.0832		A
748		703.949	704.2	A

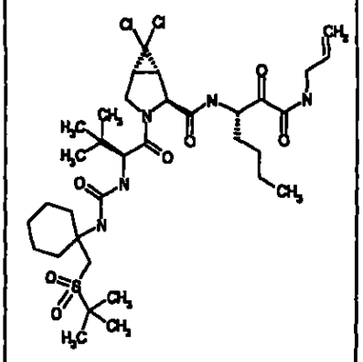
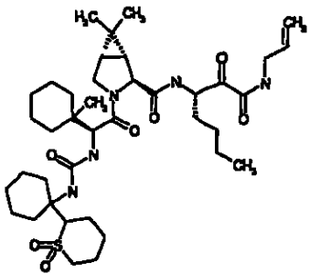
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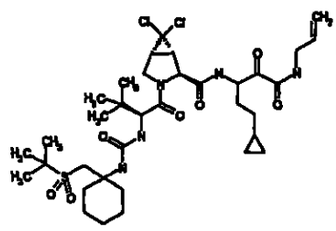
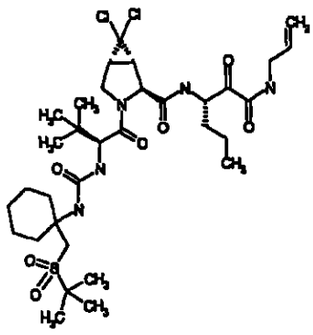
749		846.1486		A
750		737.9825		A

751		723.9554		A
752		735.9914		A

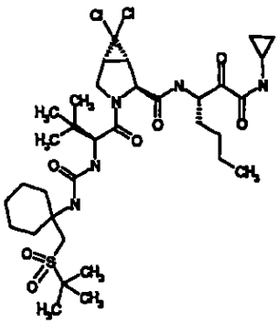
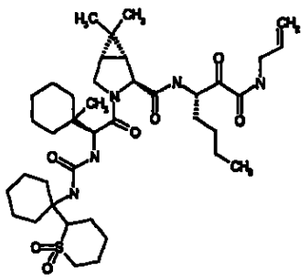
540

753		750.0185		A
754		715.9601	716.1	A

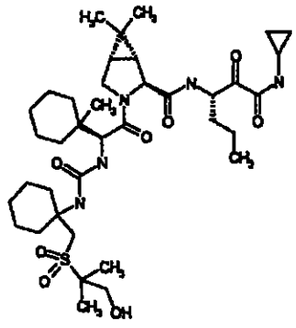
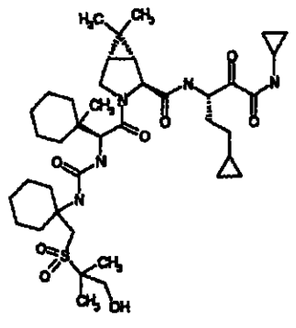
755		748.8168	748.1	A
756		746.0303	746.1	A

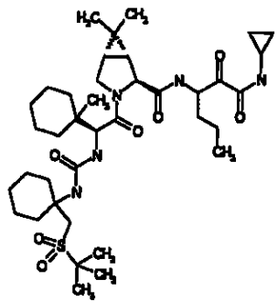
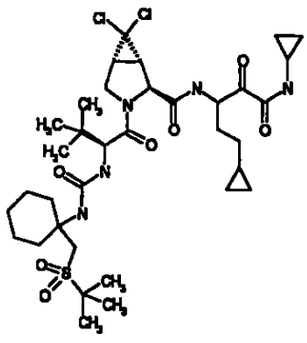
757		760.8279	760.1	A
758		734.7897	734.1	A

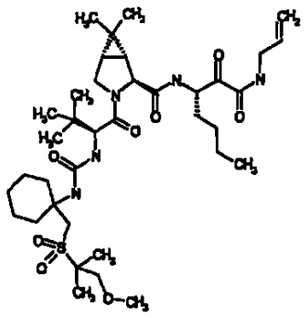
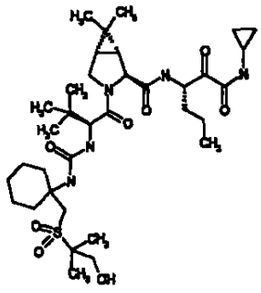
543

759		748.8168	748.1	A
760		746.0303		A

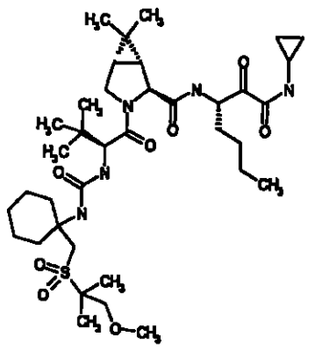
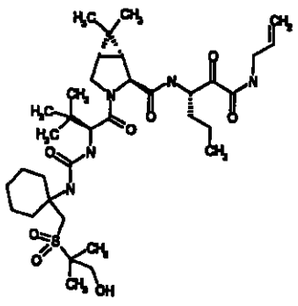
544

761		750.0185		A
762		776.0568		A

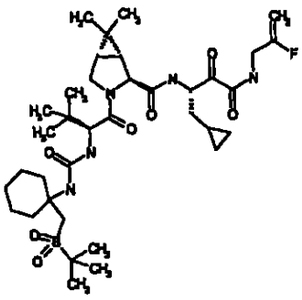
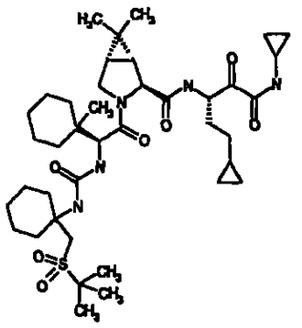
763		734.0191		B
764		760.8279	760.1	A

765		738.0074		A
766		709.9532		A

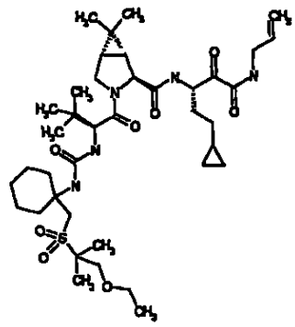
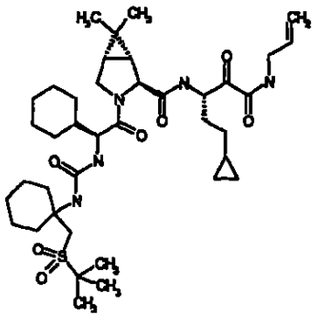
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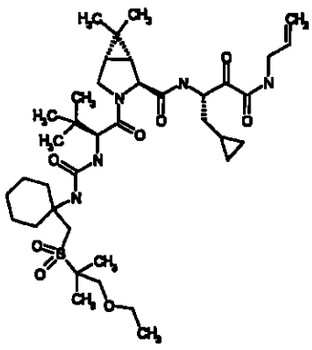
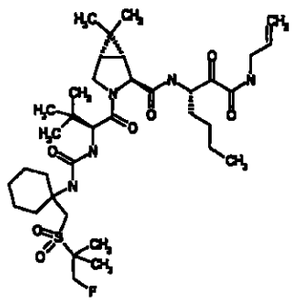
767		738.0074		A
768		709.9532		A

548

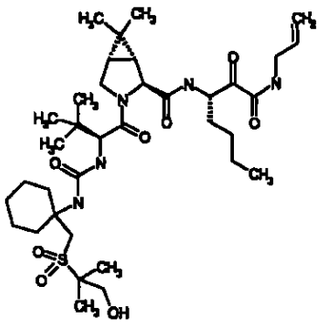
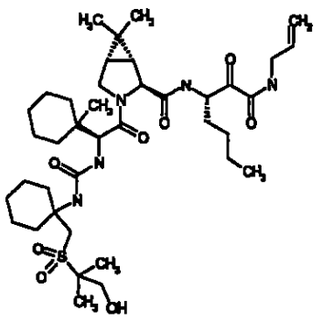
769		723.9554		A
770		760.0574		A

549

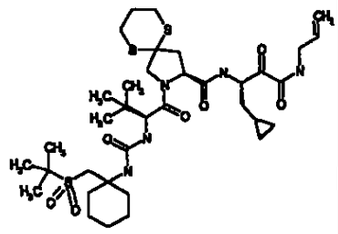
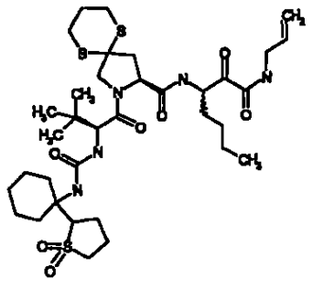
771		764.0456		A
772		746.0303		A

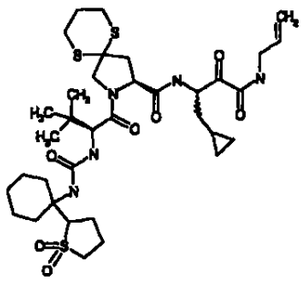
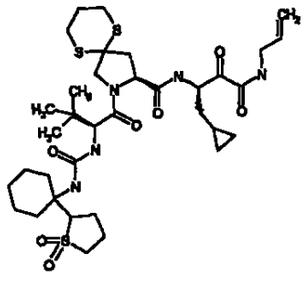
773		750.0185		A
774		725.9713		A

551

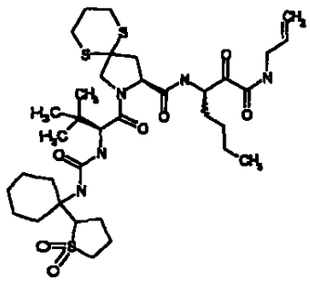
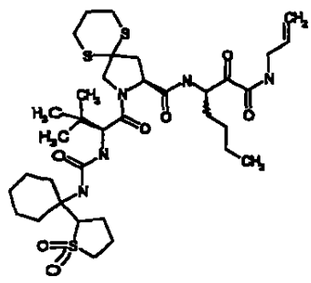
775		723.9803		A
776		764.0456		A

552

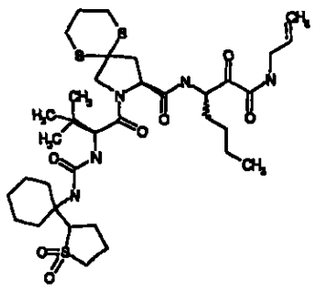
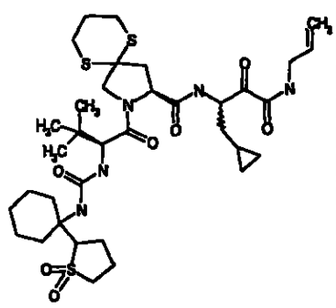
777		770.0929	770.2	B
778		756.0658	756.1	A

779		754.0499	754.1	A
780		754.0499	754.1	A

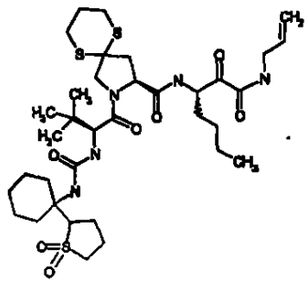
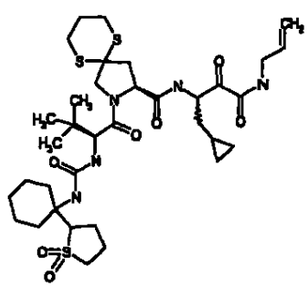
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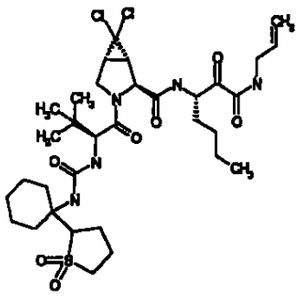
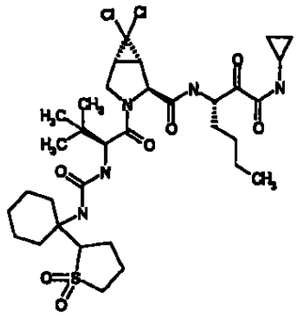
781		756.0658	756.1	A
782		756.0658	756.1	A

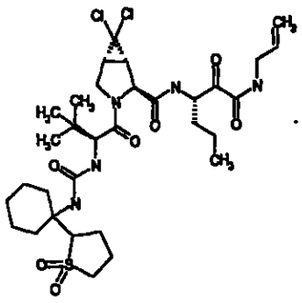
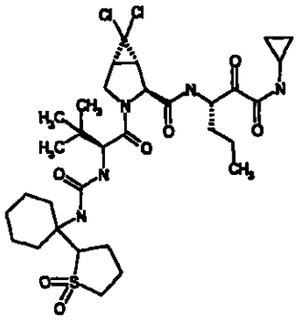
555

783		756.0658	756.1	A
784		754.0499	754.1	A

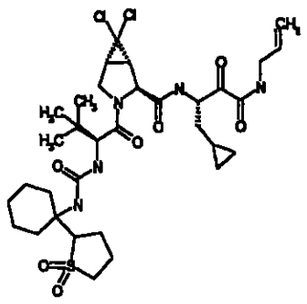
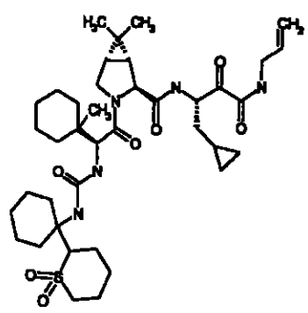
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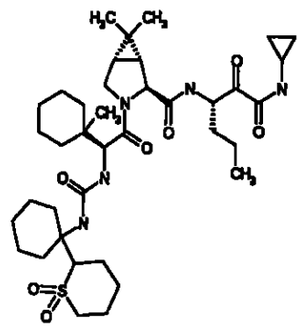
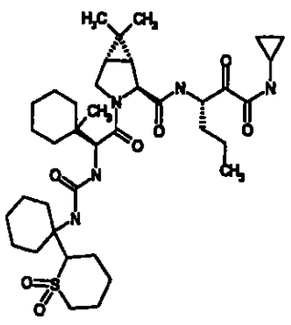
785		756.0658	756.1	A
786		754.0499	754.1	A

787		732.7737	732.1	A
788		732.7737	732.1	A

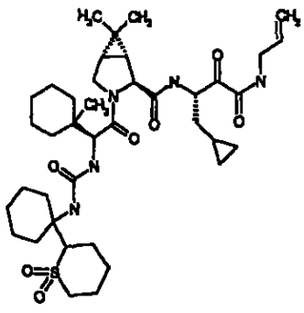
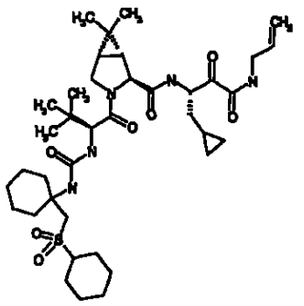
789		718.7466	718.2	A
790		718.7466	718.2	A

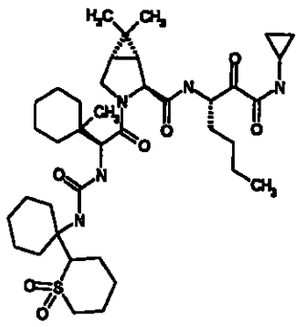
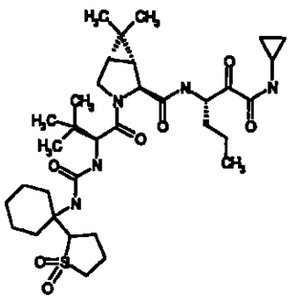
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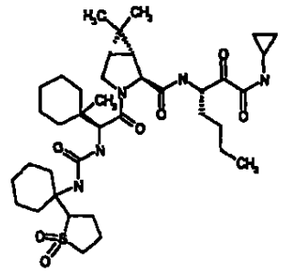
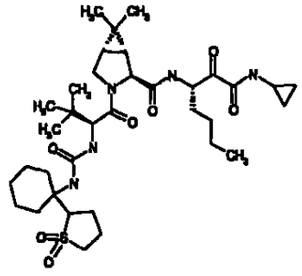
791		730.7578	730.2	A
792		744.0143		A

793		732 0032	732.1	A
794		732.0032		A

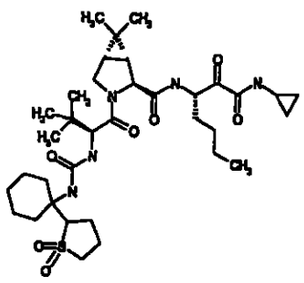
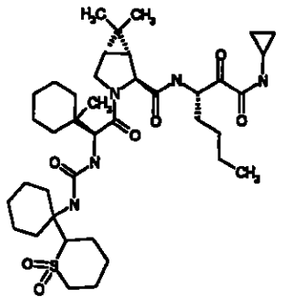
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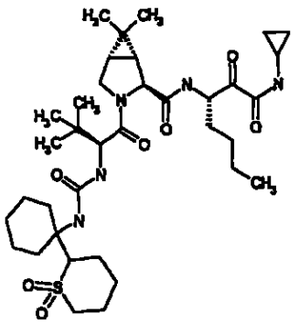
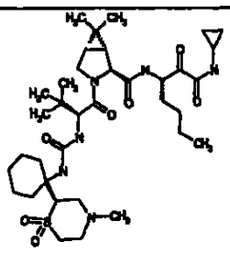
795		744.0143		A
796		732.0032	732.1	A

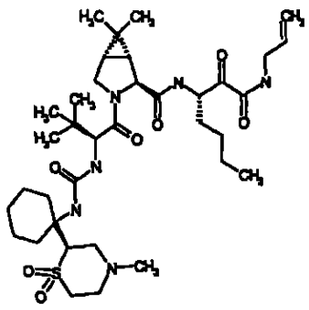
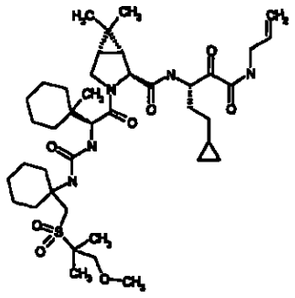
797		746.0303		A
798		677.9108	678.1	A

799		732.0032	732.2	A
800		691.9378	692.2	A

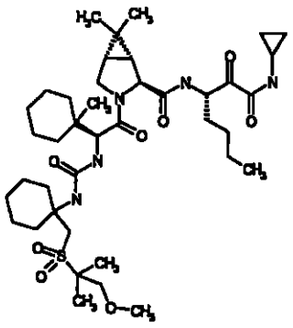
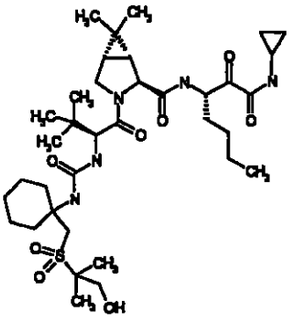
564

801		692	692.2	A
802		746.0303		A

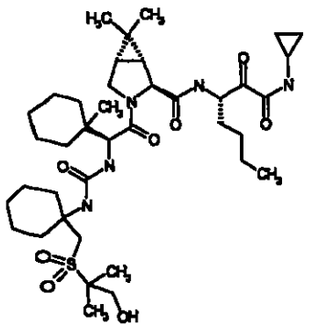
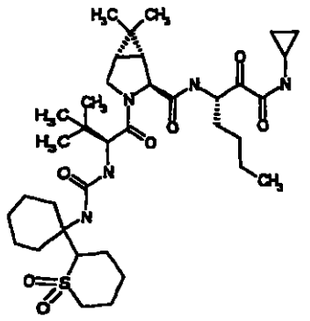
803		705.9649		A
804		720.9796		A

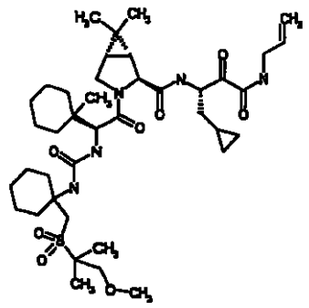
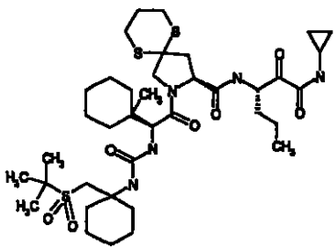
805		720.9796		A
806		790.0838		A

567

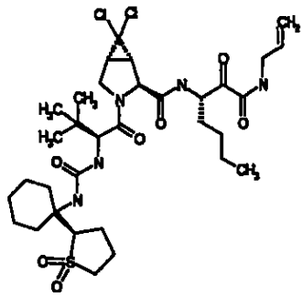
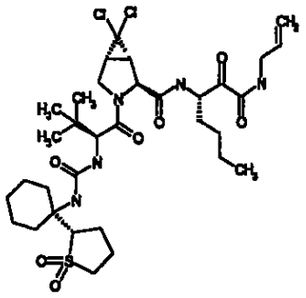
807		778.0727		A
808		723.9803		A

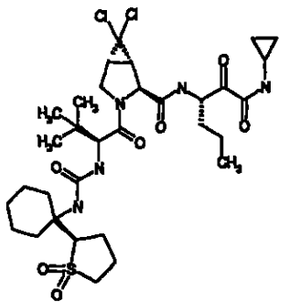
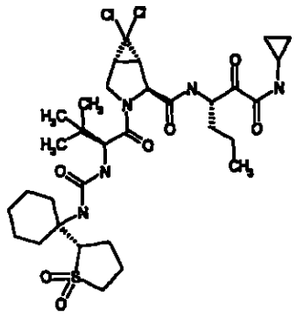
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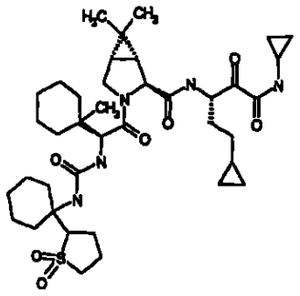
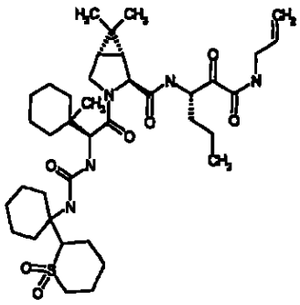
809		764.0456		A
810		705.9649	706.4	A

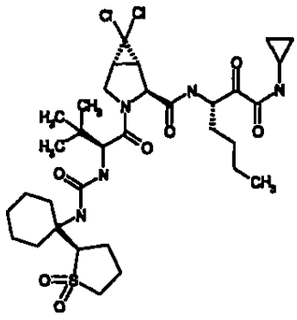
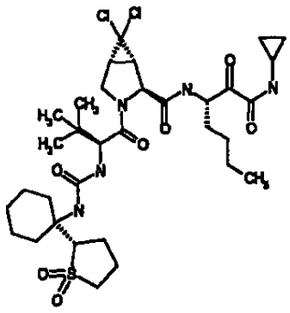
811		776.0568		A
812		798.1471	798.4	A

567
570

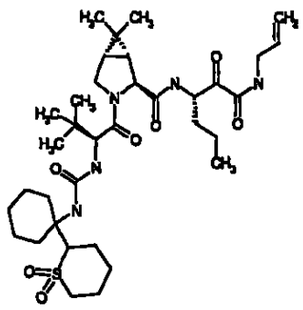
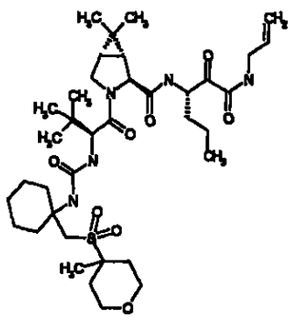
813		732.7737	732.1	A
814		732.7737	732.1	A

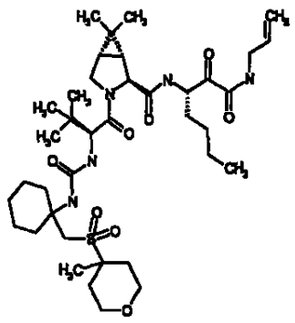
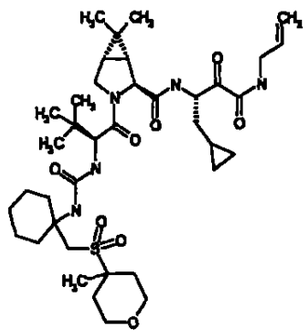
815		718.7466	718.1	A
816		718.7466	718.1	A

817		744.0143	744.1	A
818		732.0032	732.1	A

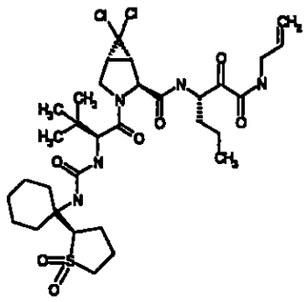
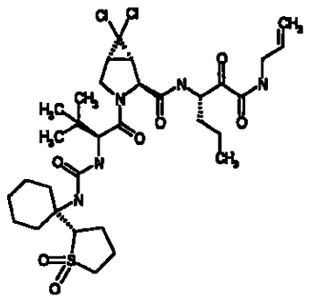
819		732.7737	732.1	A
820		732.7737	732.1	A

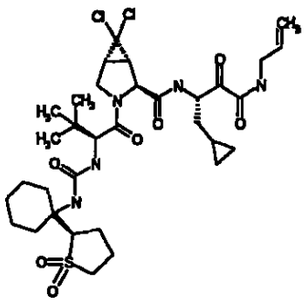
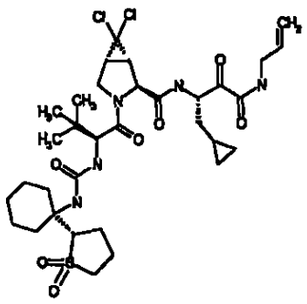
574

821		691.9378	692.1	A
822		735.9914	736.1	A

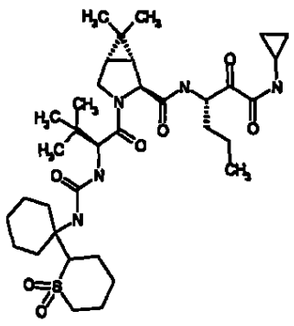
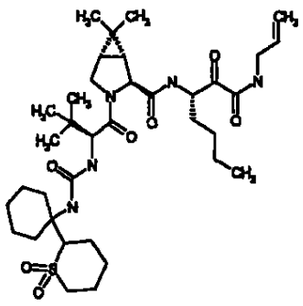
823		750.0185	750.1	A
824		748.0026	748.1	A

576

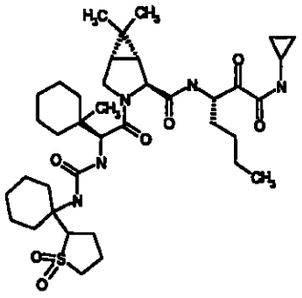
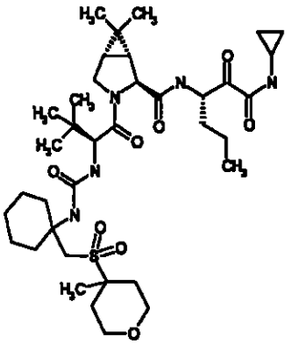
825		718.7466	718.2	A
826		718.7466	718.2	A

827		730.7578	730.2	A
828		730.7578	730.2	A

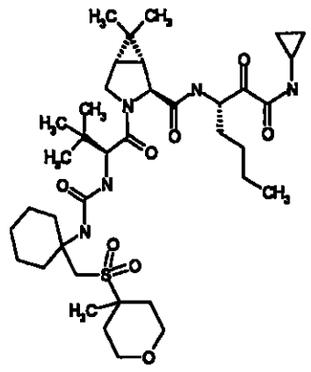
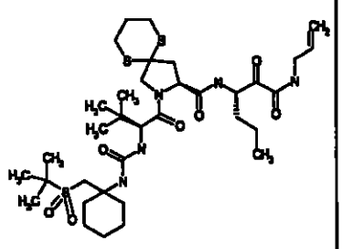
578

829		691.9378		A
830		705.9649	706.1	A

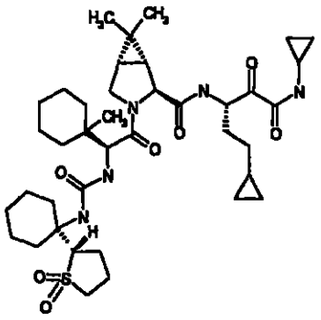
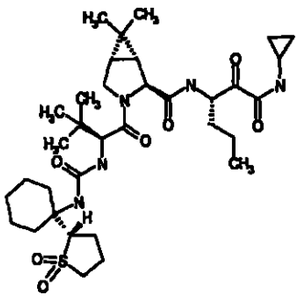
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831		732.0032	732.2	A
832		735.9914	736.1	A

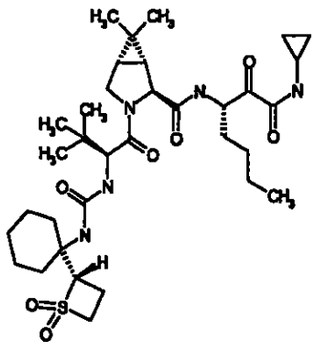
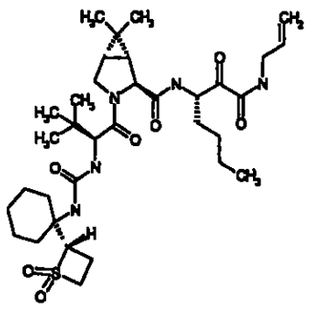
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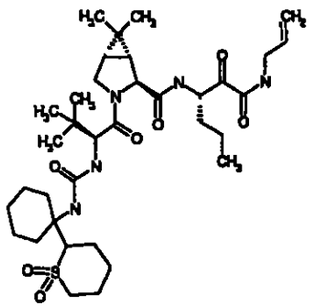
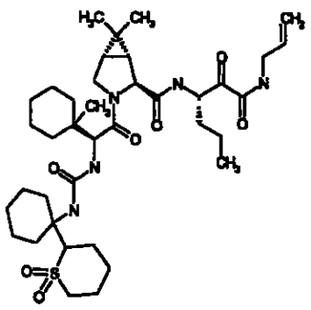
833		750.0185	750.1	A
834		758.0818	758.2	A

581

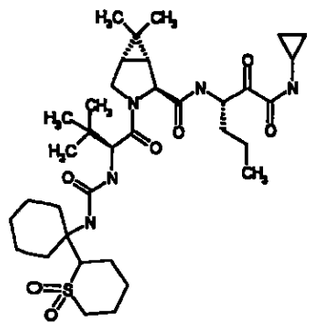
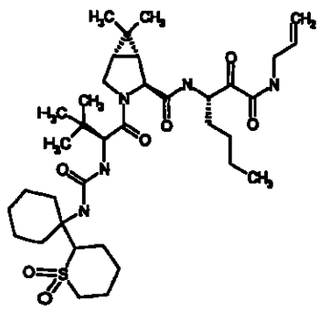
835		744.0143	744.1	A
836		677.9108		A

582

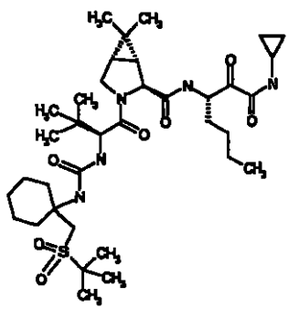
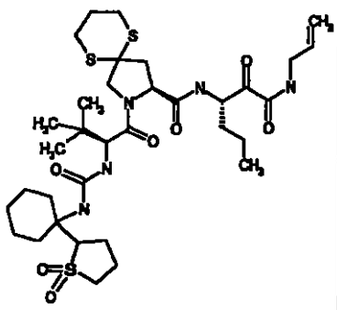
837		677.9108	678.3	A
838		677.9108	678.3	A

839		691.9378		A
840		732.0032		A

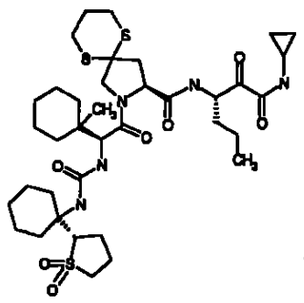
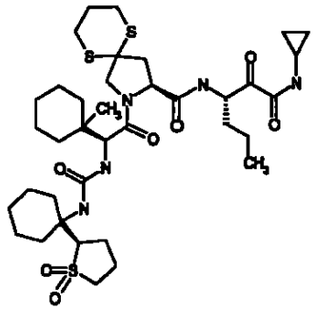
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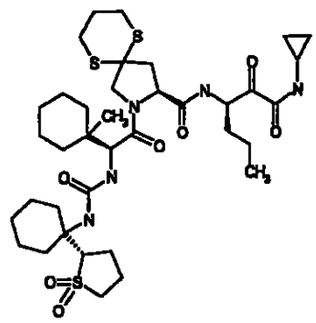
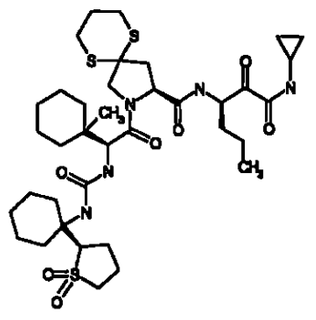
841		691.9378		A
842		705.9649		A

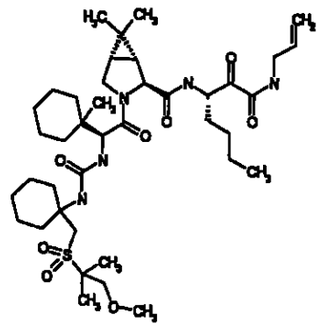
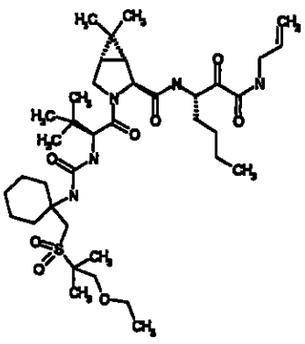
585

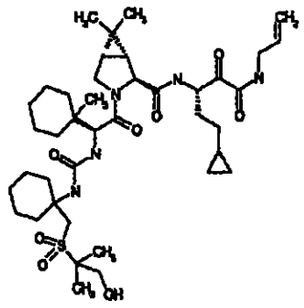
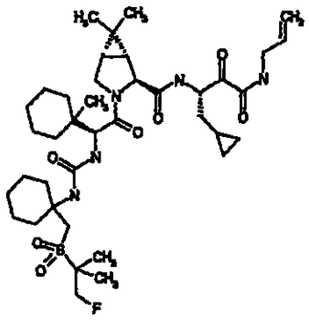
843		707.9809	708.4	11
845		742.0388	742.4	A

586

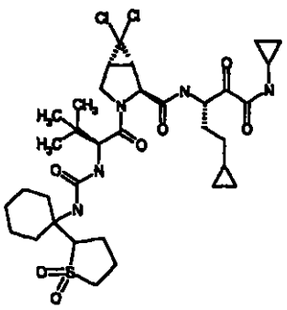
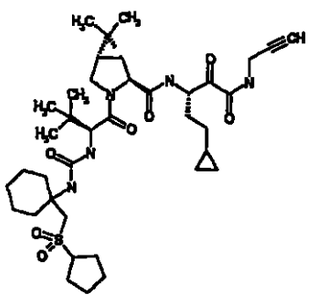
846		782.1041	782.4	A
847		782.1041	782.4	A

848		782.1041	782.4	B
849		782.1041	782.4	B

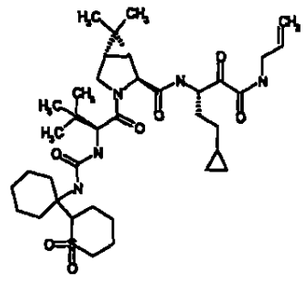
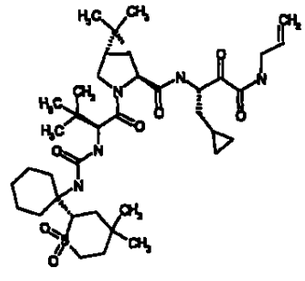
850		778.0727		A
851		752.0345		A

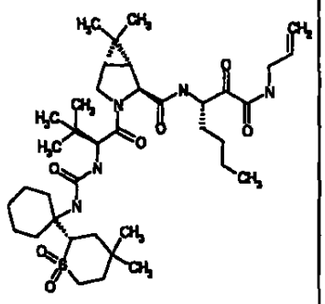
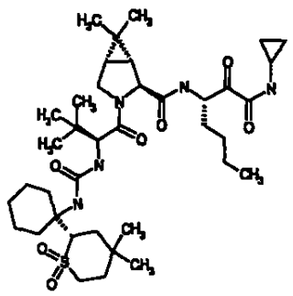
852		776.0568		A
853		764.0207		A

590

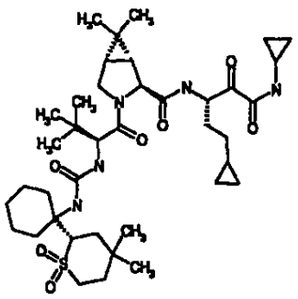
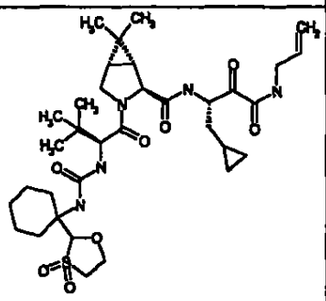
854		744.7849	744.4	A
855		729.9872	730.2	A

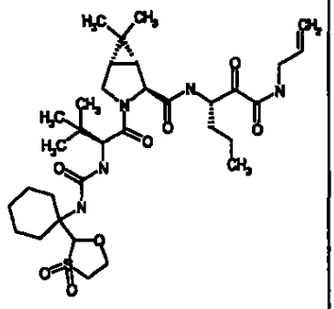
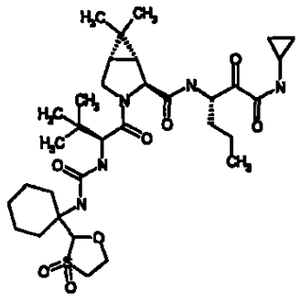
591

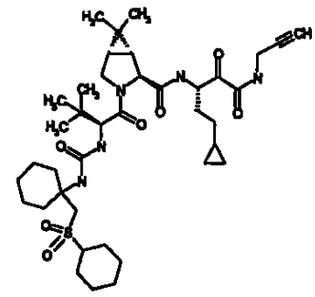
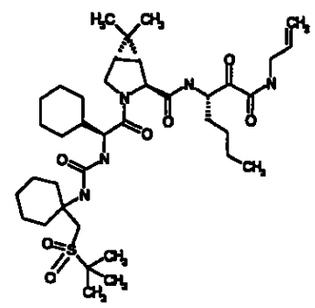
856		717.9761		5
857		732.0032	732.4	A

858		734.0191	734.4	A
859		734.0191	734.41	A

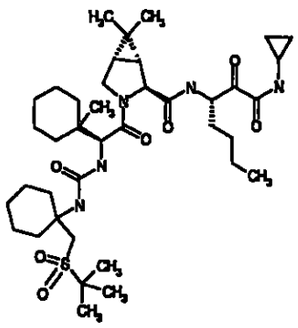
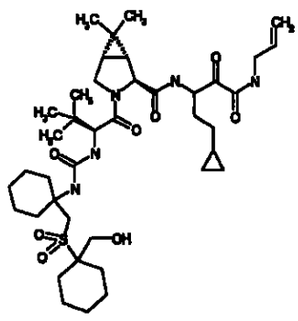
593

860		746.0303	746.5	A
861		691.8942	692.4	A

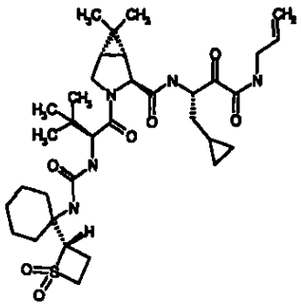
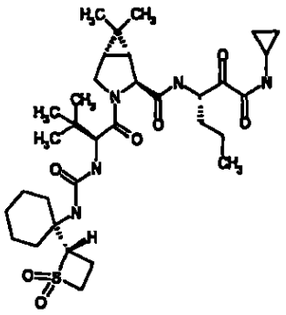
862		679.8831	680.38	A
863		679.8831	680.4	A

864		744.0143	744.1	A
865		734.0191	734.4	A

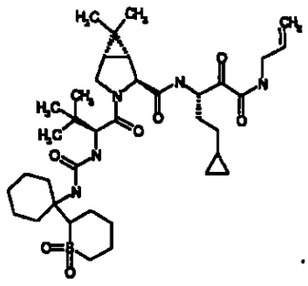
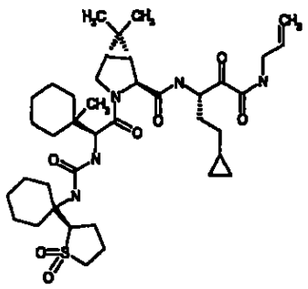
596

866		748.0462	748.4	A
867		776.0568		A

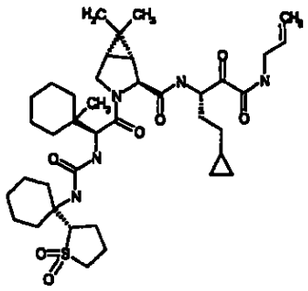
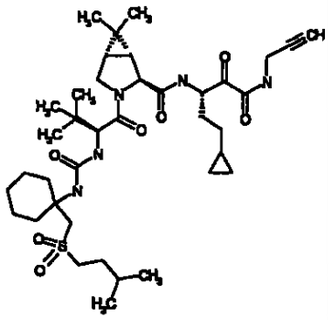
597

868		675.8948		A
869		663.8837		A

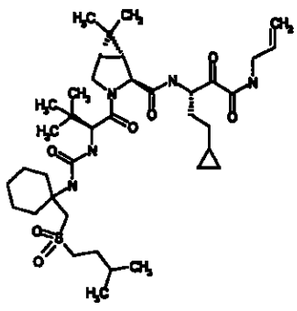
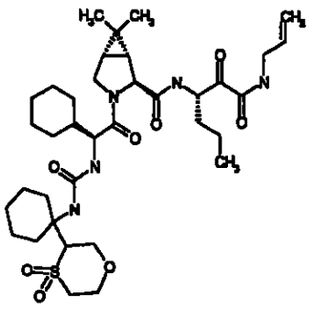
598

870		717.9761		A
871		744.0143		A

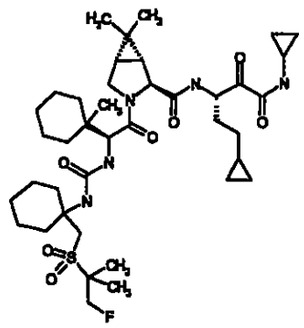
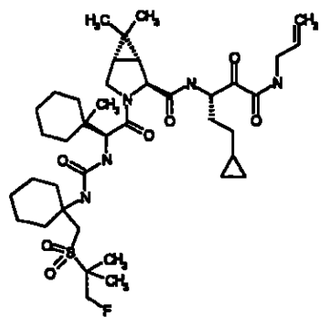
599

872		744.0143		A
873		732.0032	732.1	A

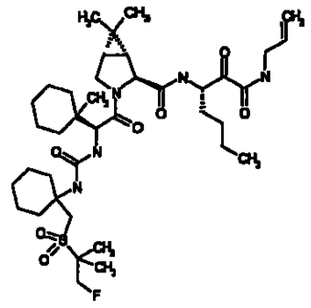
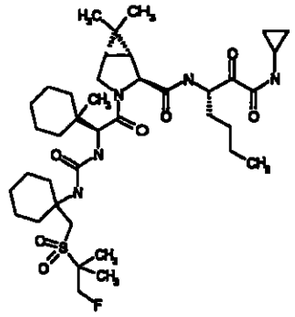
600

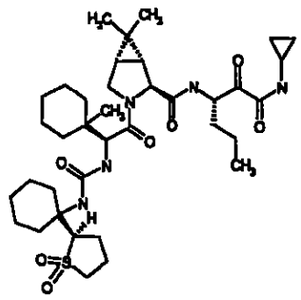
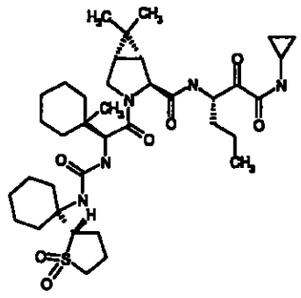
874		734.0191	734 1	A
875		719.9484		A

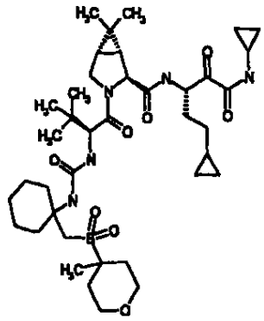
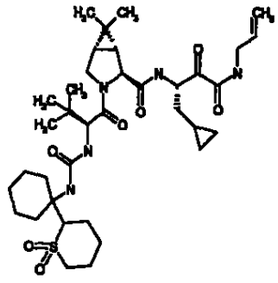
601

876		778.0478		A
877		778.0478		A

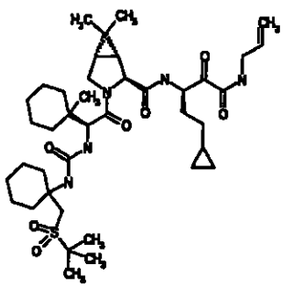
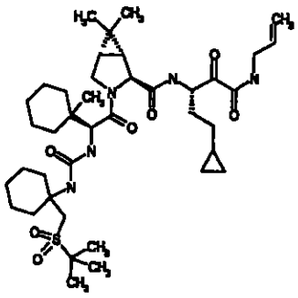
602

878		766.0366		A
879		766.0366		A

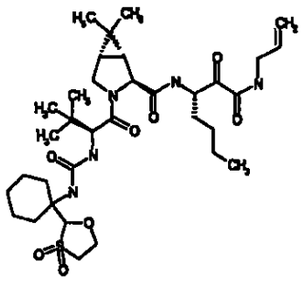
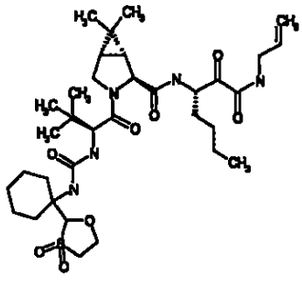
880		717.9761	718.1	A
881		717.9761	718.1	A

882		762.0297	762.1	A
883		703.949	704.1	A

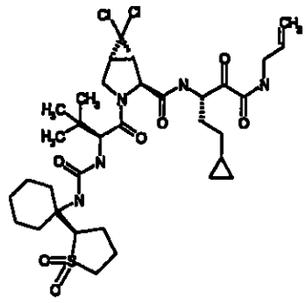
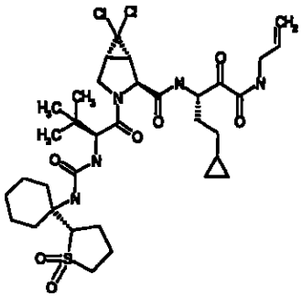
605

883-a		760.0574		B
883-b		760.0574		A

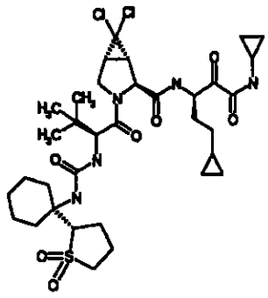
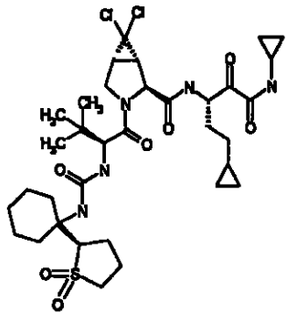
606

883-c		693.9102		3
883-d		693.9102		A

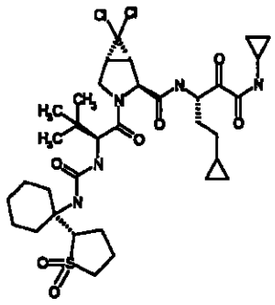
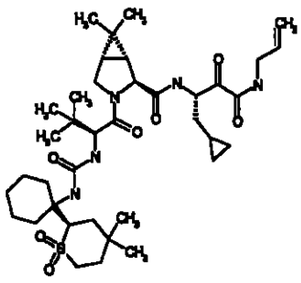
607

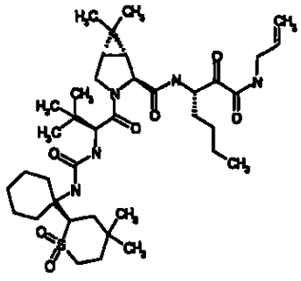
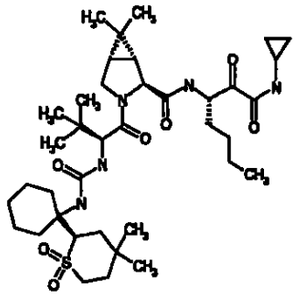
883-e		744.7849		A
883-f		744.7849		A

608

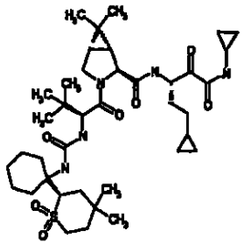
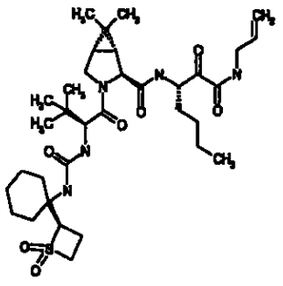
883-fa		744.7849		A
883-g		744.7849		A

609

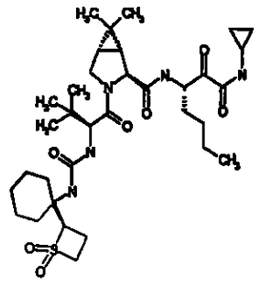
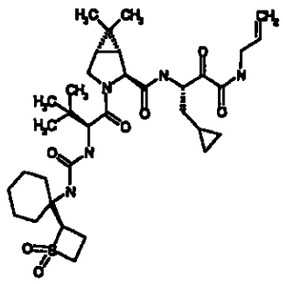
883-h		744.7849		A
883-l		732.0032		A

883-j		734.0191		A
883-k		734.0191		A

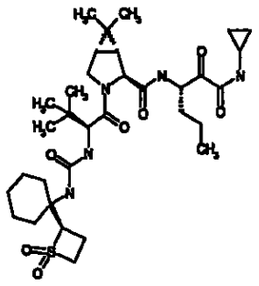
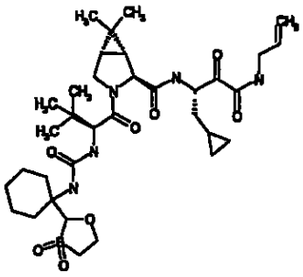
611

883-l		746.0303		A
883-m		677.9108		A

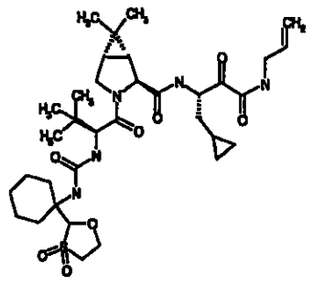
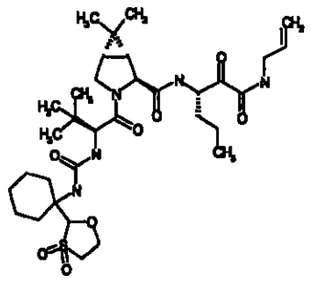
612

883-n		677.9108		A
883-o		675.8948		A

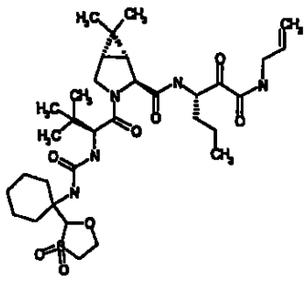
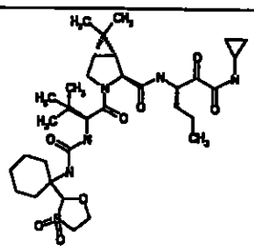
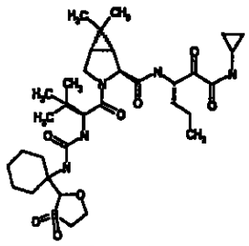
613

883-p		663.8837		A
883-q		691.8942		A

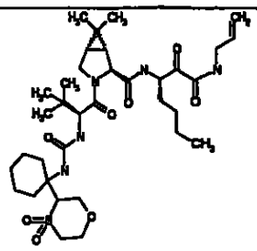
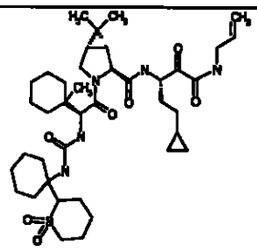
614

883-r		691.8942		A
883-s		679.8831		A

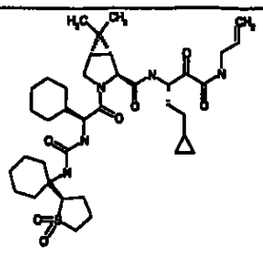
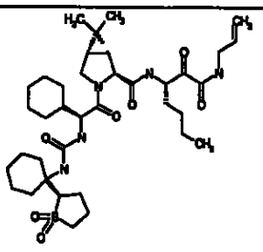
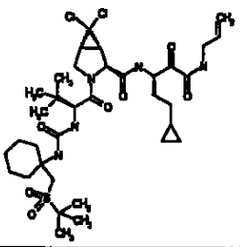
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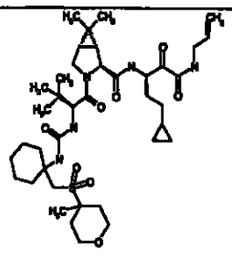
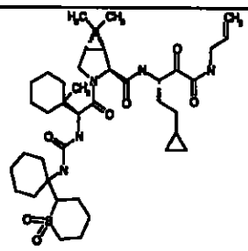
883-t		679.8831		A
883-u		679.8831		A
883-v		679.8831		A

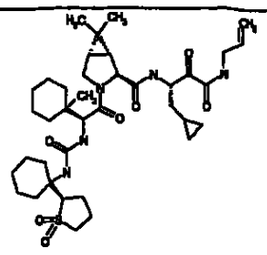
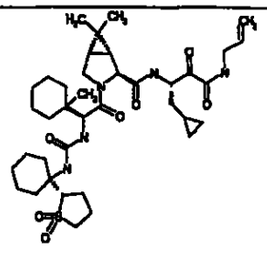
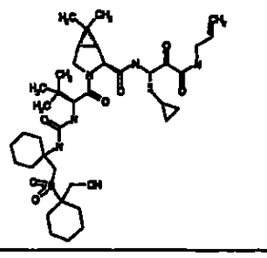
616

883-w		707.9372		3
883-x		758.0414		A

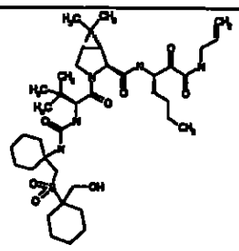
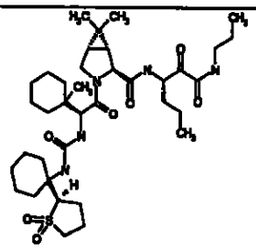
617

883-y		729.9872		A
883-z		717.9761		A
883-aa		760.8279		A

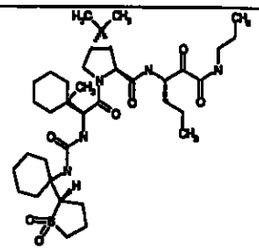
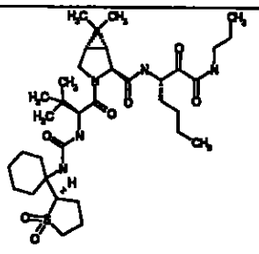
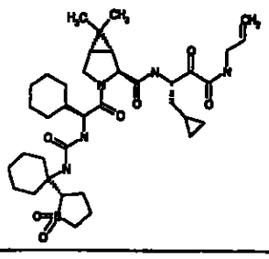
883-ab		762.0297		A
883-ac		758.0414		A

883-ad		729.9872		A
883-ae		729.9872		A
883-af		762.0297		A

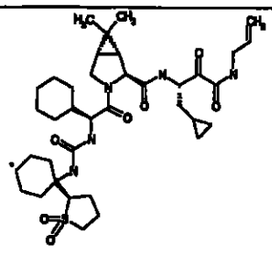
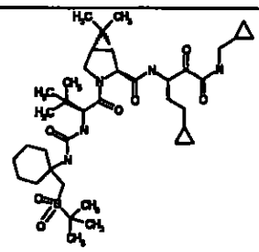
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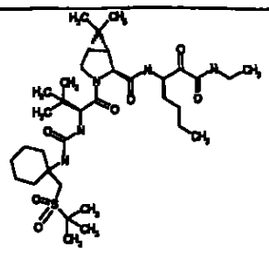
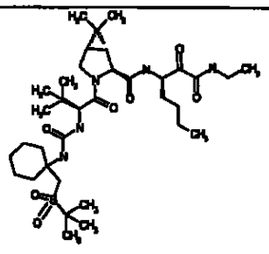
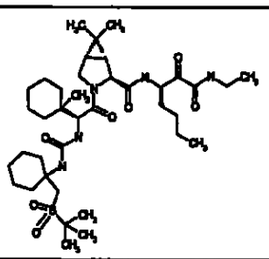
883-ag		764.0456		A
883-ah		719.992		A

621

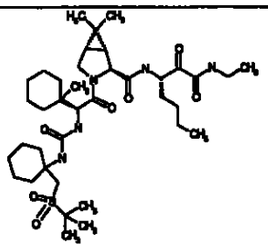
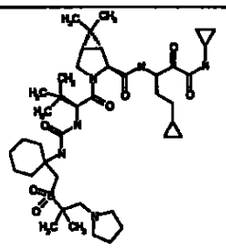
883-ai		719.9922		A
883-aj		693.9538		A
883-ak		715.9601		A

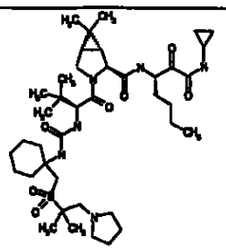
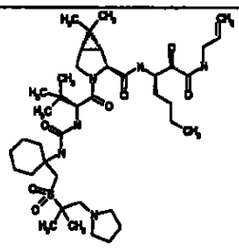
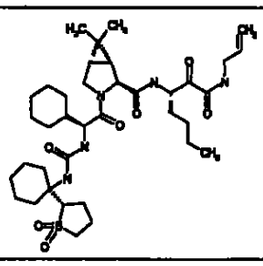
622

883-al		715.9601		A
883-am		734.0191		A

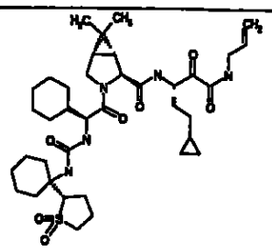
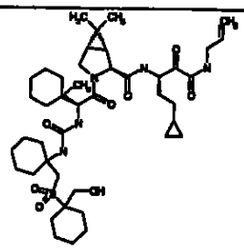
883-an		695.9697		C
883-ao		695.9697		A
883-ap		736.0351		B

624

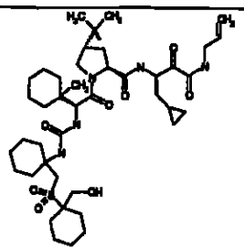
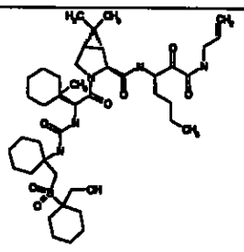
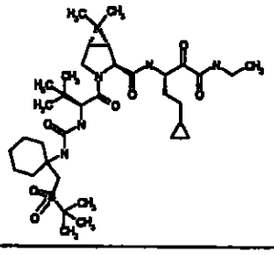
883-aq		736.0351		A
883-ar		789.0991		A

883-as		777.088		A
883-at		777.088		A
883-au		717.9761		A

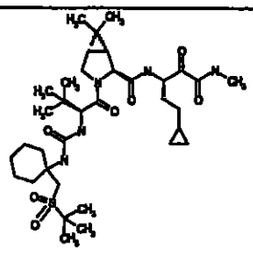
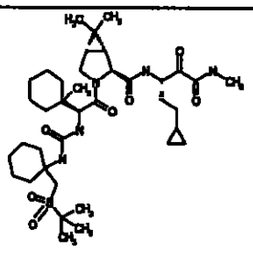
626

883-av		729.9872		A
883-aw		816.1221		A

627

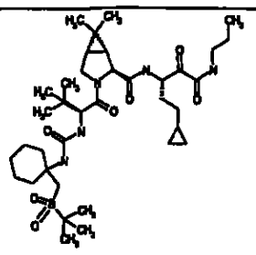
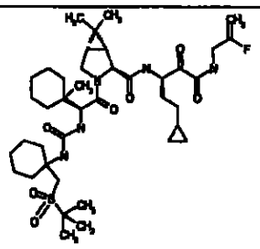
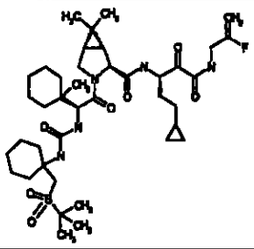
883-ax		802.095		A
883-ay		804.1109		A
883-az		707.9809		A

628

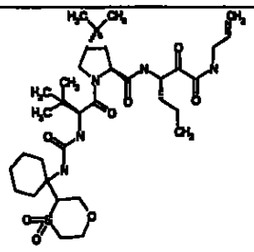
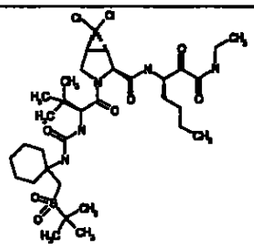
883-ba		693.9538		A
883-bb		734.0191		A

626

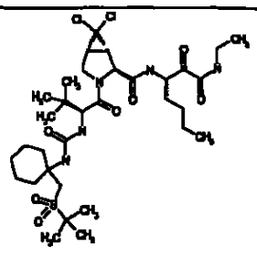
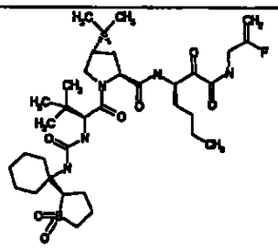
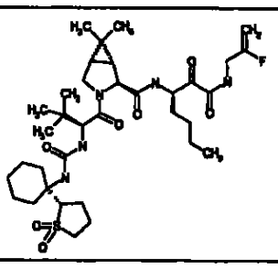
629

883-bc		722.008		A
883-bd		778.0478		b
883-be		778.0478		A

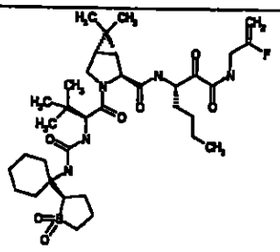
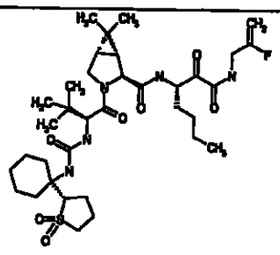
630

883-bf		693.9102		A
883-bg		736.8056		B

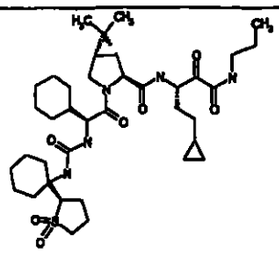
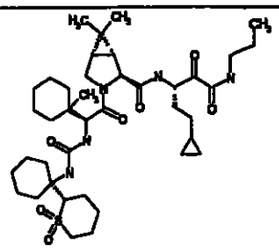
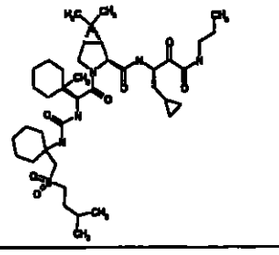
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883-bh		736.8056		A
883-bl		709.9283		B
883-bj		709.9283		B

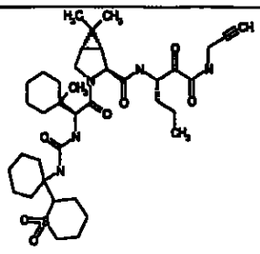
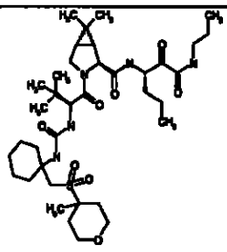
632

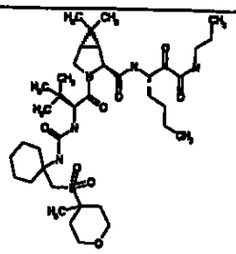
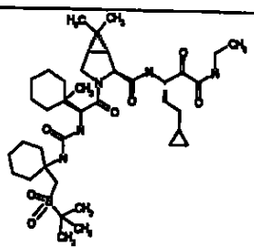
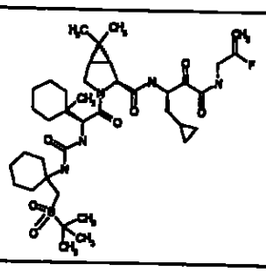
883-bk		709.9283		A
883-bl		709 9283		A

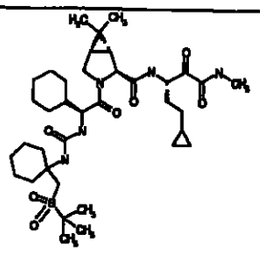
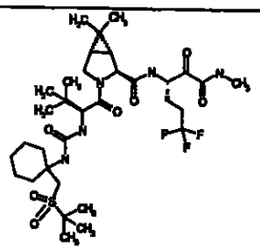
633

883-bm		732.0032		A
883-bn		760.0574		A
883-bo		762.0733		A

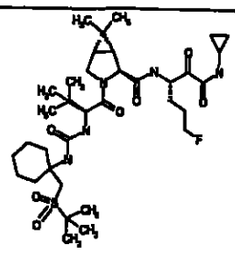
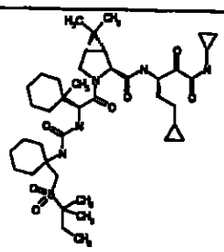
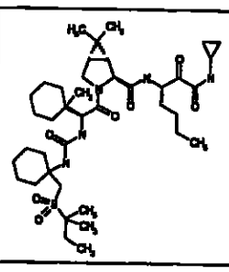
634

883-bp		729.9872		A
883-bq		738.0074		A

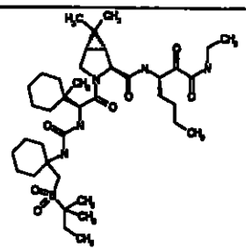
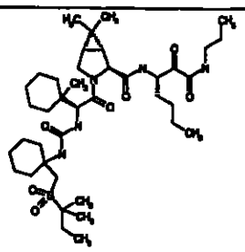
883-br		752.0345		A
883-bs		748.0462		A
883-bt		764.0207		A

883-bu		719.992		A
883-bv		721.8868		A

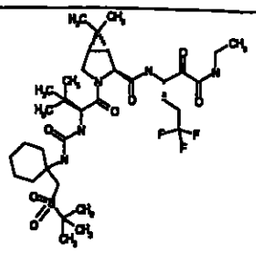
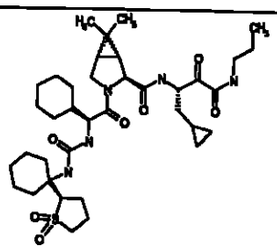
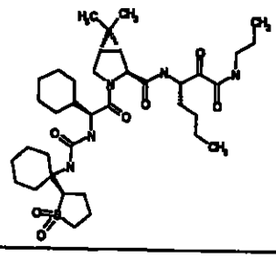
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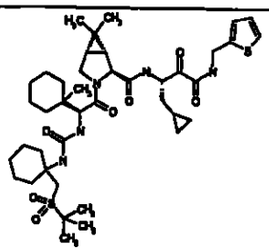
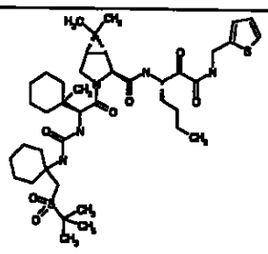
883-bw		711.9442		A
883-bx		774 0844		A
883-by		762.0733		A

638

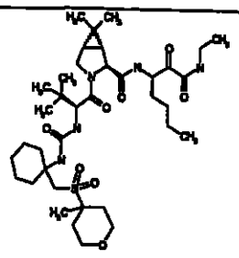
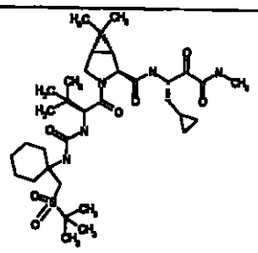
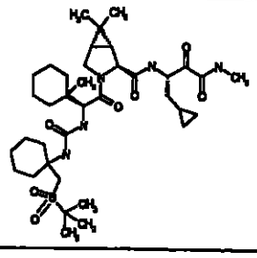
883-bz		750.0621		A
883-ca		764.0892		A

639

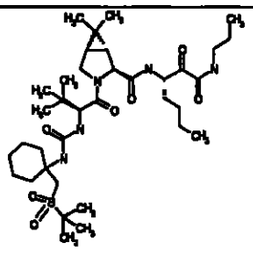
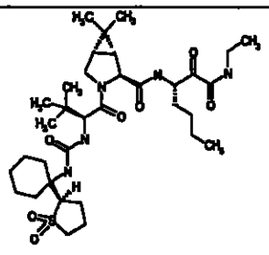
883-cb		735.9139		A
883-cc		717 9761		A
883-cd		719.992		A

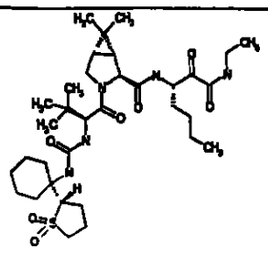
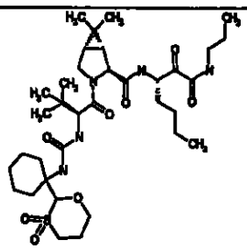
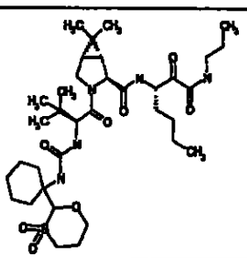
883-ce		802.1166		A
883-cf		804.1325		A

641

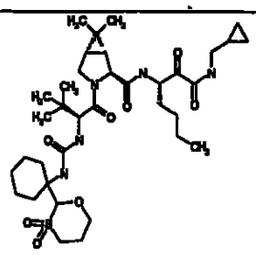
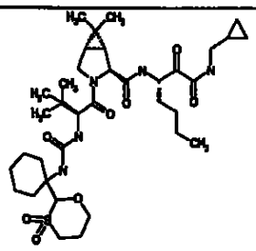
883-cg		738.0074		A
883-ch		679.9267		A
883-ci		719.992		A

642

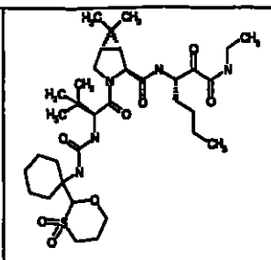
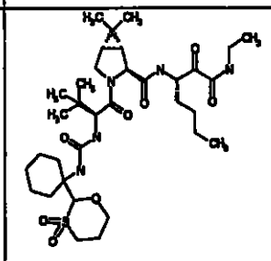
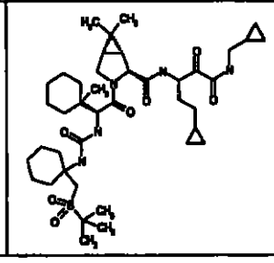
883-cj		709.9968		A
883-ck		679.9267		A

883-ci		679.9267		A
883-cm		709.9532		A
883-cn		709.9532		A

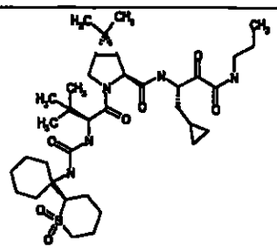
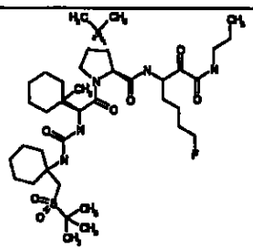
644

883-co		721.9643		A
883-cp		721.9643		A

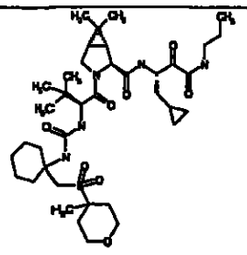
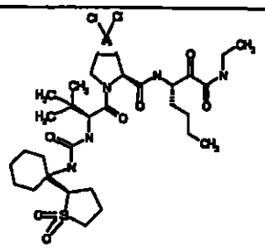
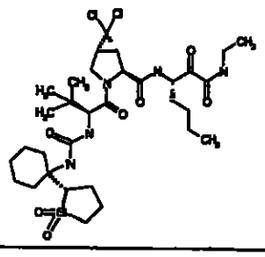
645

883-cq		695.9261		A
883-cr		695.9261		B
883-cs		774.0844		A

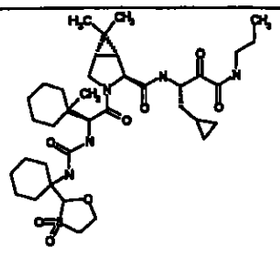
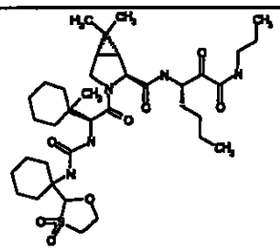
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883-ct		705.9649		A
883-cu		768.0526		A

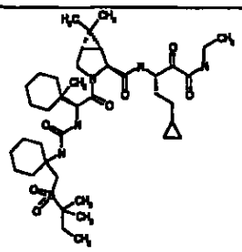
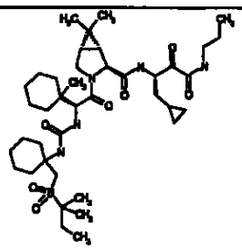
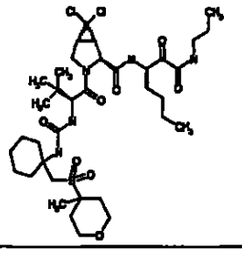
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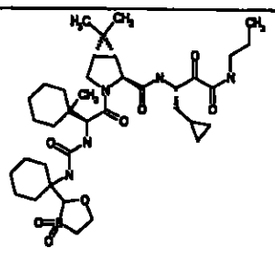
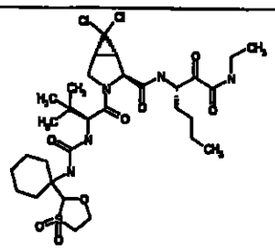
883-cv		750.0185		A
883-cw		720.7626		A
883-cx		720.7626		A

648

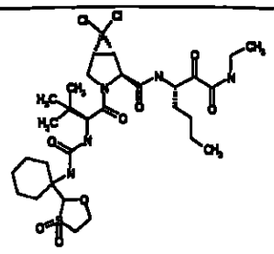
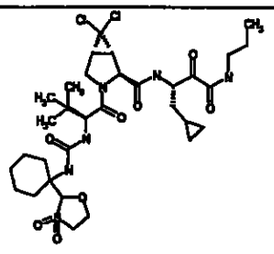
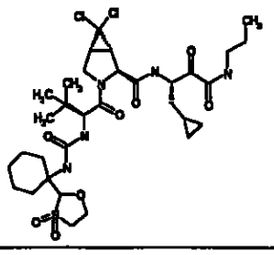
883-cy		733.9755		A
883-cz		735.9914		A

649

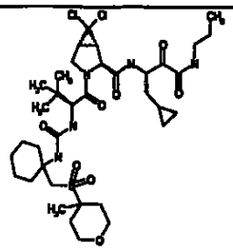
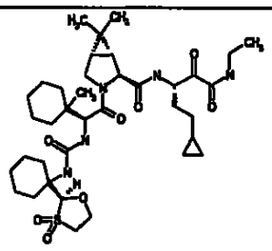
883-da		762.0733		A
883-db		762.0733		A
883-dc		792.8703		A

883-dd		733.9755		A
883-de		722.7349		A

651

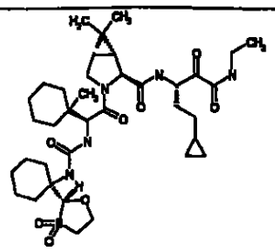
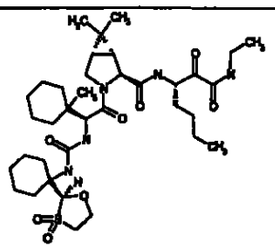
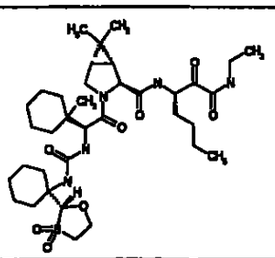
883-df		722.7349		A
883-dg		734.746		A
883-dh		734.746		A

652

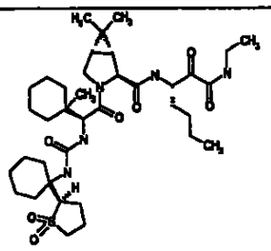
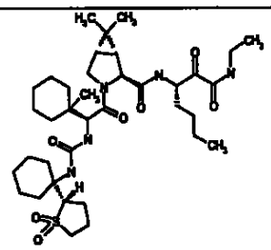
883-di		790.8544		A
883-dj		733.9755		A

68

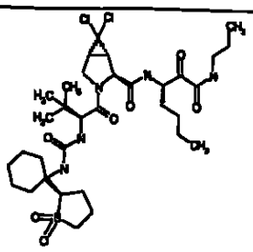
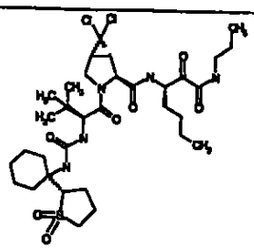
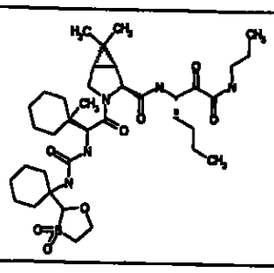
653

883-dk		733.9755		A
883-dl		721.9643		A
883-dm		721.9643		A

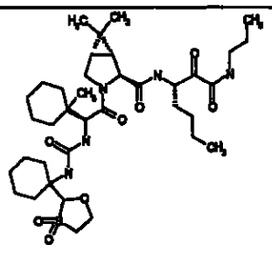
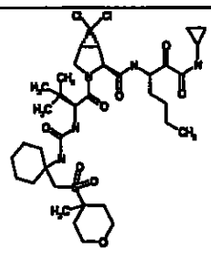
654

883-dn		719.992		A
883-do		719.992		A

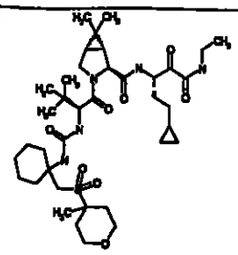
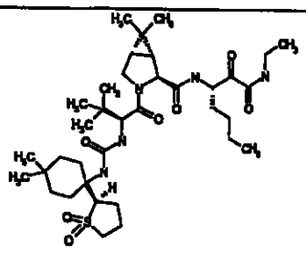
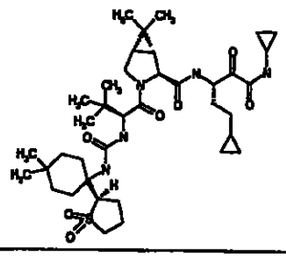
655

883-dp		734.7897		A
883-dq		734.7897		A
883-dr		735.9914		A

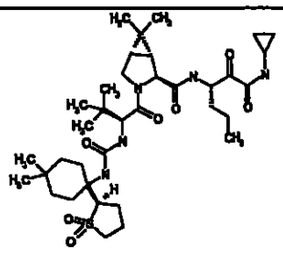
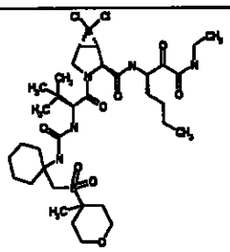
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883-ds		735.9914		A
883-dt		790.8544		A

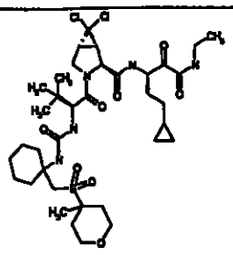
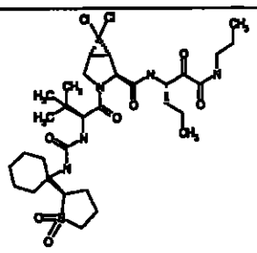
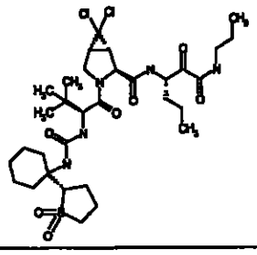
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883-du		750.0185		A
883-dv		707.9809		A
883-dw		732.0032		A

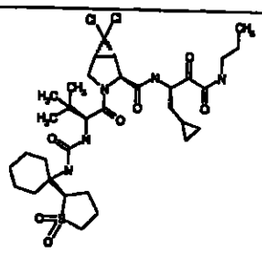
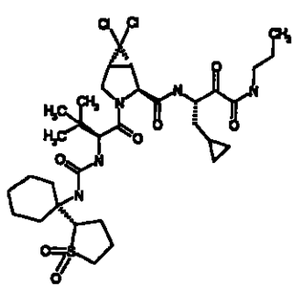
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883-dx		705.9649		A
883-dy		778.8432		A

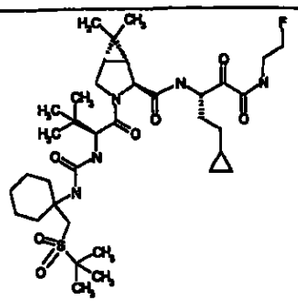
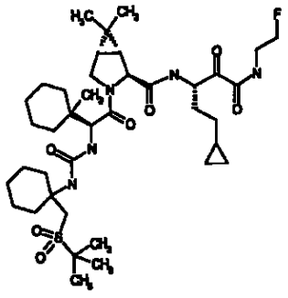
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883-dz		790.8544		A
883-ea		720.7626		A
883-eb		720.7626		A

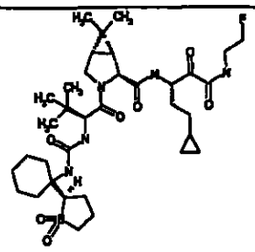
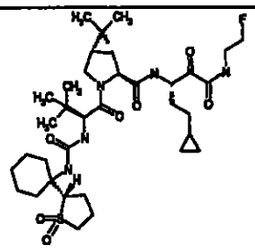
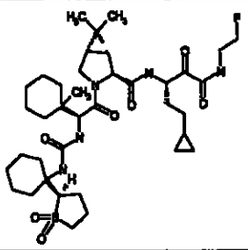
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883-ec		732.7737		A
883-ed		732.7737		A

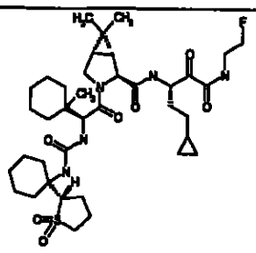
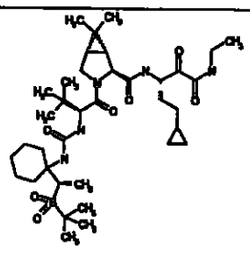
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883-ee		725.9713		A
883-ef		766.0366		A

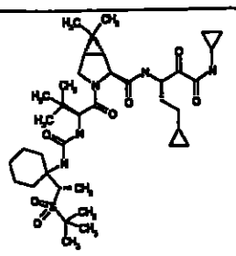
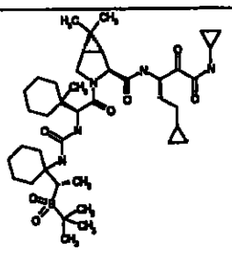
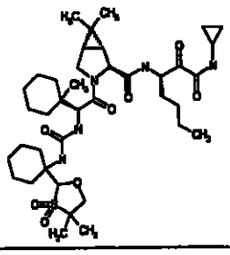
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883-eg		709.9283		A
883-eh		709.9283		A
883-ei		749.9936		A

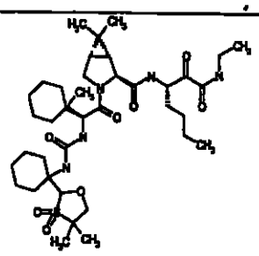
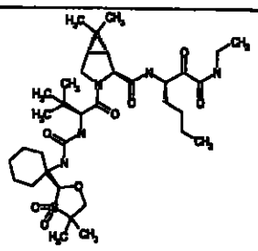
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883-ej		749.9936		A
883-ek		722.008		A

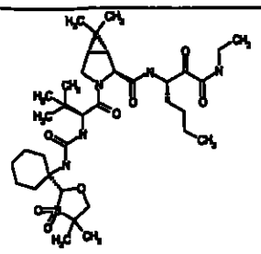
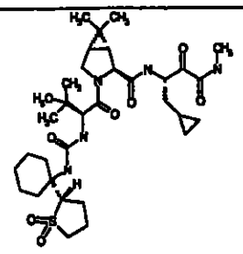
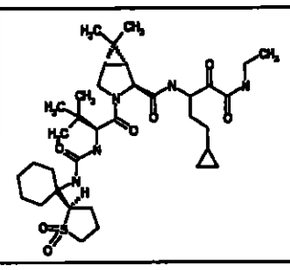
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883-el		734.0191		A
883-em		774.0844		A
883-en		762.0297		A

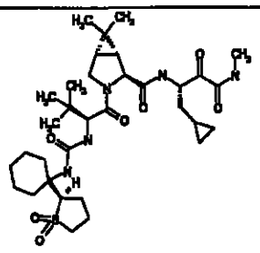
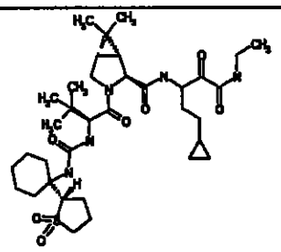
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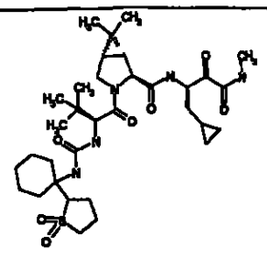
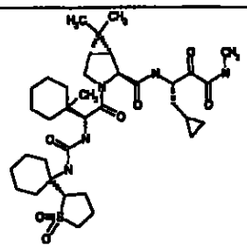
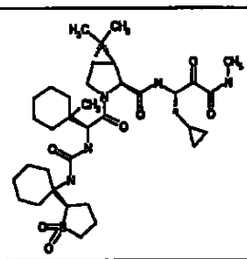
883-eo		750.0185		A
883-ep		709.9532		A

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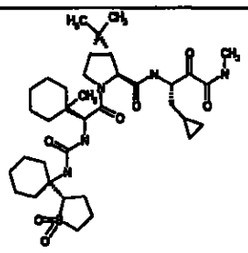
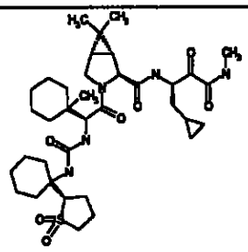
883-eq		709.9532		A
883-er		663.8837		A
883-es		691.9378		A

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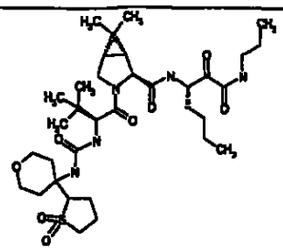
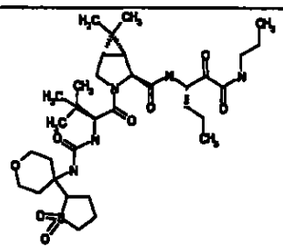
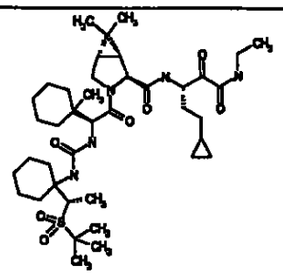
883-et		663.8837		A
883-eu		691.9378		A

883-ev		663.8837		A
883-ew		703.949		A
883-ex		703.949		A

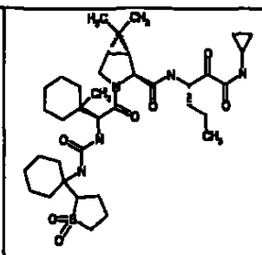
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883-ey		703.949		A
883-ez		703.949		A

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883-fa		695.9261		B
883-fb		681.899		A
883-fc		762.0733		A

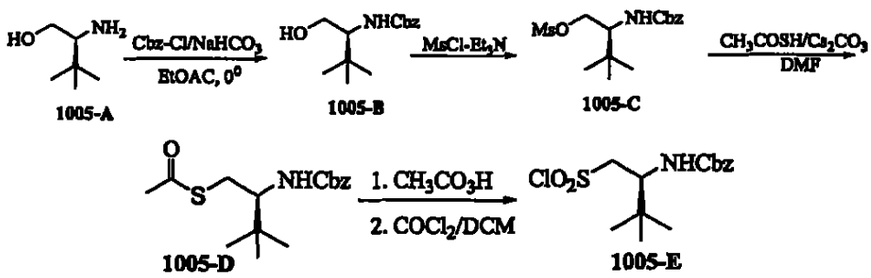
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883-fd		717.9761		A

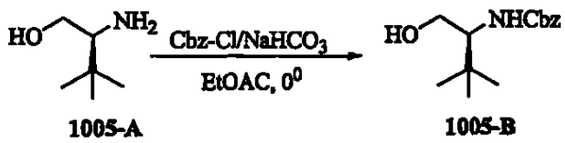
Also disclosed are the following compounds in **Table 4** and **Table 4A.**

The preparation of the compounds in **Table 4** and **Table 4A** is described below:

EXAMPLE 1005:



STEP 1



To a solution of 5g of **1005-A** (commercially available from Aldrich) in 100 ml of EtOAc at 0^0C were added 40 ml of saturated $NaHCO_3$ solution followed by 6.5 ml of Cbz-Cl in one portion. The resulting mixture was stirred for 2h and layers were separated. The aqueous layer was back extracted with

50 ml of EtOAc. The combined organic layer was washed once with brine, dried over $MgSO_4$ and concentrated to a colorless liquid which solidified on standing. 10.7g of **1005-B** as white solids were obtained.

MS: 274 $[M+Na]^+$.

STEP 2



1005-B **1005-C**

To a solution of 10.7g of **1005-B** in 120 ml of DCM at 0^0C were added 7.04 ml of triethylamine and 4.05 ml of methanesulfonyl chloride. The mixture was stirred at 0^0C for 10 minutes and 1.5h at room temperature. The mixture was washed with 1M $KHSO_4$ solution, water, brine and dried over $MgSO_4$. Concentration of solvent gave the crude product which was purified on silica gel column eluted with DCM. 13g of **1005-C** were obtained as colorless thick oil. MS: 352 $[M+Na]^+$.

STEP 3



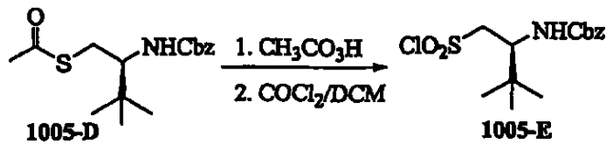
1005-C **1005-D**

To a suspension of 8.3g of Cs_2CO_3 in 100 ml of anhydrous DMF were added 3.3 ml of thioacetic acid. To the dark brown slurry was added a solution of 12.97g of **1005-C** in 30 ml of anhydrous DMF. The resulting mixture was stirred overnight at room temperature, diluted with 300 ml of ice-water and extracted with 2x250 ml of EtOAc. The combined organic layer was washed with water, brine and dried over $MgSO_4$. Evaporation of solvent gave ~10g of the crude product which was purified over silica gel column with 10% EtOAc in hexane. 4.8g of **1005-D** as white solids were obtained. MS: 310 $[M+H]^+$,

673

332 $[M+Na]^+$.

STEP 4



1005-D 1005-E

To a solution of 4.4g of **1005-D** in 15 ml of AcOH was added a solution of 15 ml of 30% H_2O_2 and 30 ml of AcOH. The resulting solution was stirred at room temperature for 20 h. 75 mg of 10% Pd/C were added and the mixture was stirred for 1h, filtered through a celite pad and rinsed with MeOH. The combined filtrate was concentrated and co-evaporated with 3x100 ml of toluene to give solids. 90 ml of anhydrous DCM were added to dissolve solids and to the solution was added 15 ml of 20% phosgene in toluene (Fluka) followed by 1.8 ml of anhydrous DMF. Gas evolved and the mixture was stirred at room temperature for 2 h and concentrated to yield solid residue. Purification on silica gel eluted with DCM gave 3.94 g of **1005-E** as solids. MS: 356, 358 $[M+Na]^+$.



1005-E 1005-F 1005-G 1005-J

STEP 5

A mixture of 900 mg of **1005-E**, 1.0 ml of t-Butylamine and 0.4 ml of NMM in 40 ml of DCM was stirred at room temperature for 0.5 h, washed with 1M KHSO4 solution, brine and dried over $MgSO_4$. Evaporation of solvent gave 445 mg of the crude product which was purified on silica gel with DCM and 5% EtOAc in DCM. 617 mg of **1005-F** were obtained. MS: 379 $[M+Na]^+$.

STEP 6

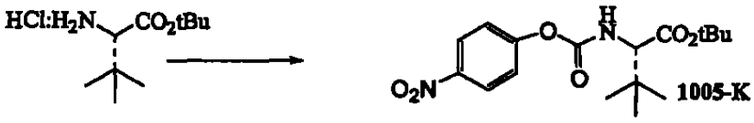
A mixture of 600 mg of **1005-F**, 2.64 g of cesium carbonate and 0.5 ml methyl iodide in 10 ml of anhydrous DMF was stirred at room temperature

674

overnight, diluted with 50 ml of ice-cold water and extracted with 2x50 ml EtOAc. The combined organic solution was washed twice with water, once with brine, dried over MgSO4. Removal of solvent under vacuum gave 620 mg of **1005-G** as white solids. MS: 385 $[M+H]^+$.

STEP 7

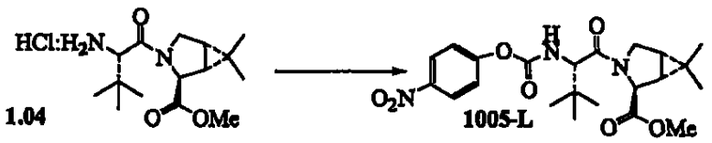
A solution of **1005-G** (600 mg) and $Pd(OH)_2$ (70mg) in MeOH was placed under an atmosphere of hydrogen overnight. The solids were filtered and washed thoroughly with MeOH. The volatiles were removed under reduced pressure to give the amine (**1005-J**; 380mg). MS: 251 $[M+H]^+$.



STEP 8

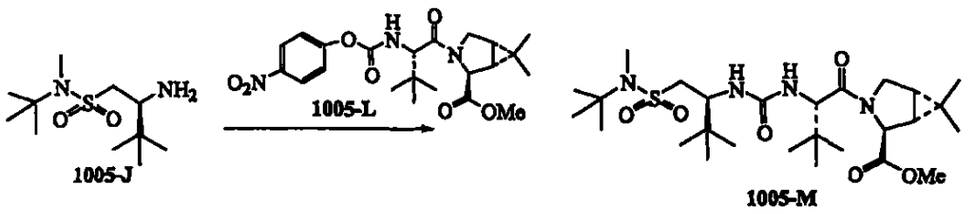
To a solution of the of the hydrochloride salt (Bachem; 2.24g) in dichloromethane (50ml) was added NMM (2.6ml) followed by the p-nitrophenyl chloroformate (2.42g) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was washed with cold aq. 1N HCl, sat aq. sodium bicarbonate, dried and the volatiles were removed under reduced pressure. The crude reaction product by silica gel chromatography using EtOAc:hexanes (1:10) as eluent to give the carbamate (**1005-K**; 2.97g).

STEP 9



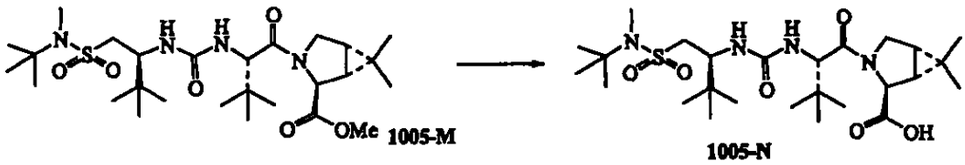
Using the procedure set forth in **STEP 8** the carbamate **1005-L** was prepared from the amine-hydrochloride salt **1.04**.

STEP 10



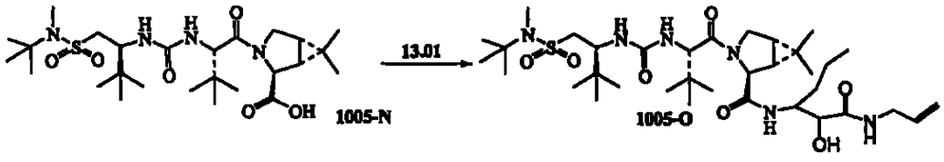
NMM (0.12ml) was added to a mixture of the amine (**1005-J**; 0.20g) and the carbamate (**1005-L**; 0.375g) in acetonitrile (15ml) and the resulting mixture was stirred at room temperature, under an atmosphere of nitrogen, overnight. The volatiles were removed under reduced pressure and the residue was partitioned between EtOAc and water. The organic phase was separated, dried and concentrated. The crude reaction product was purified by silica gel column chromatography using EtOAc: Hexanes (2:3) as eluent, providing the desired urea (**1005-M**; 0.43g). MS: 559.28 $[M+H]^+$.

STEP 11



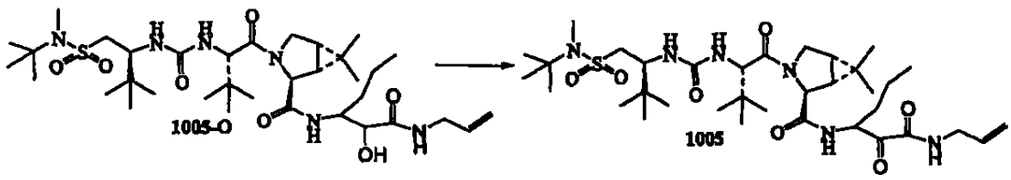
Lithium hydroxide (0.020g) in water (2ml) was added to a solution of the methyl ester (1005-M; 0.41g) in dioxane (15ml) and the resulting mixture was stirred at room temperature overnight. Aqueous HCl (0.01N) was added and the organics were extracted into EtOAc. The organic phase was separated, dried and concentrated to yield the carboxylic acid (**1005-N**; 0.395g). MS: 545.32 $[M+H]^+$.

STEP 12



Hunigs base (0.050ml) was added to a mixture of the carboxylic acid (**1005-N**; 0.030g) and the hydrochloride salt (**13.01**; 0.015g) in dichloromethane (5ml) at -20C, under an atmosphere of nitrogen. The reaction was maintained at this temperature for a period of 20h. Aqueous work-up gave a crude reaction product (**1005-O**) which was used in **STEP12**, below.

STEP 13

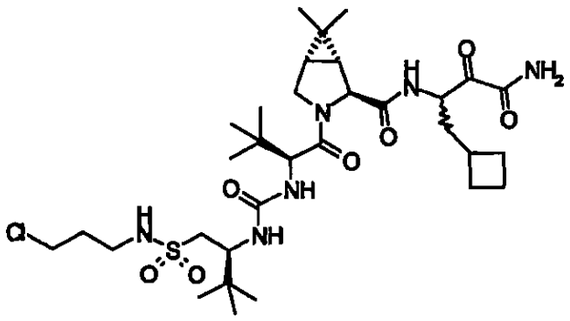
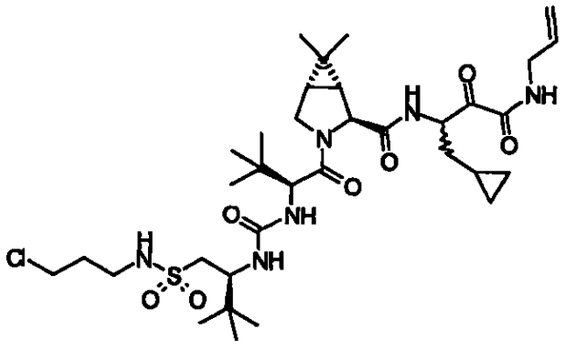
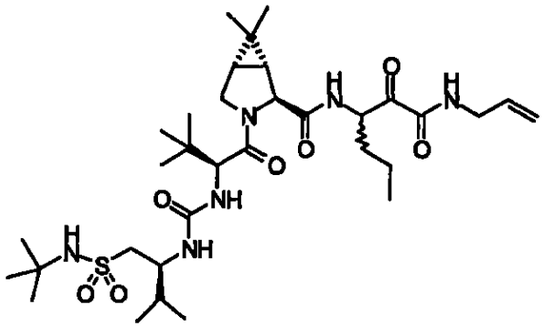


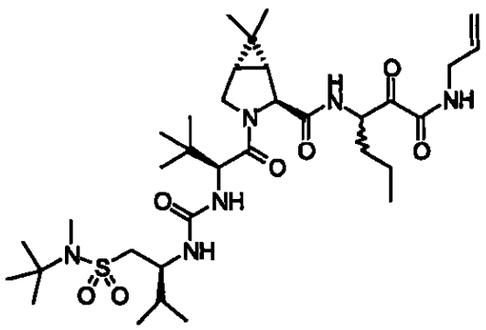
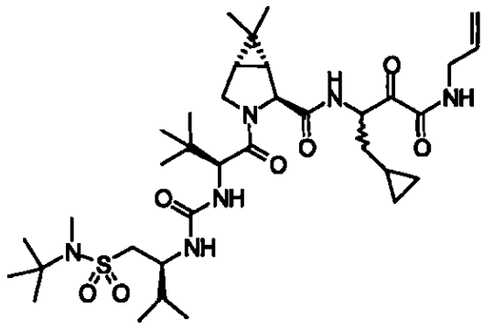
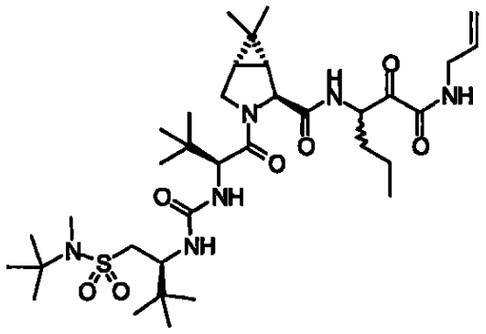
To crude (**1005-O**; above in **STEP 11**) in dichloromethane (3ml) was added Dess-Martin periodinane (0.050g) and the resulting mixture was stirred at room temperature for a period of 24h. Aqueous work-up and silica gel plate chromatography using dichloromethane:methanol (20:1) as eluent gave the desired α-keto-amide (0.0282g), as a white solid. Ki* ranges are: A = <75 nM; B = 75 - 250 nM; C = >250 nM.

Table 4

Prep. Ex.	COMPOUND	FABMS: MH+	Ki* range

677

1000		703.7	A
1001		729.7	B
1002		683.3	C

1003		697.3	A
1004		709.3	A
1005		711.3	B

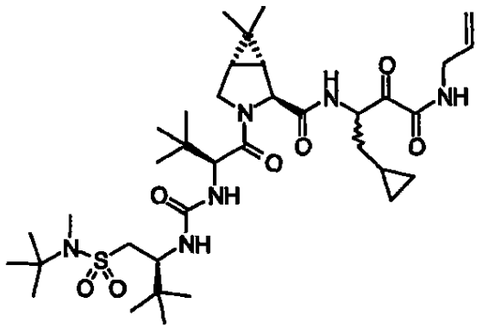
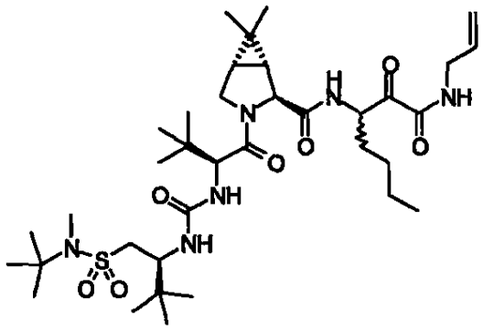
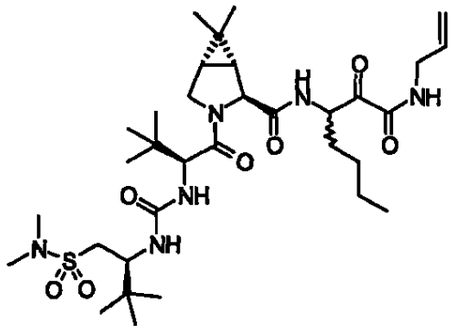
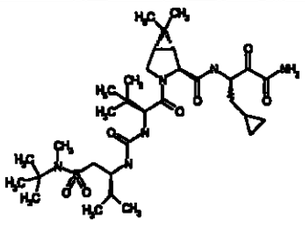
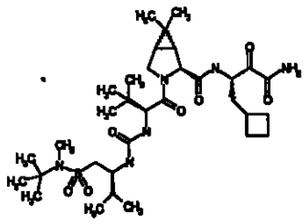
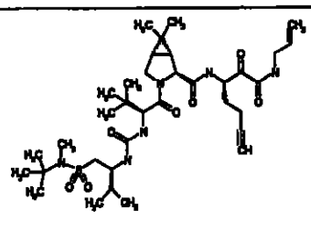
1006		723.3	B
1007		725.3	B
1008		683.3	B

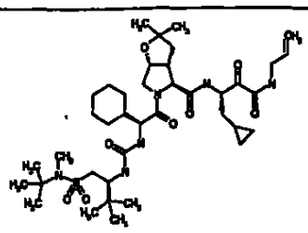
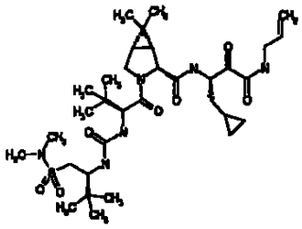
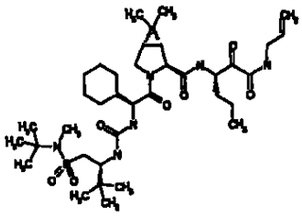
Table 4A lists still additional compounds representing the present invention:

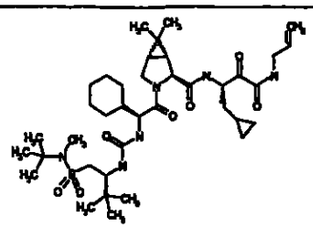
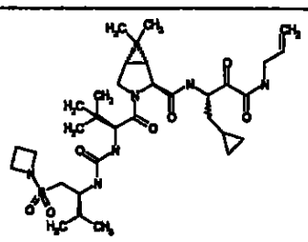
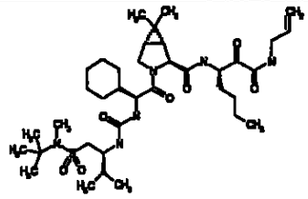
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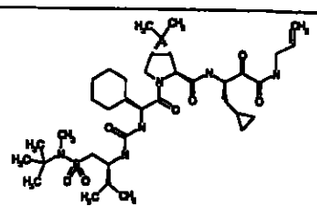
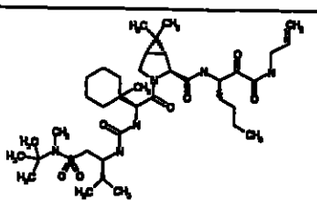
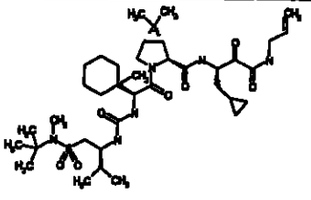
Table 4A

Prep. Ex.	Compound	Select Mass Spectra Data	Ki* Range
1100			A
1101			A
1102			A

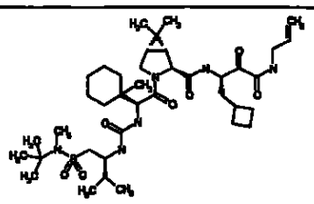
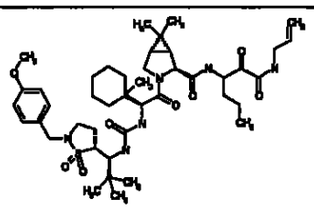
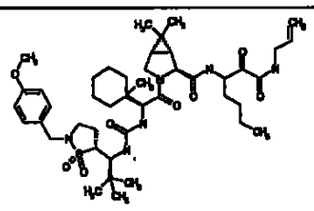
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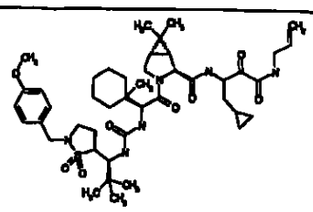
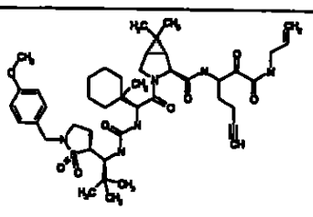
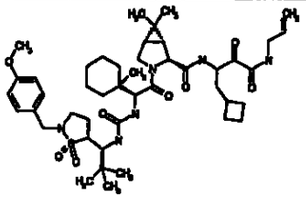
1103			B
1104			B
1105			B

1106			B
1107			A
1108			A

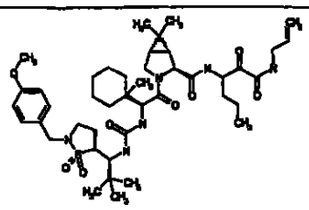
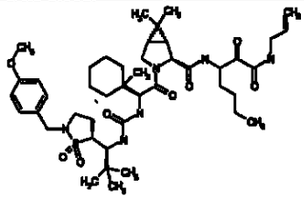
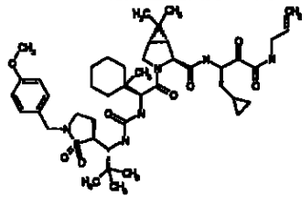
1109			B
1110			A
1111			C

684

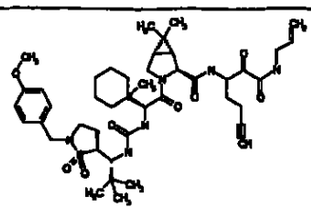
1112			A
1113			C
1114			C

1115			C
1116			C
1117			C

686

1118			C
1119			C
1120			

687

1121			C

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 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. Sali *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

690

that wavelength yielding the maximum fractional difference in absorbance between substrate and product (product OD - substrate OD)/substrate OD).

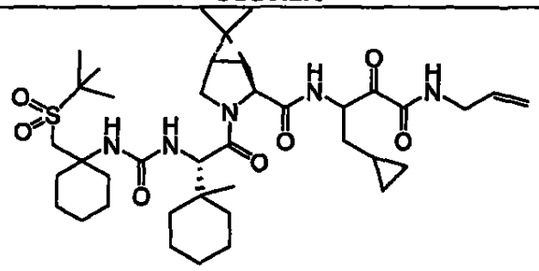
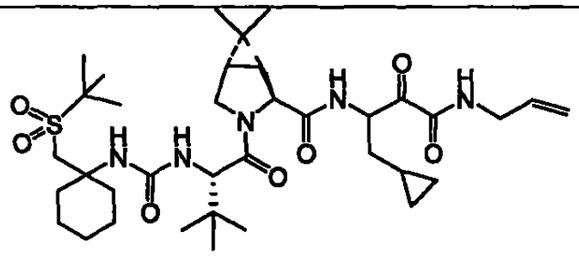
Protease Assay: HCV protease assays are performed at 30°C using a 200 µl reaction mix in a 96-well microtiter plate. Assay buffer conditions (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 µM EDTA and 5 µM DTT) are optimized for the NS3/NS4A heterodimer (D. L. Sali *et al, ibid.*)). 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

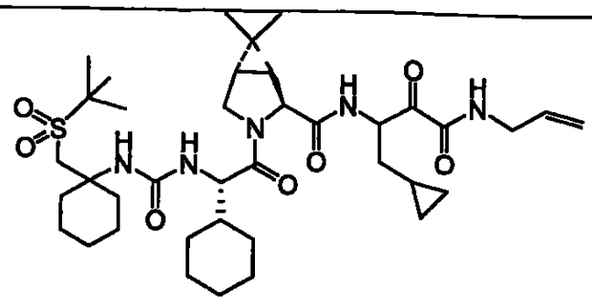
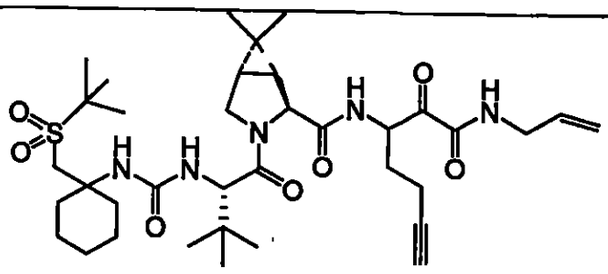
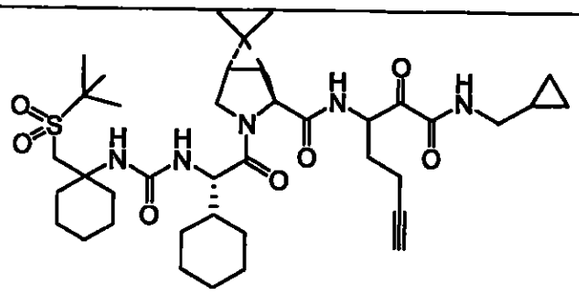
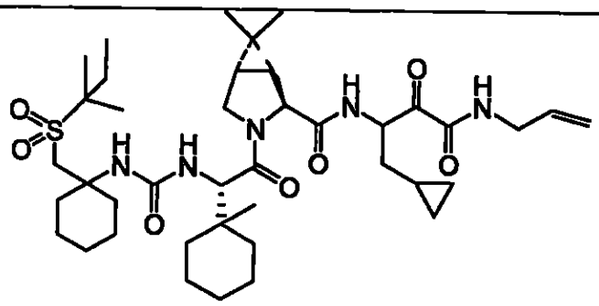
691

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 following **Table 5** lists the obtained Ki* values (in nanoMolar) for some of the inventive compounds. Several others are noted in the **Tables** on earlier pages.

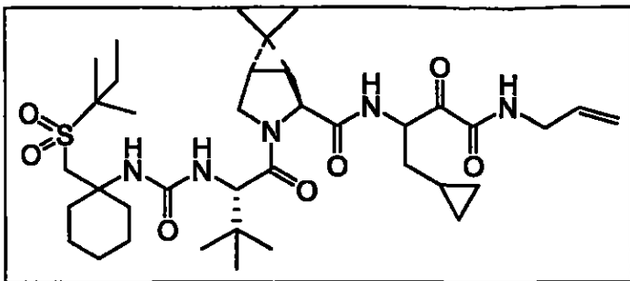
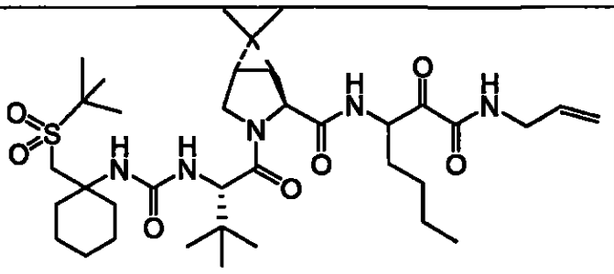
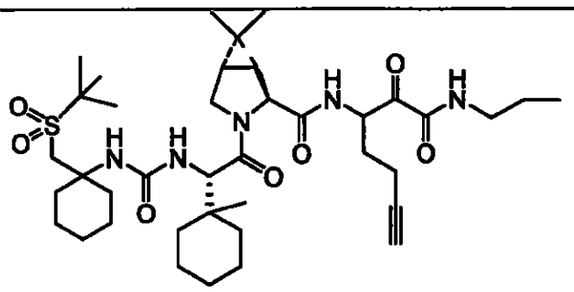
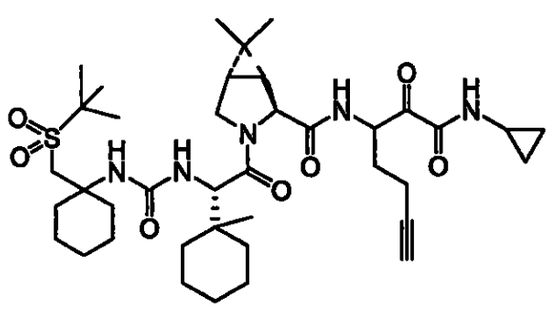
Table 5

Structure	Ki* (nM)
	10
	14

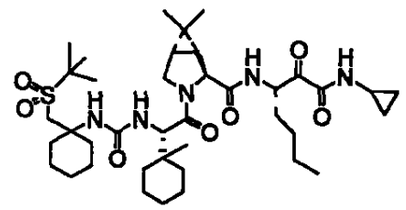
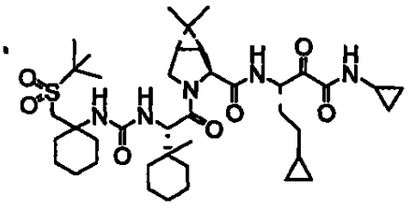
692

	4.1
	2
	19
	9

693

	14
	11
	4
	6

694

	5
	3

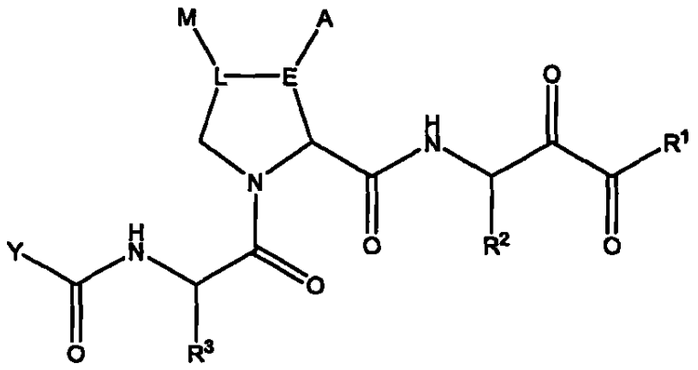
While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

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CLAIMS

What is claimed is:

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



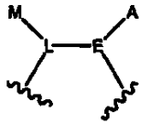
Formula I

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:



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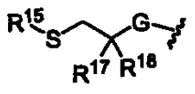
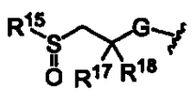
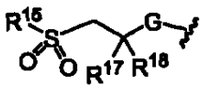
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

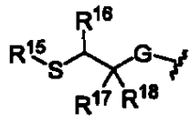
E is C(H) or C(R);

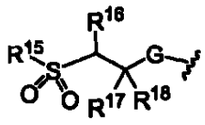
L is C(H), C(R), $CH_2C(R)$, or $C(R)CH_2$;

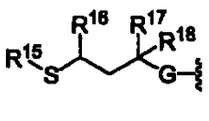
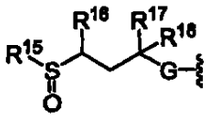
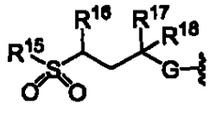
R, R', R^2, and R^3 can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately R and R' in NRR' are connected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

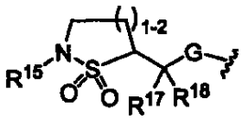
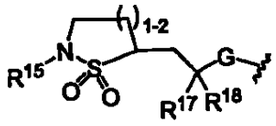
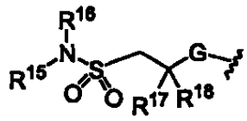
and Y is selected from the following moieties:


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and


wherein G is NH or O; and R^{15}, R^{16}, R^{17} and R^{18} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl,

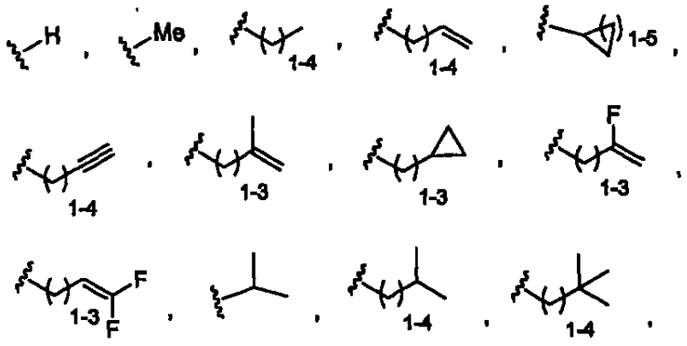
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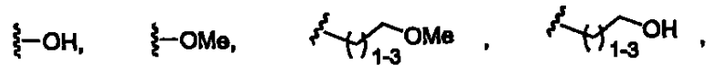
heterocyclyl, aryl, and heteroaryl, or alternately, (i) R^{15} and R^{16} are connected to each other to form a four to eight-membered cyclic structure, and (ii) likewise, independently R^{17} and R^{18} are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl;

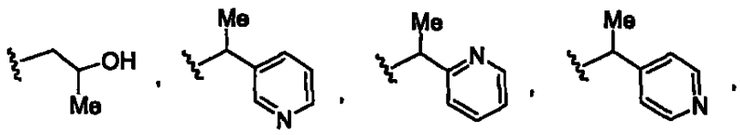
wherein each of said alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties selected from the group consisting of: hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, amido, alkylamino, arylamino, alkylsulfonyl,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

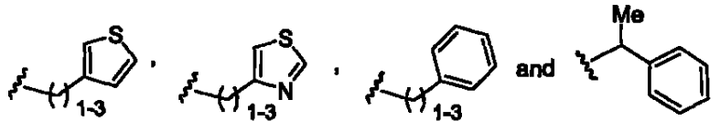
3. The compound of claim 2, wherein R^{14} is selected from the group consisting of:



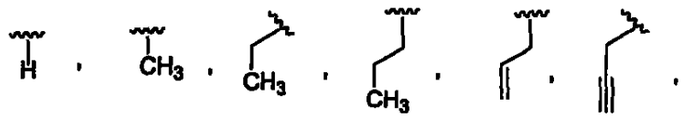


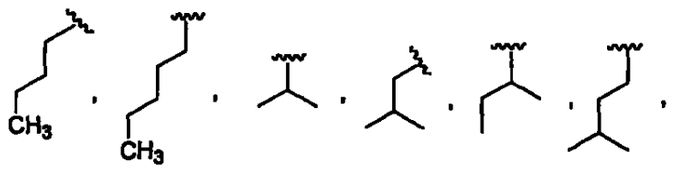


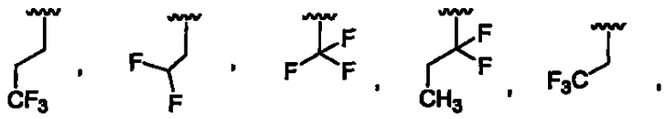


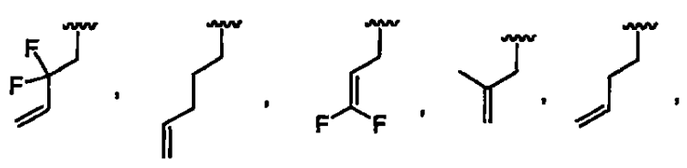


4. The compound of claim 1, wherein R^2 is selected from the group consisting of the following moieties:

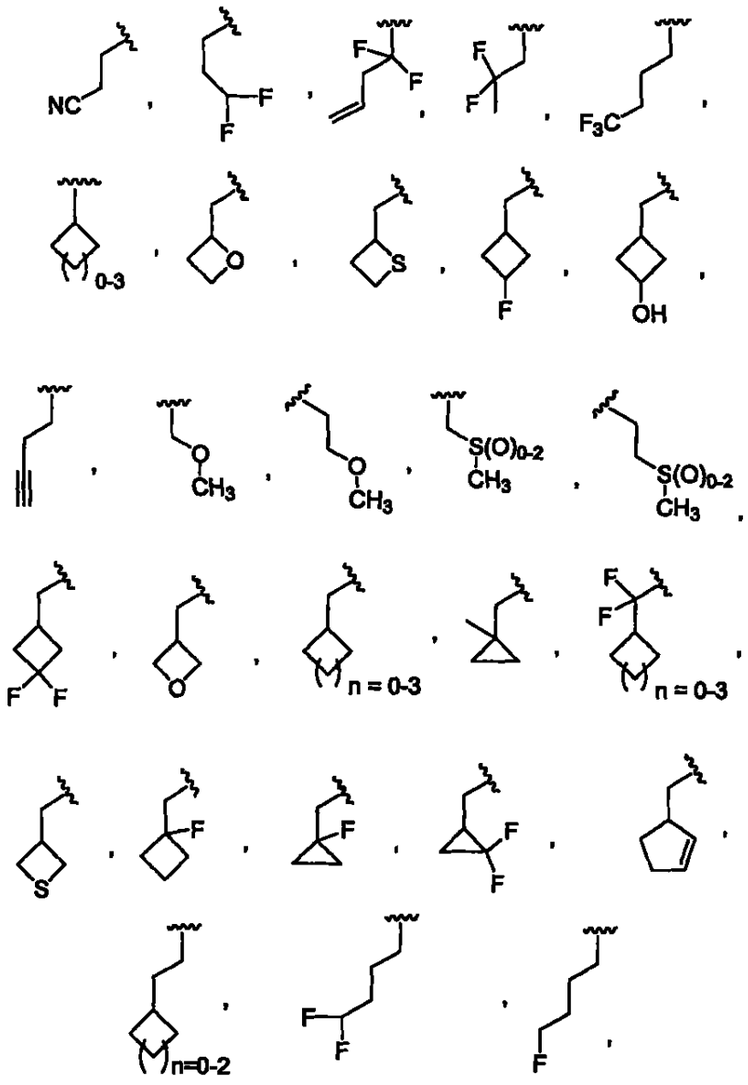




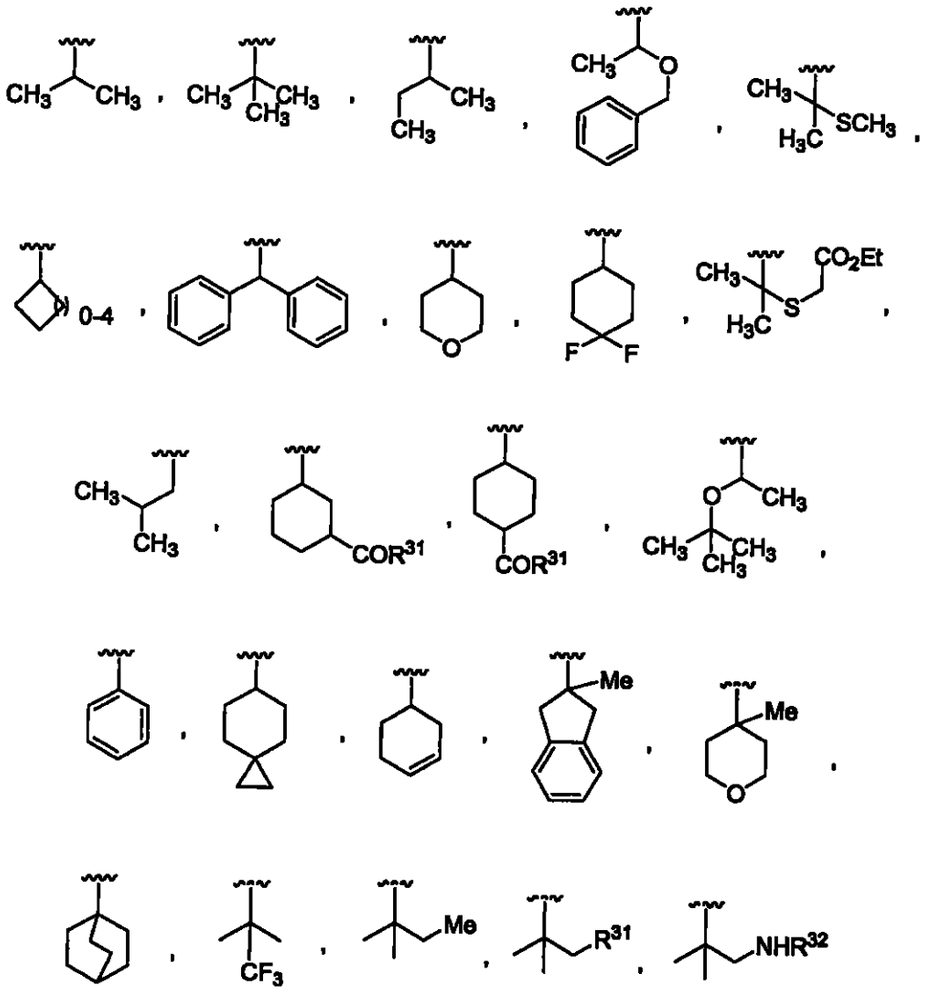


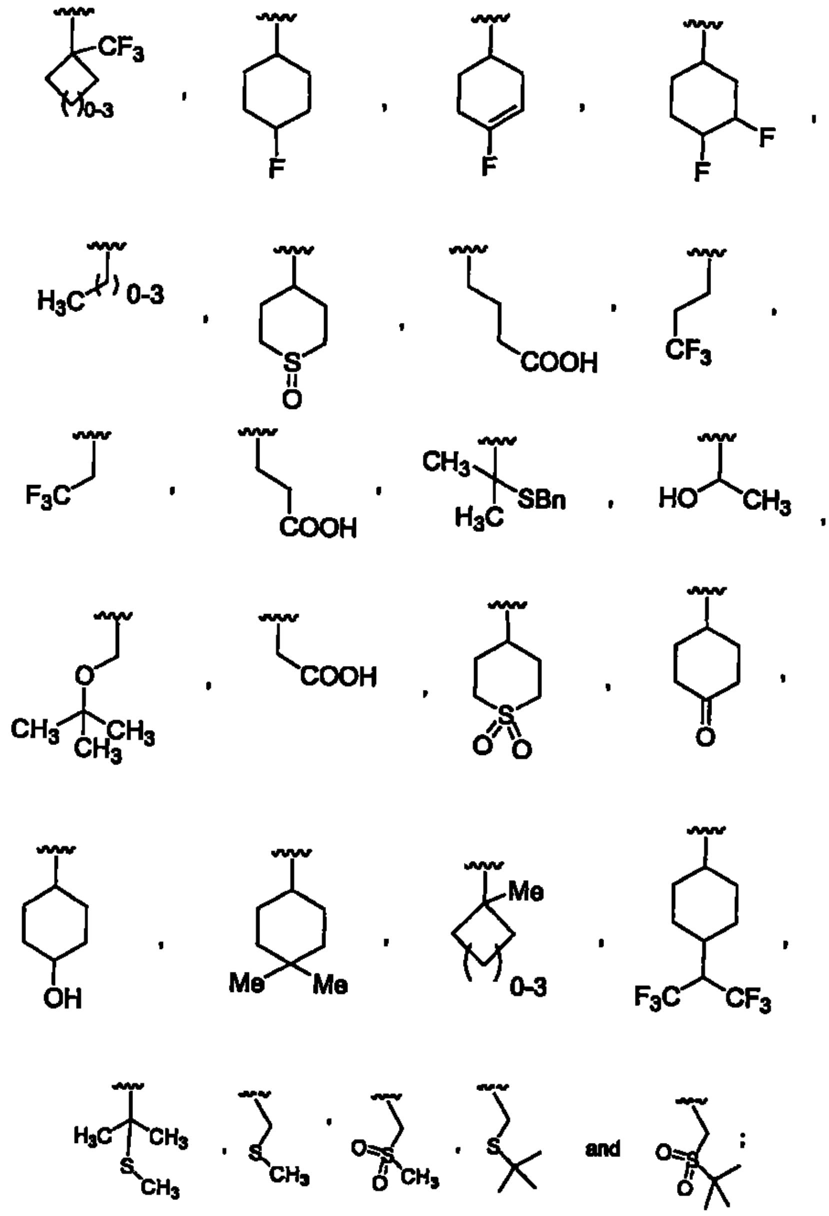


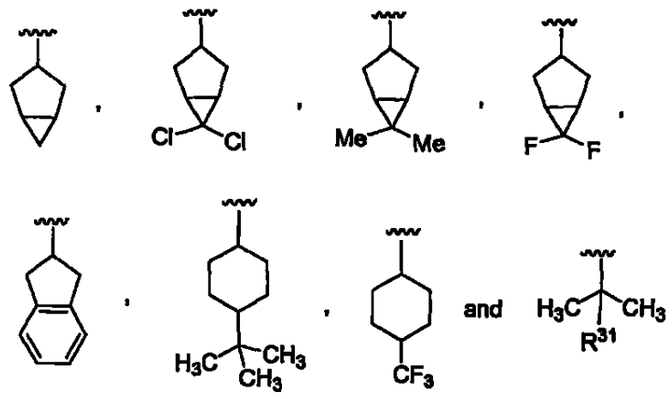
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5. The compound of claim 1, wherein R^3 is selected from the group consisting of:


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

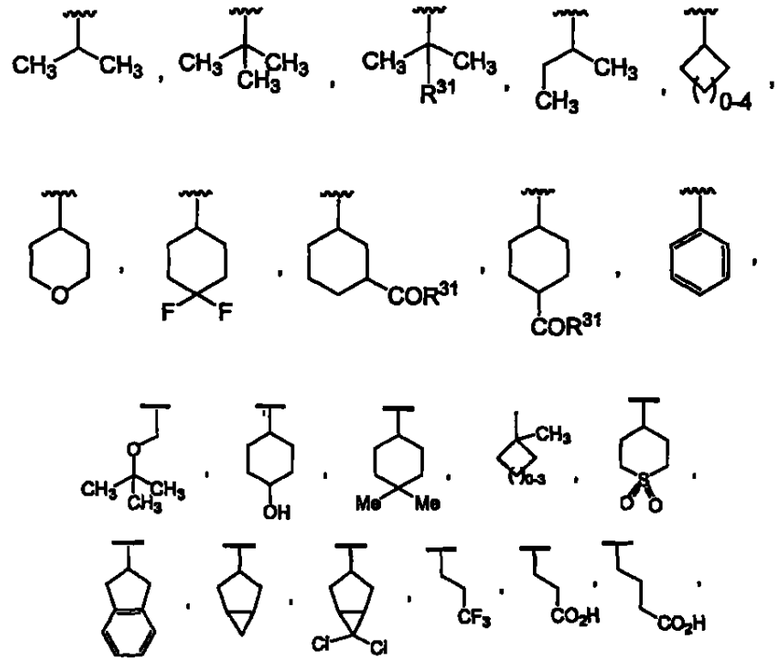

CF3
0-3
F
F
F
F
H3C
0-3
S
O
COOH
CF3
F3C
COOH
CH3
SBn
H3C
HO
CH3
O
CH3
CH3
CH3
COOH
S
O
O
O
OH
Me
Me
Me
0-3
F3C
CF3
H3C
CH3
S
CH3
S
CH3
O=S
O
CH3
S
and
O=S
O
;

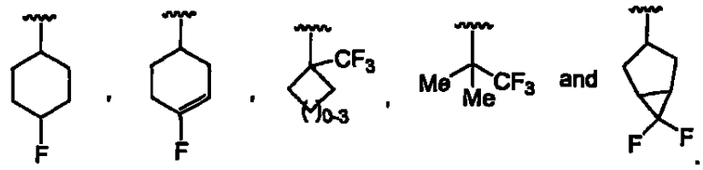


wherein R^{31} is OH or O-alkyl; and

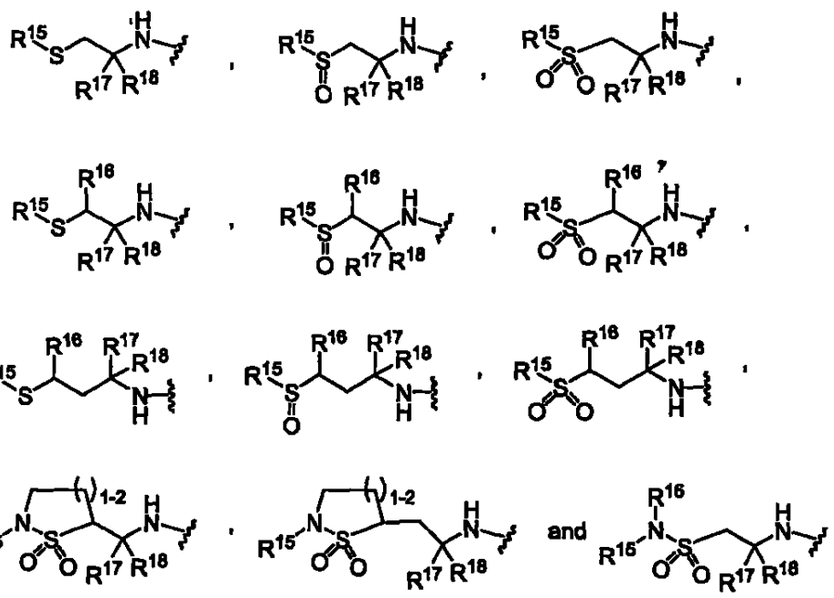
R^{32} is H, $C(O)CH_3$, C(O)OtBu or C(O)N(H)tBu.

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:

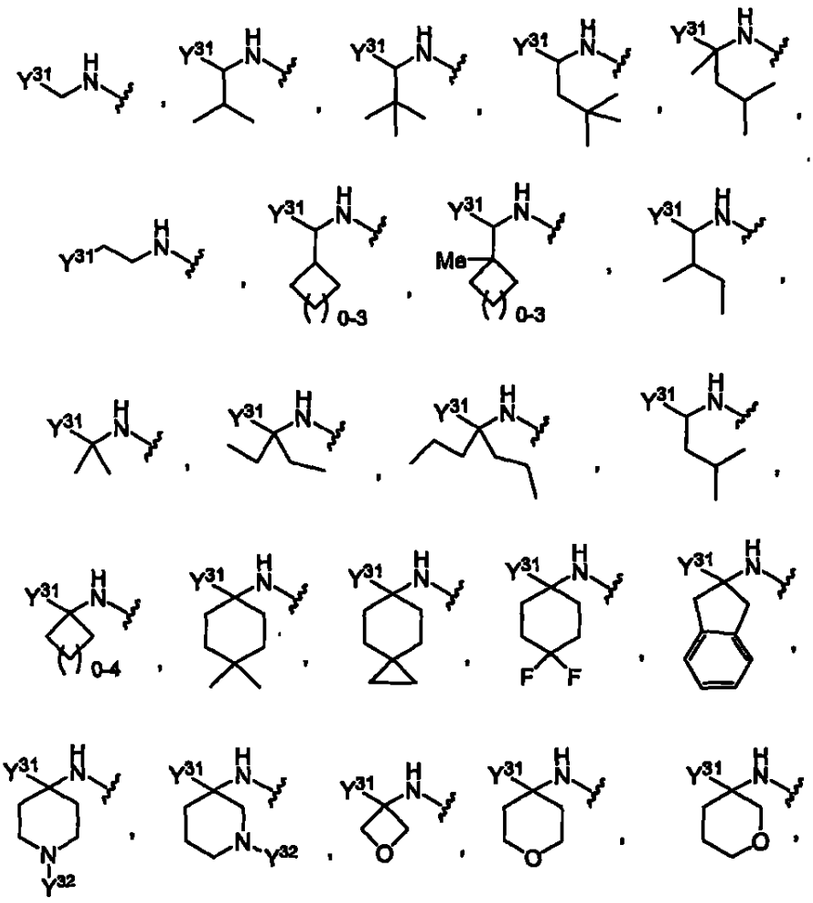


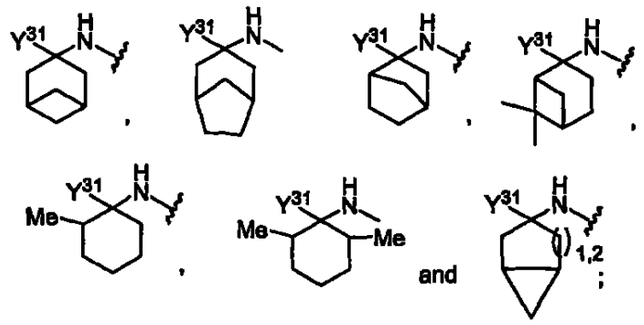
wherein R^{15}, R^{16}, R^{17} and R^{18} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately, R^{15} and R^{16} are connected to each other to form a four to eight-membered cycloalkyl or heterocyclic structure; R^{17} and R^{18} are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl or heterocyclyl can be unsubstituted or optionally

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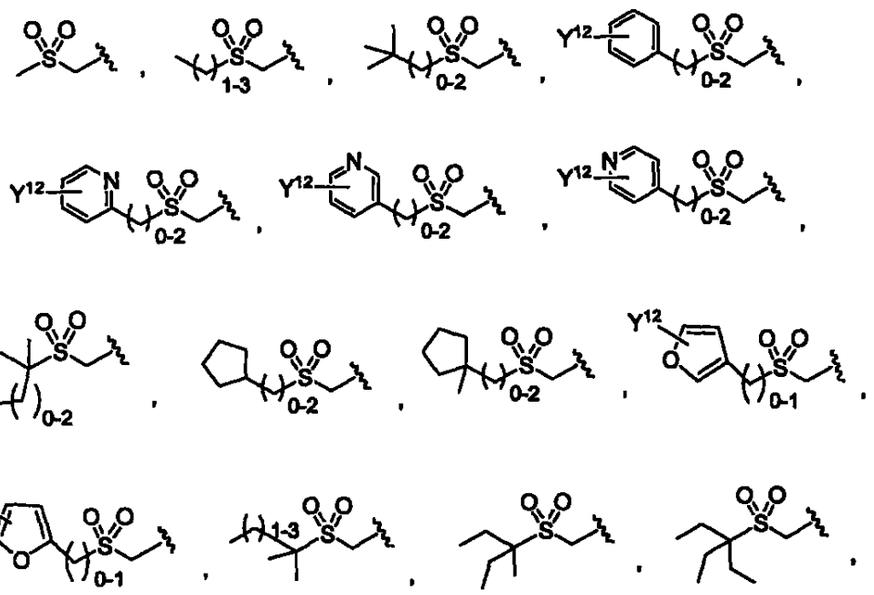
independently substituted with one or more moieties selected from the group consisting of: hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, amido, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, sulfonamido, alkylsulfonamido, arylsulfonamido, alkyl, aryl, heteroaryl, carboxy, carbalkoxy,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

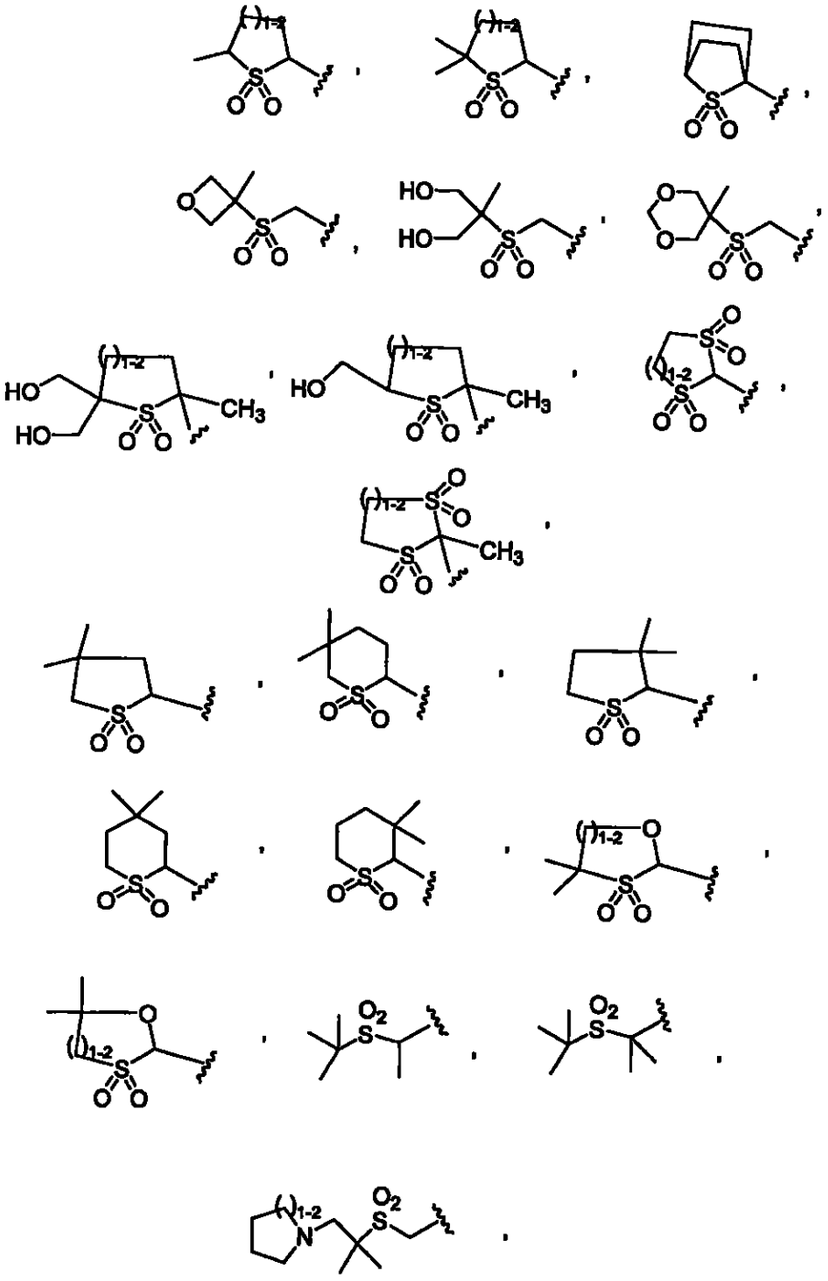
8. The compound of claim 7, Y is selected from the group consisting of:

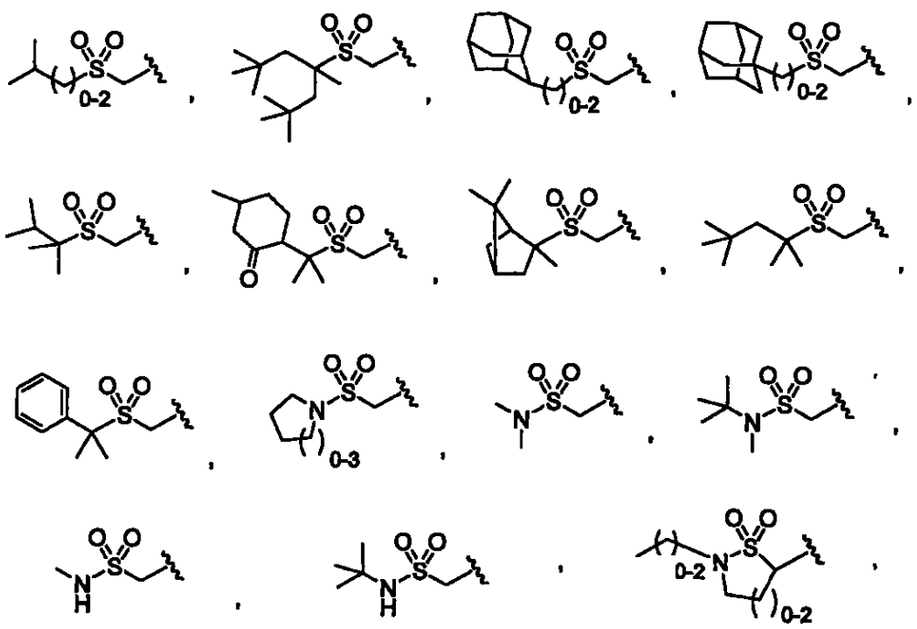


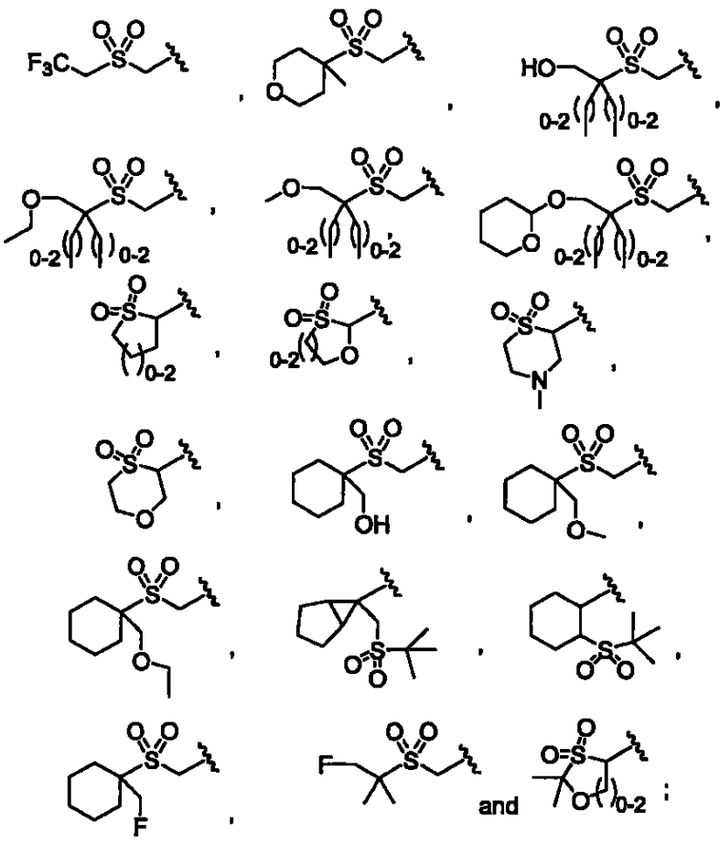


wherein Y^{31} is selected from the group consisting of:

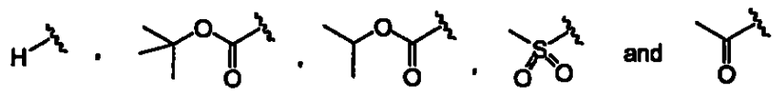








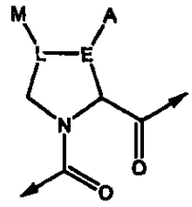
Y^{32} is selected from the group consisting of:



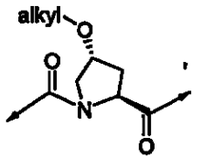
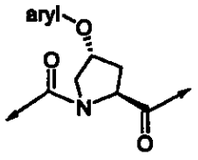
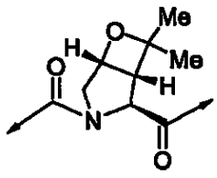
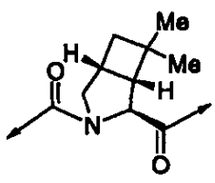
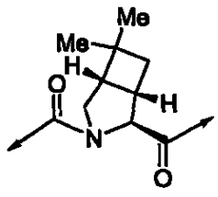
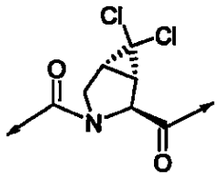
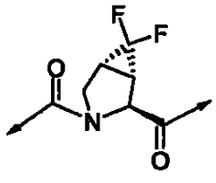
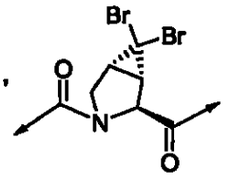
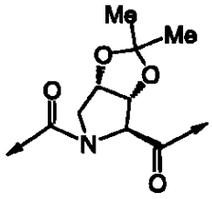
and Y^{12} is selected from the group consisting of H, CO_2H, CO_2Me, OMe, F, Cl, Br, NH_2, $N(H)S(O_2)CH_3$, $N(H)C(O)CH_3$, NO_2, $S(O_2)NH_2$, CF_3, Me, OH, OCF_3, and $C(O)NH_2$.

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

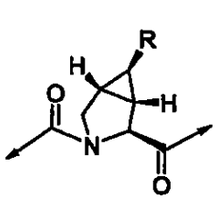
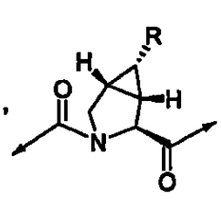
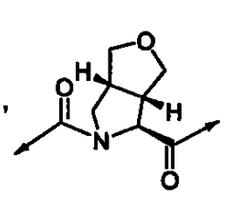
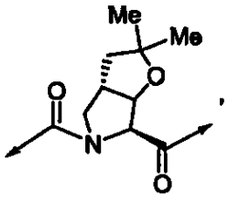
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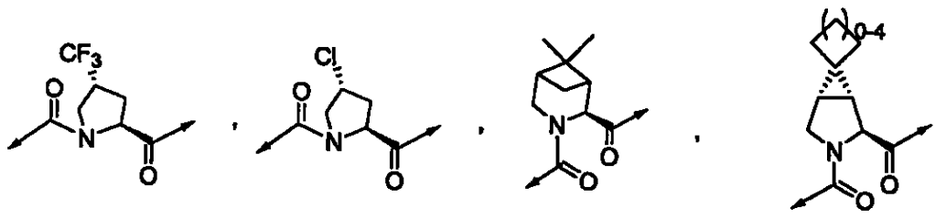
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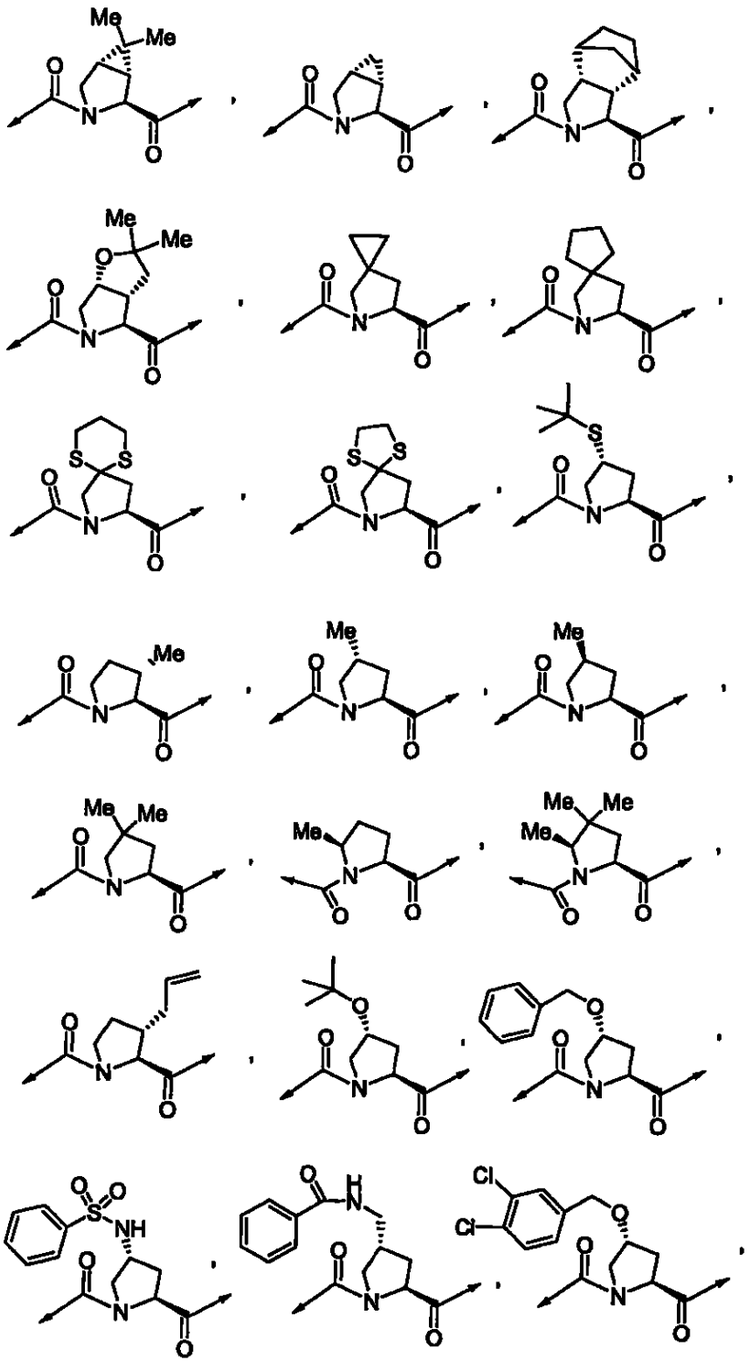
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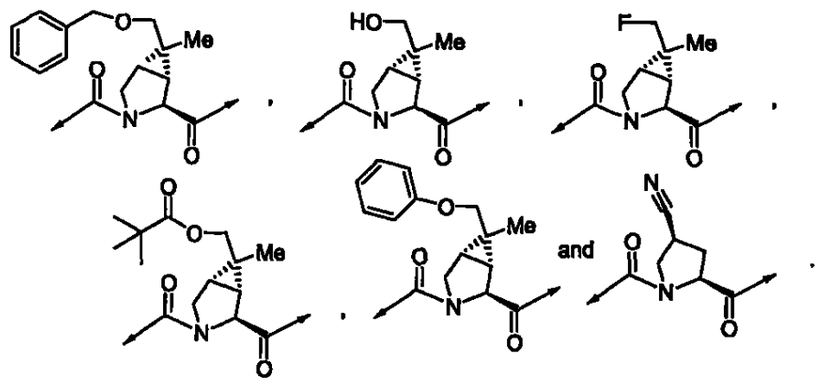





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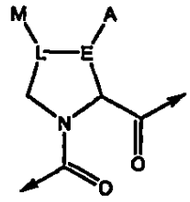


711



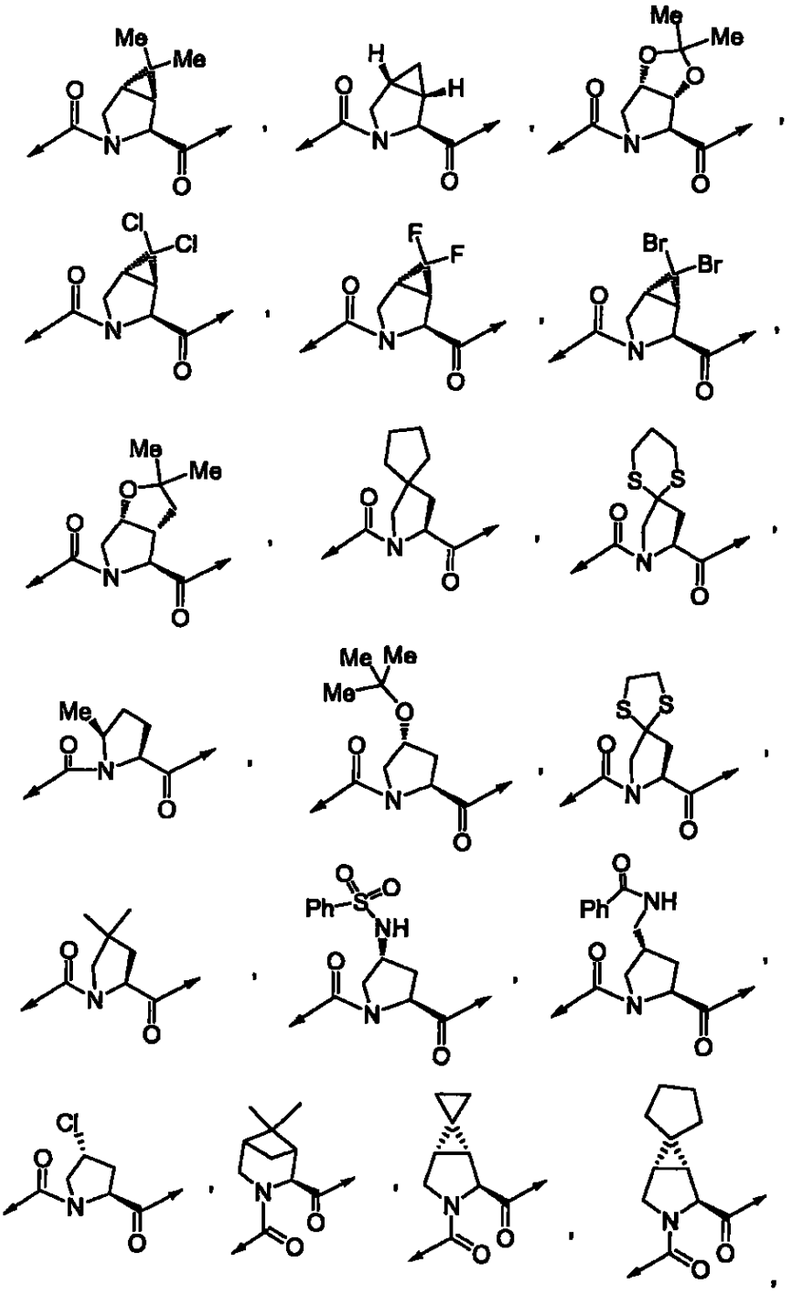


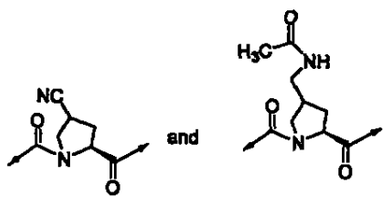
10. The compound of claim 9, wherein the moiety:



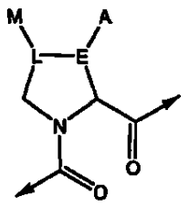
is selected from the following structures:

713

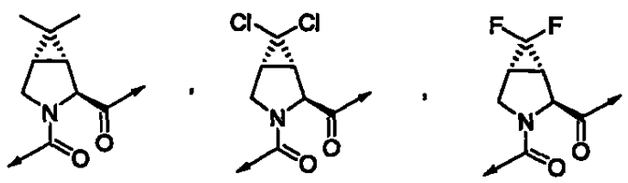


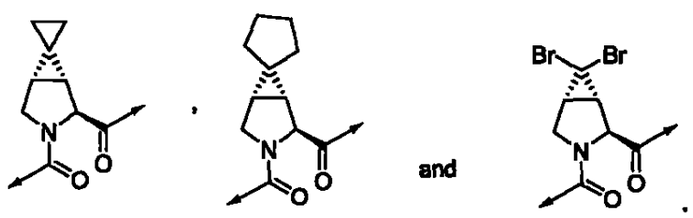


11. The compound of claim 10, wherein the moiety:



is selected from the following structures:



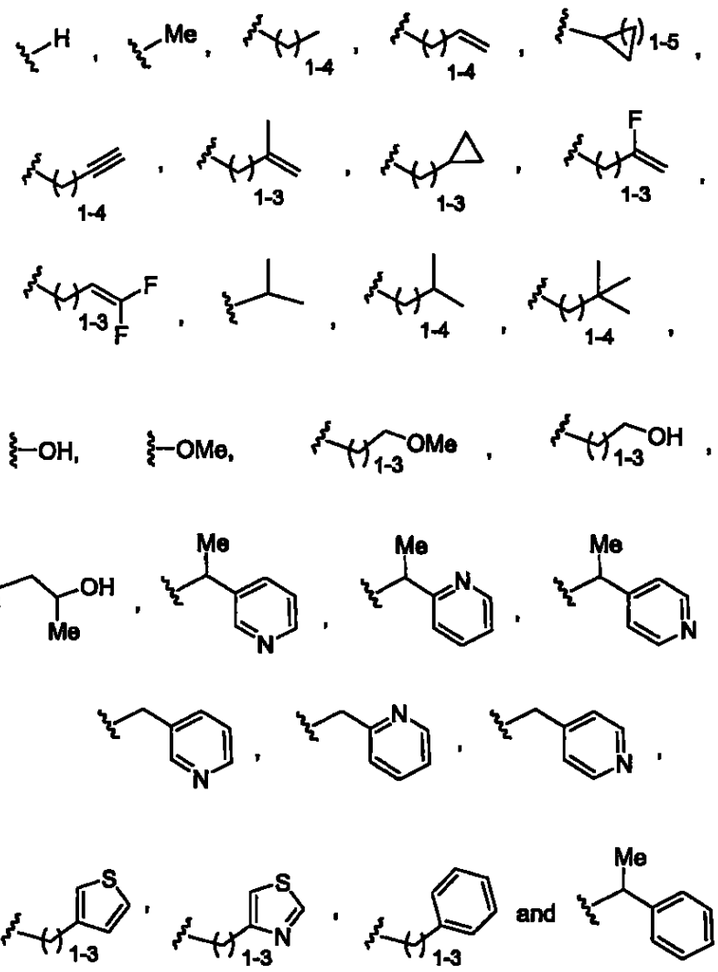


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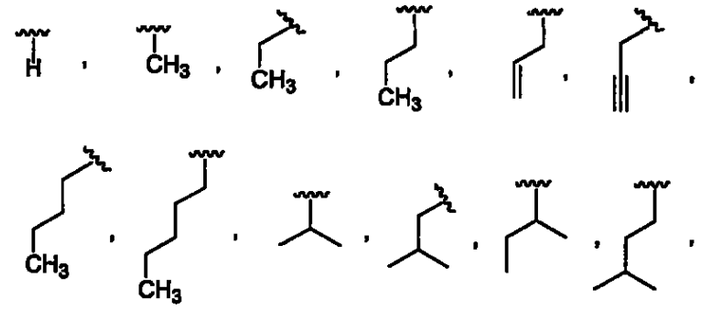
12. The compound of claim 1, wherein:

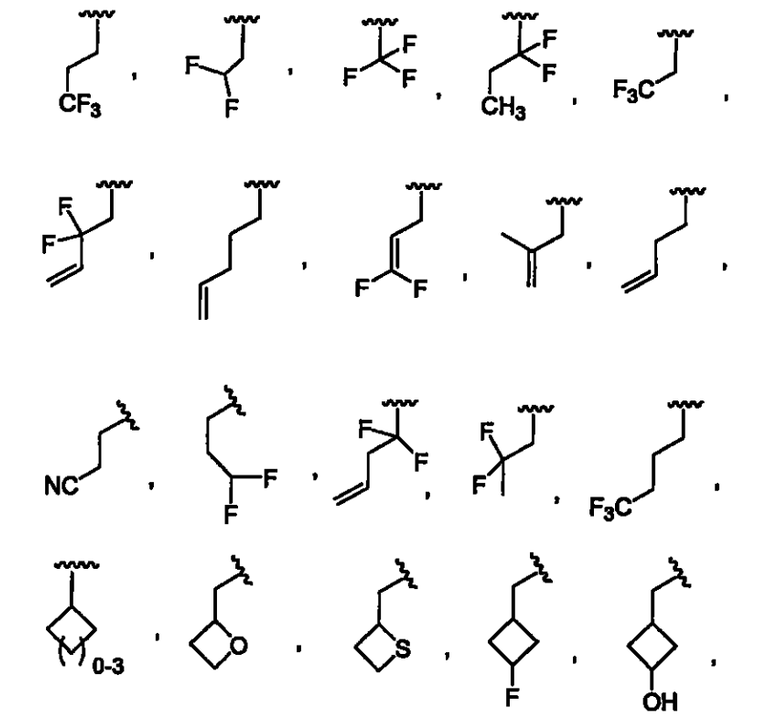
R^1 is NHR^{14}, where R^{14} is selected from the group consisting of:

715

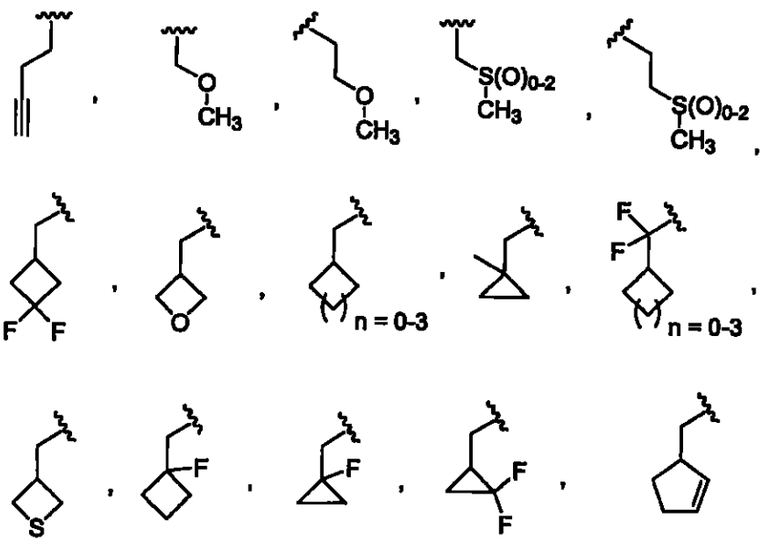


R^2 is selected from the group consisting of the following moieties:

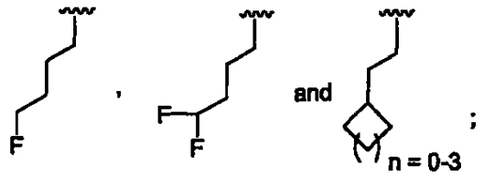



CF3
F
F
F
F
F
CH3
F3C
F
F
F
F
NC
F
F
F
F
F
F3C
0-3
O
S
F
OH

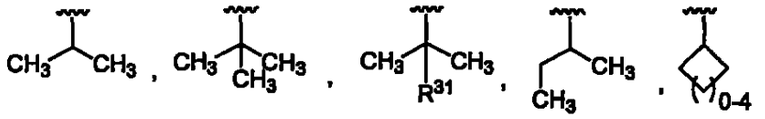
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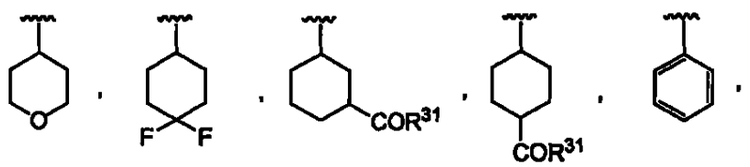

O
CH3
O
CH3
S(O)0-2
CH3
S(O)0-2
CH3
F
F
O
n = 0-3
F
F
n = 0-3
S
F
F
F
F

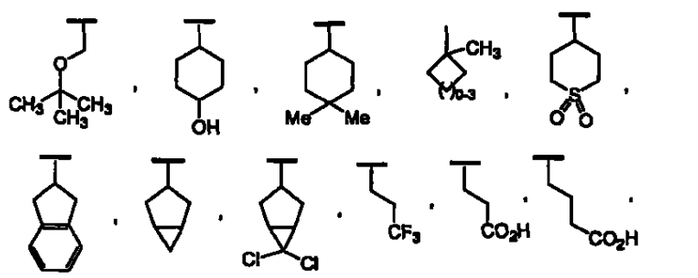
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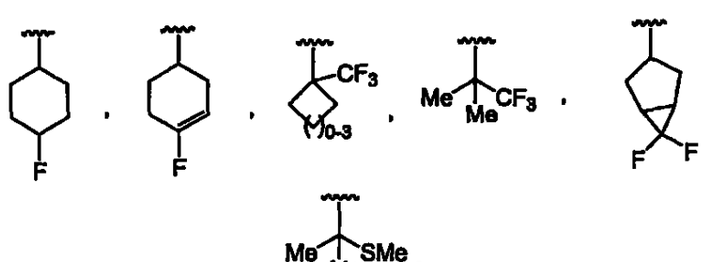


R^3 is selected from the group consisting of the following moieties:

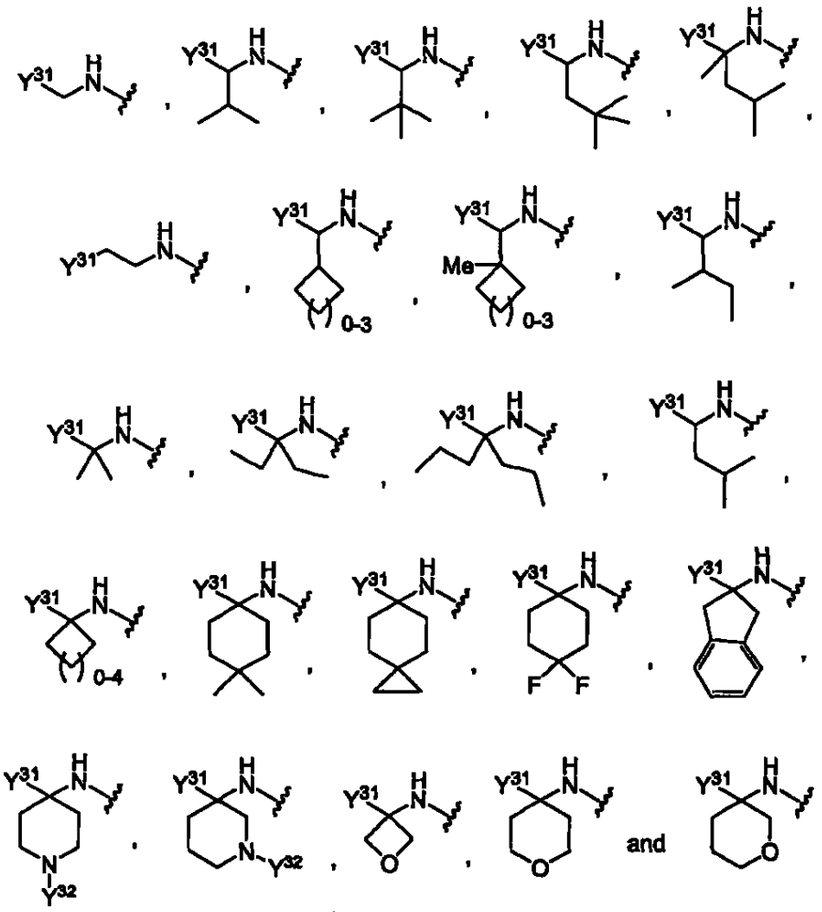






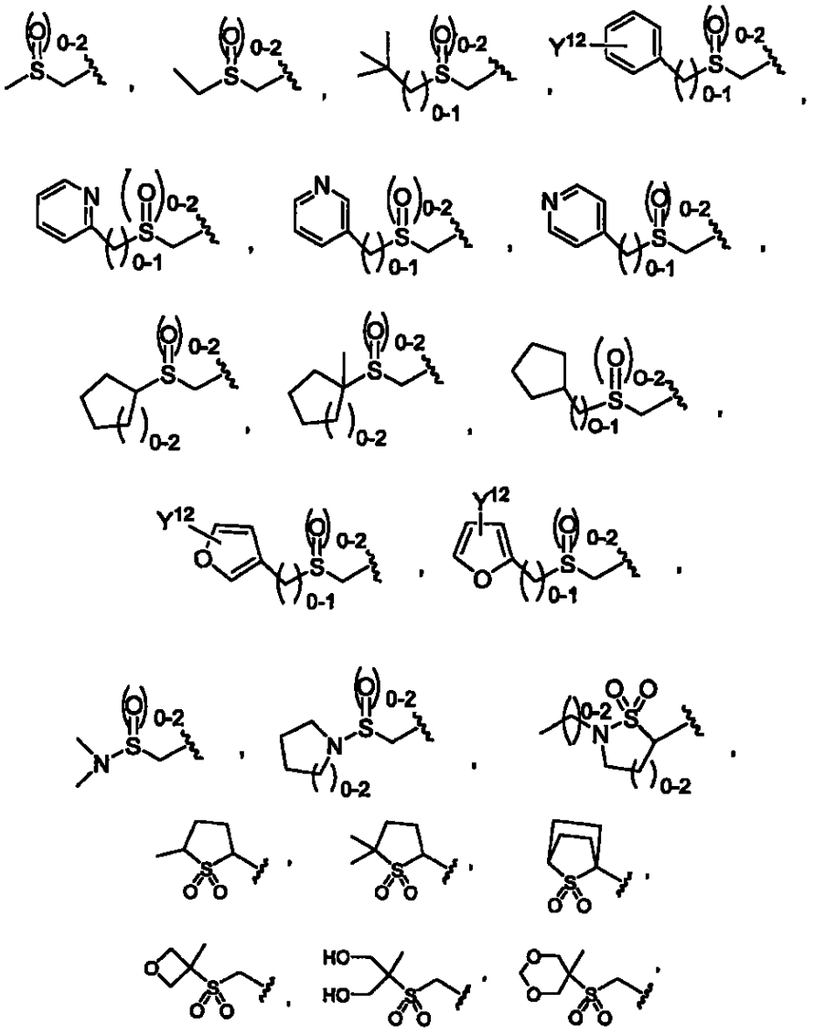


Y is selected from the group consisting of:

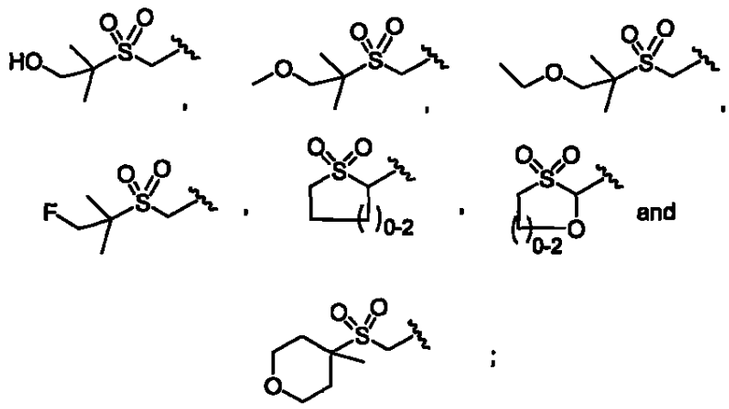


wherein Y^{31} is selected from the group consisting of:

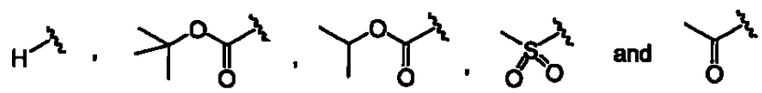
719



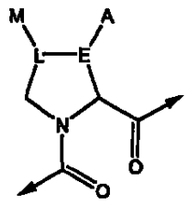
720



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

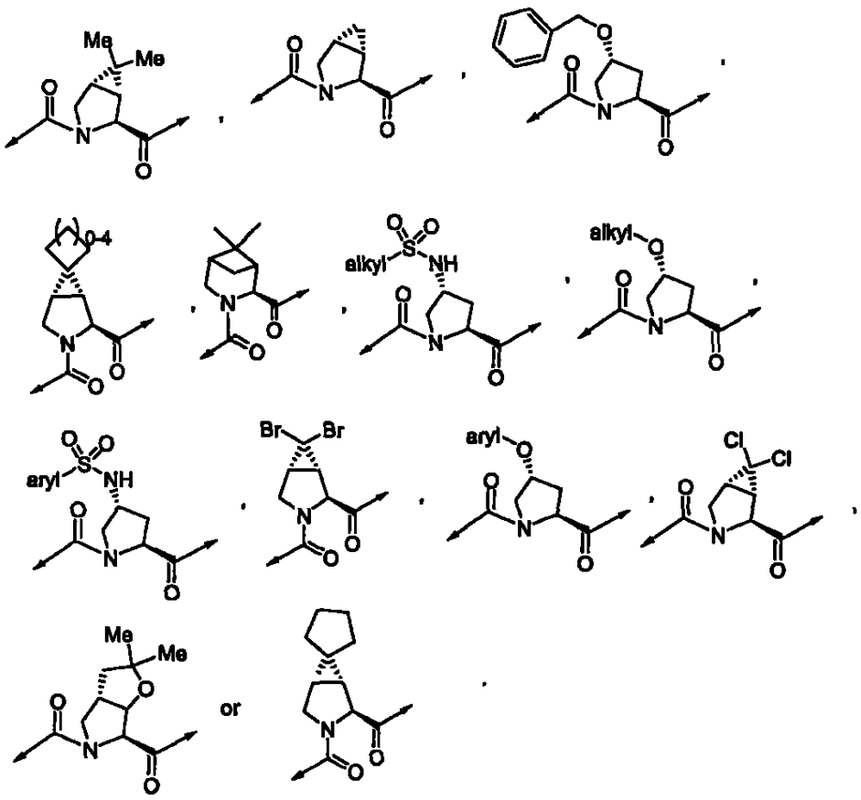


and Y^{12} is selected from the group consisting of H, CO_2H, CO_2Me, OMe, F, Cl, Br, NH_2, $N(H)S(O_2)CH_3$, $N(H)C(O)CH_3$, NO_2, $S(O_2)NH_2$, CF_3, Me, OH, OCF_3, and $C(O)NH_2$; and the moiety:



is:

721



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

14. The pharmaceutical composition of claim 13 for use in treating disorders associated with HCV.

15. The pharmaceutical composition of claim 13 additionally comprising at least one pharmaceutically acceptable carrier.

16. The pharmaceutical composition of claim 15, additionally containing at least one antiviral agent.

17. The pharmaceutical composition of claim 16, still additionally containing at least one interferon.

722

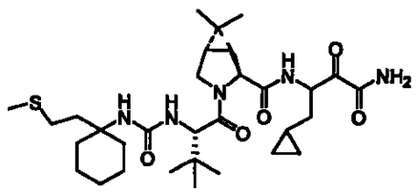
18. The pharmaceutical composition of claim 17, wherein said at least one antiviral agent is ribavirin and said at least one interferon is α-interferon or pegylated interferon.

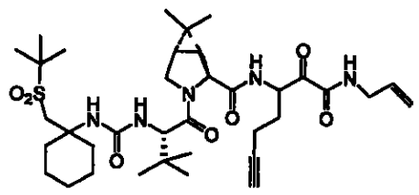
19. A method of treating disorders associated with the HCV, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound of claim 1.

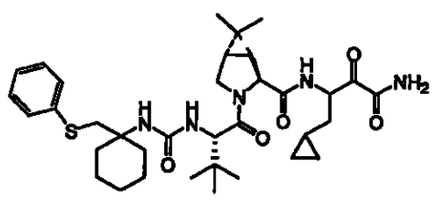
20. The method of claim 19, wherein said administration is oral or subcutaneous.

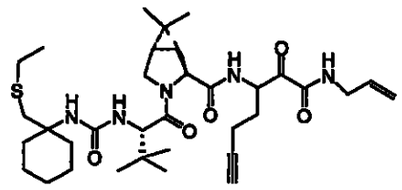
21. A method of preparing a pharmaceutical composition for treating the disorders associated with the HCV, said method comprising bringing into intimate contact at least one compound of claim 1 and at least one pharmaceutically acceptable carrier.

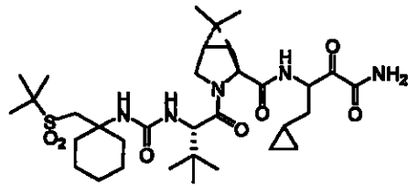
22. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound being selected from the compounds of structures listed below:

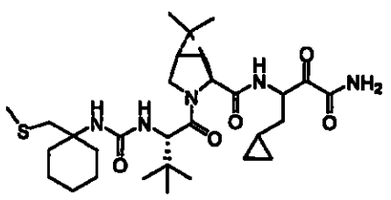


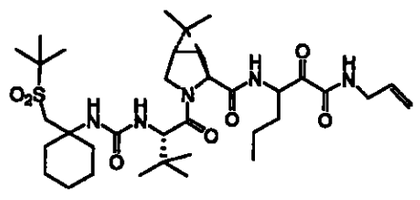


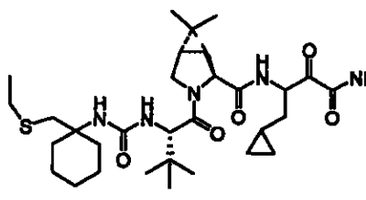


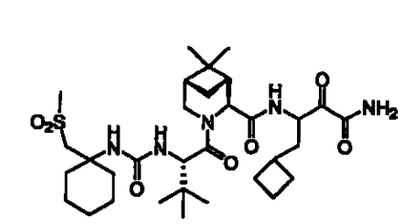


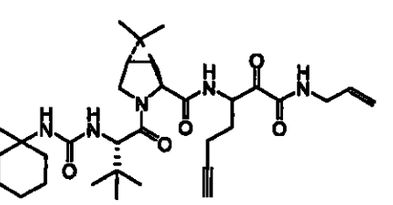


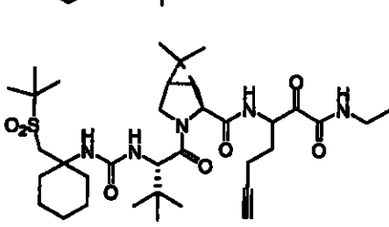


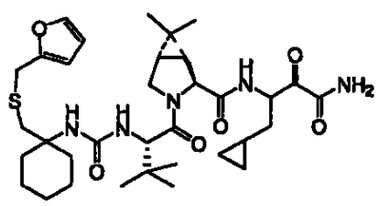


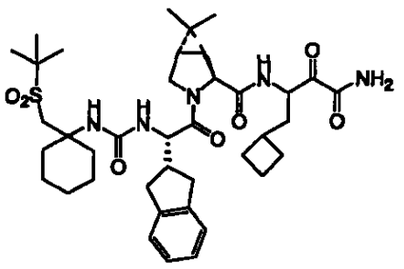


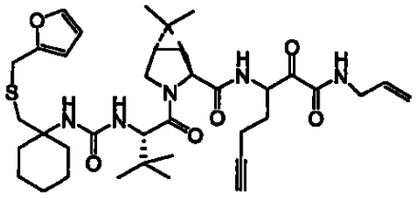


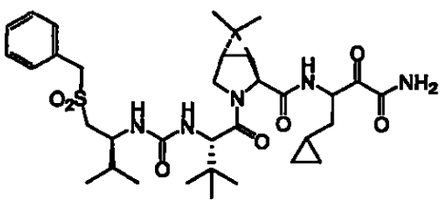


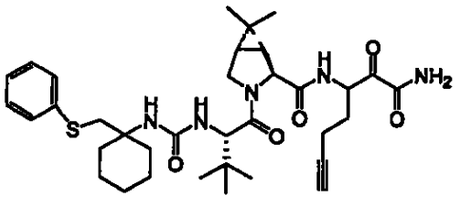


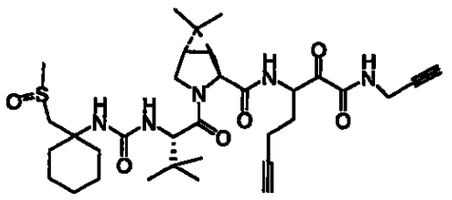


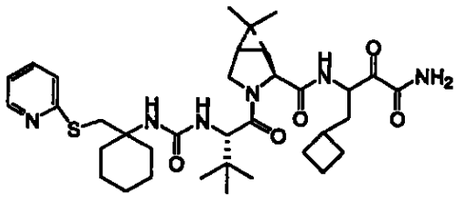


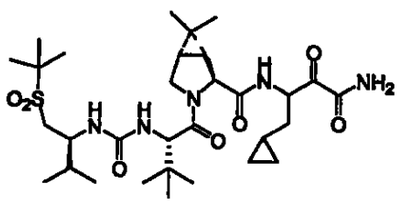


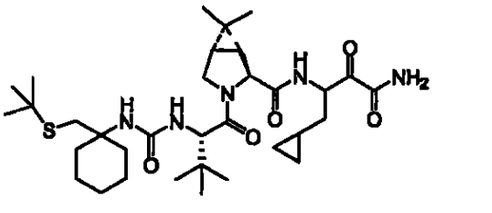


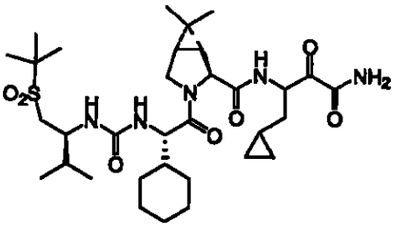


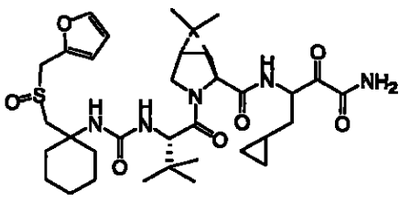


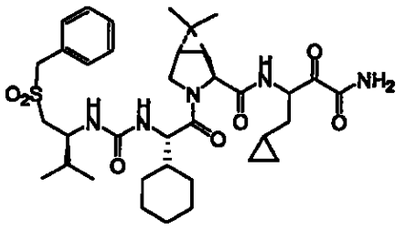


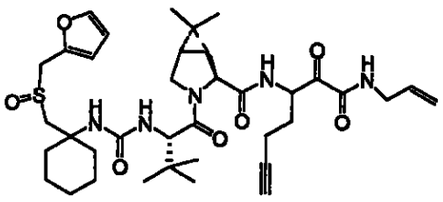


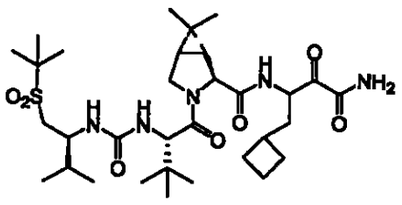


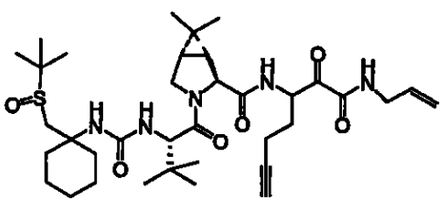


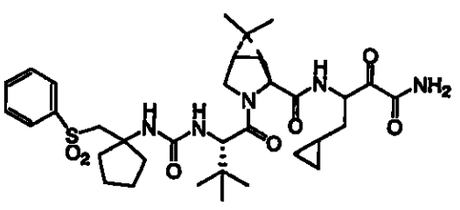


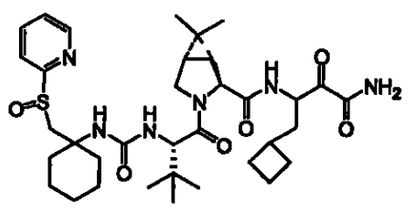


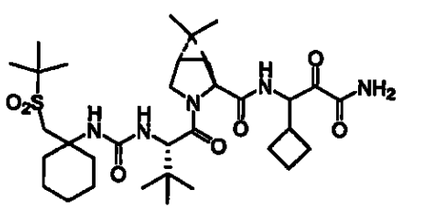


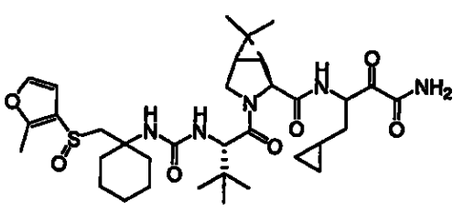


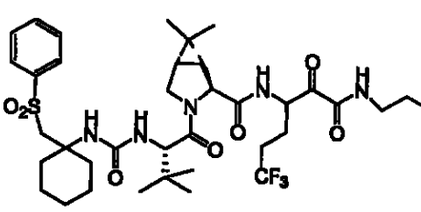


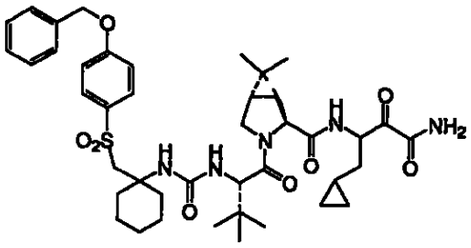


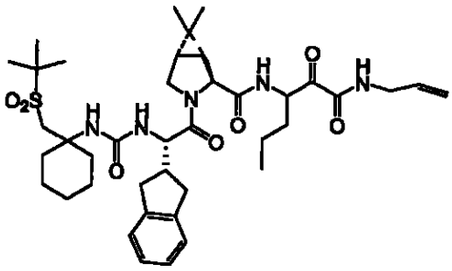


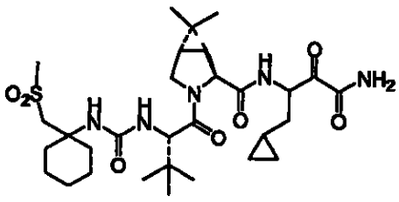


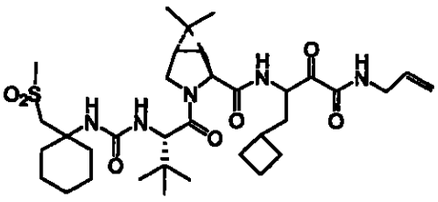


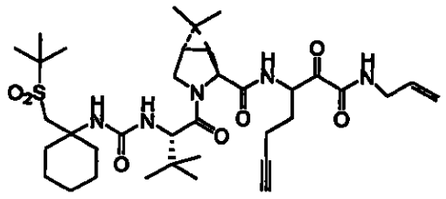


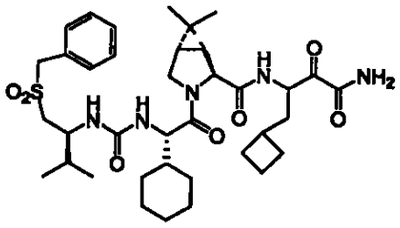


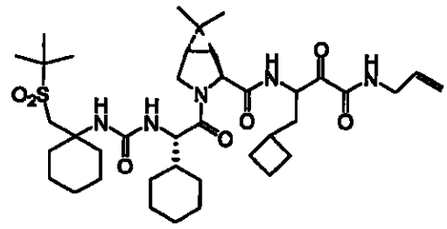


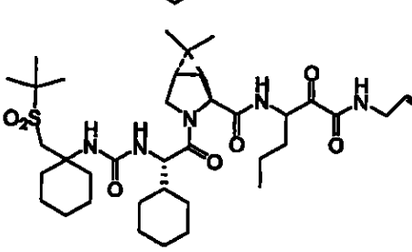


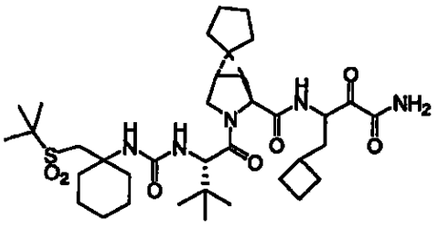


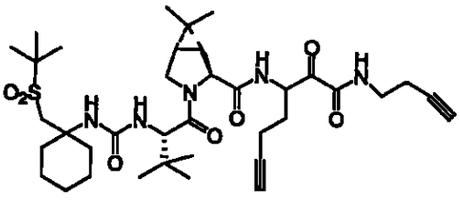


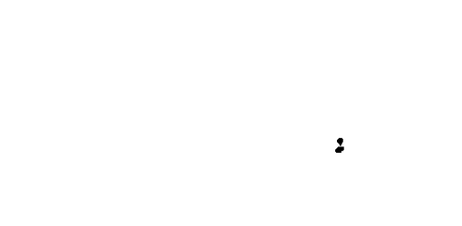


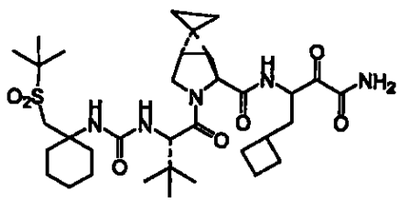


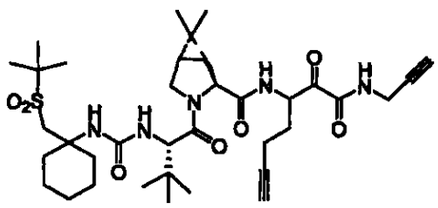


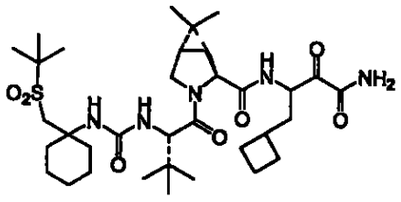


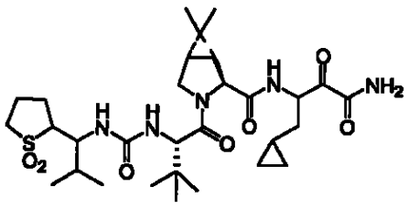


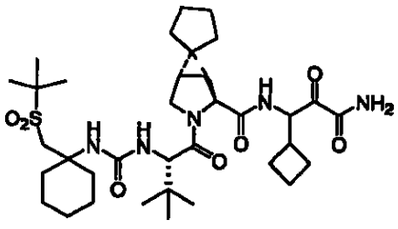


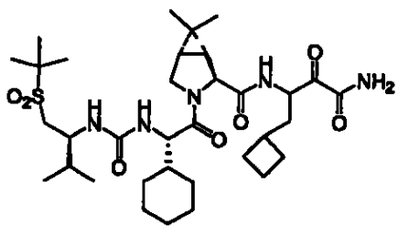


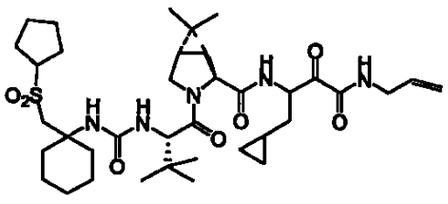


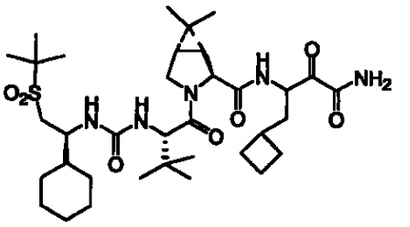


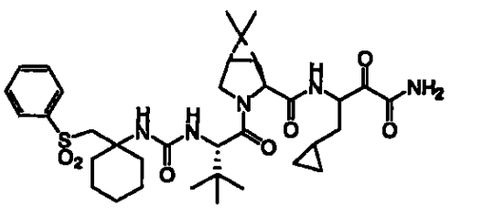


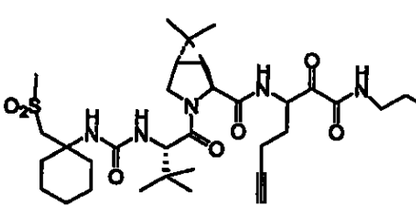


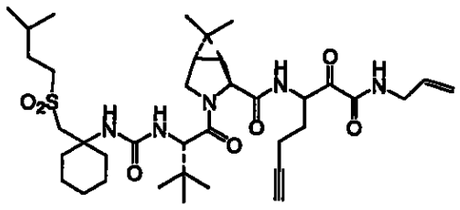


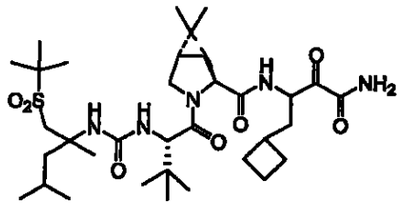


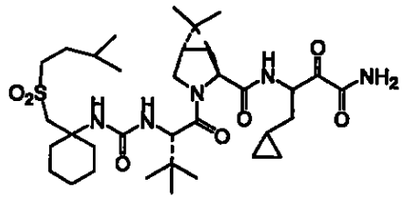


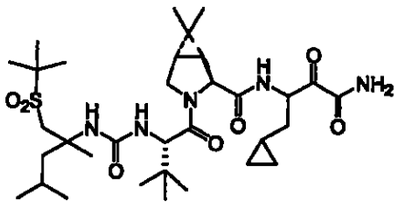


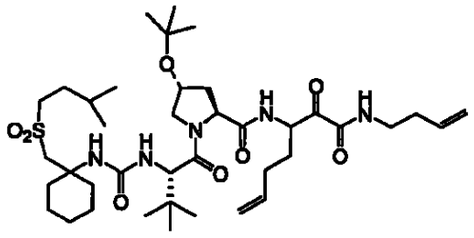


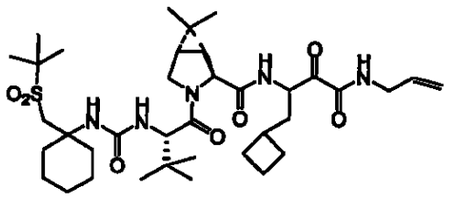


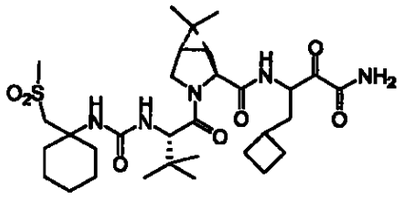


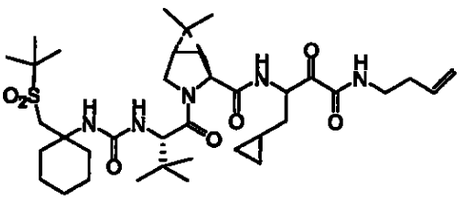


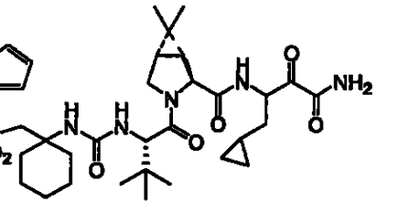


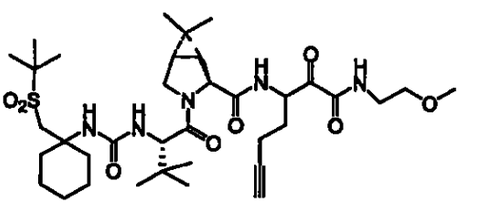


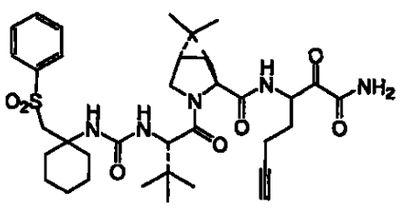


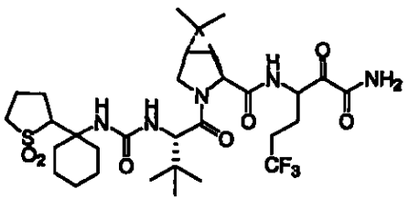


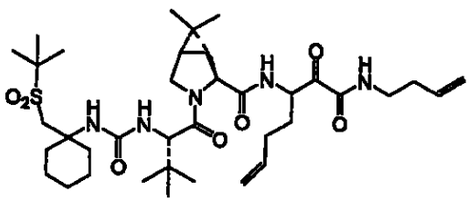


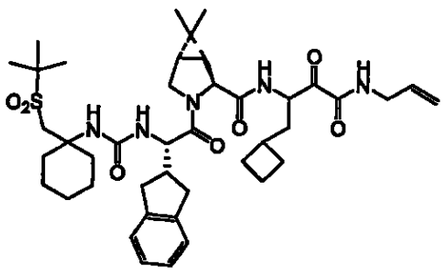


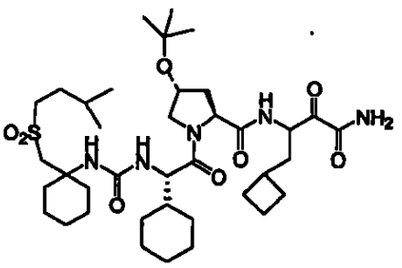


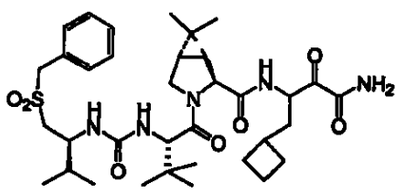


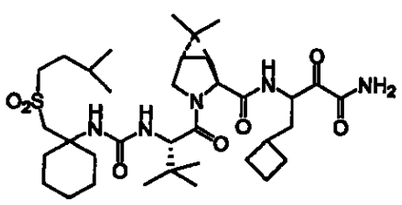


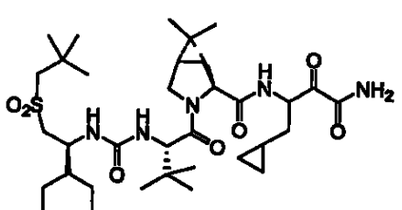


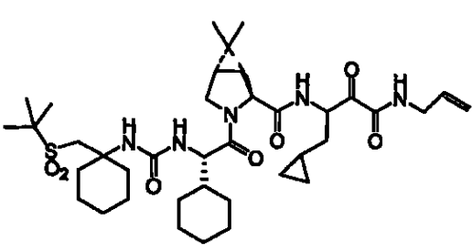


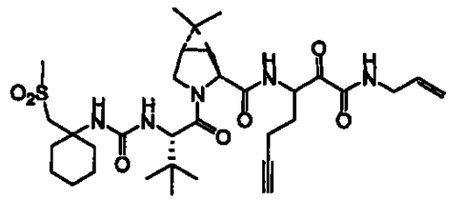


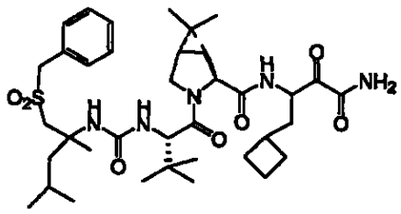


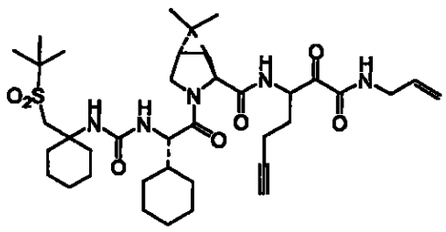


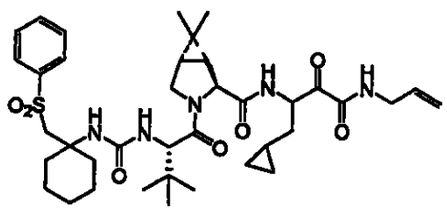


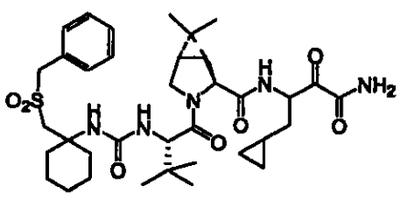


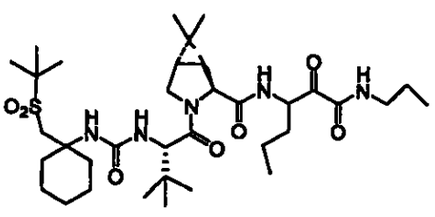


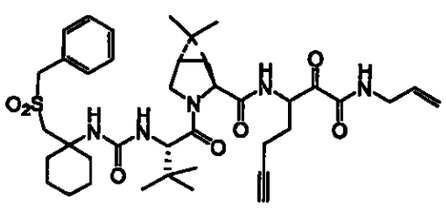


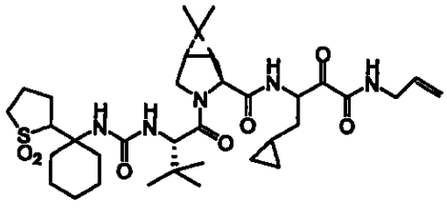


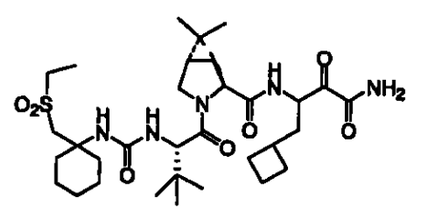


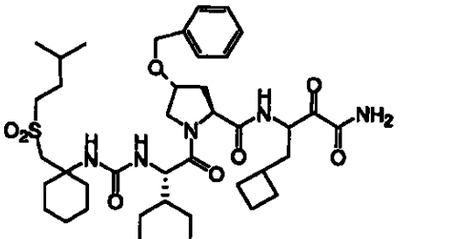




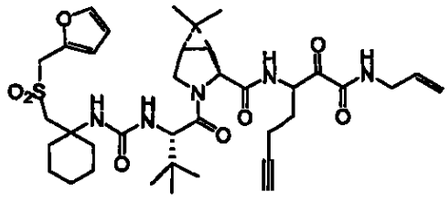


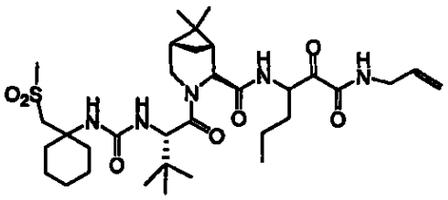


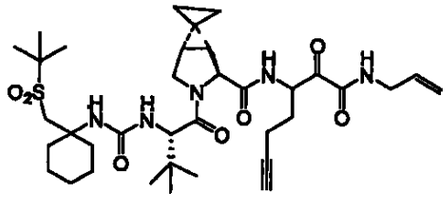


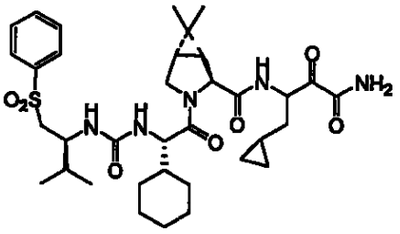


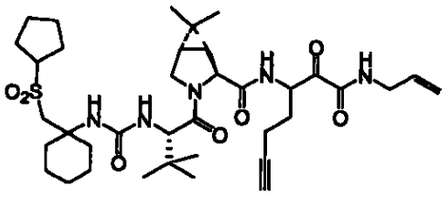
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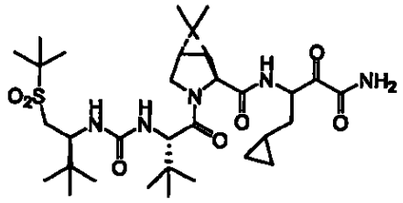


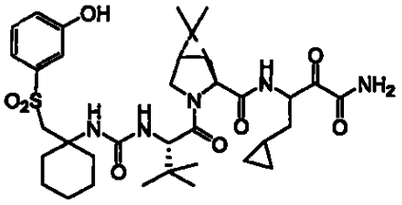


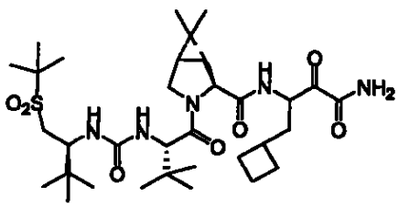


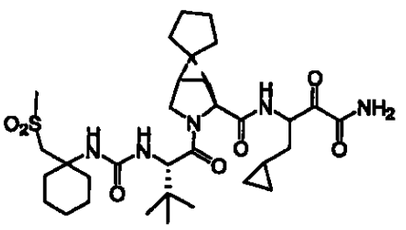


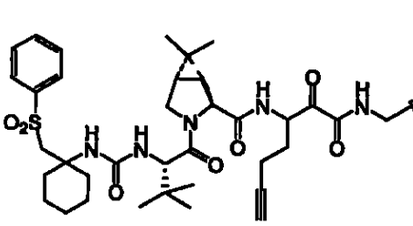


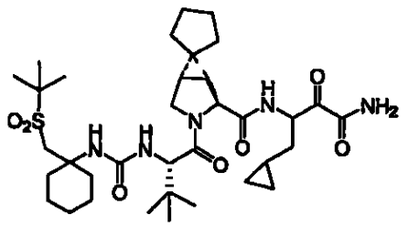


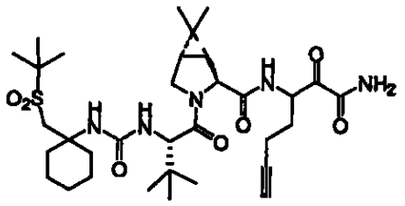


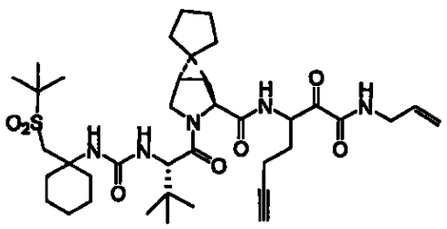


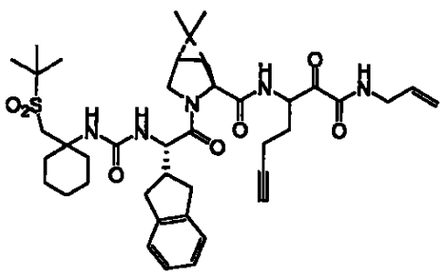


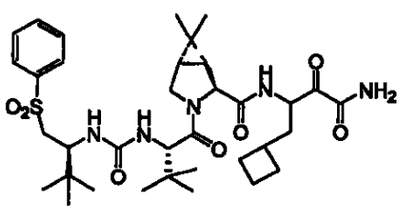


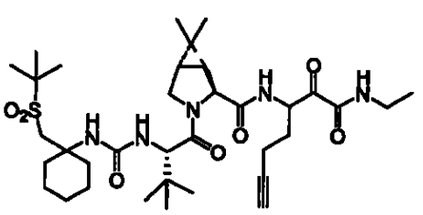


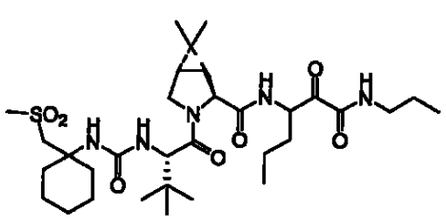


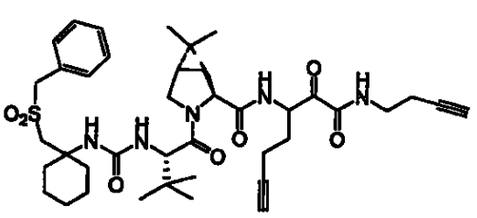


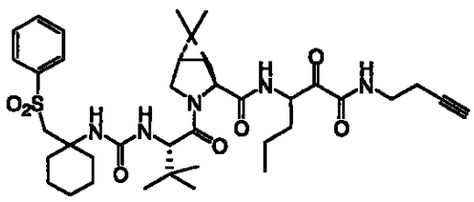


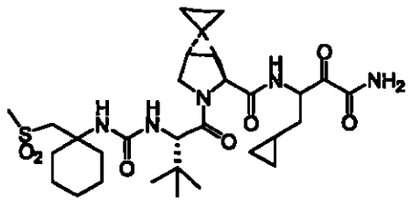


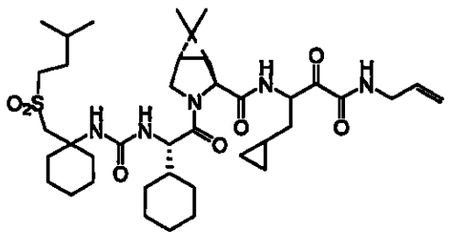


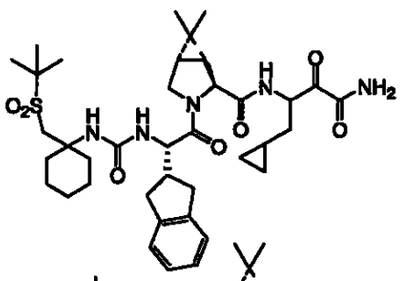


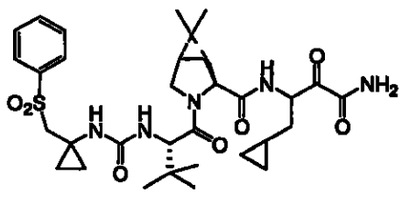


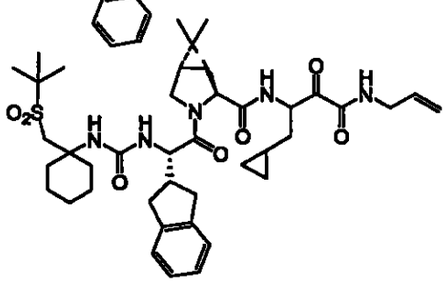


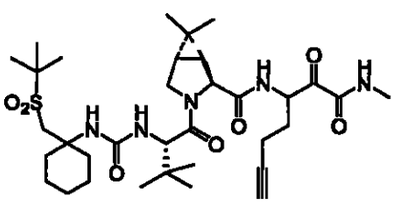


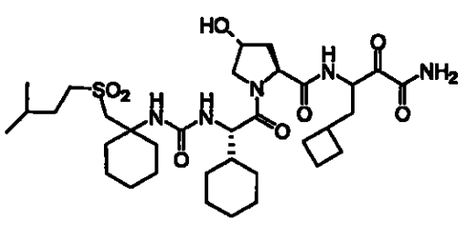


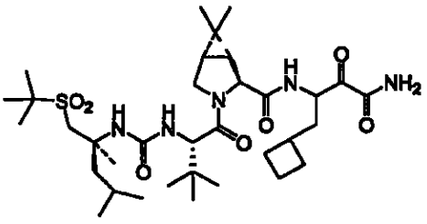


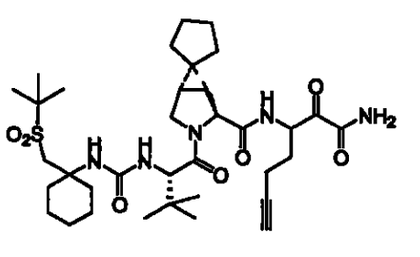




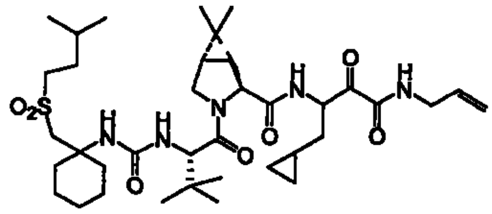
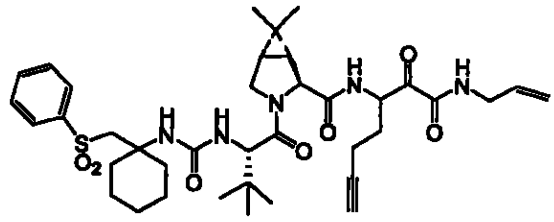
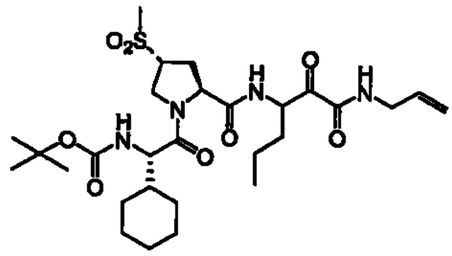
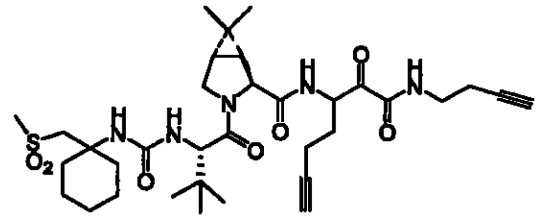
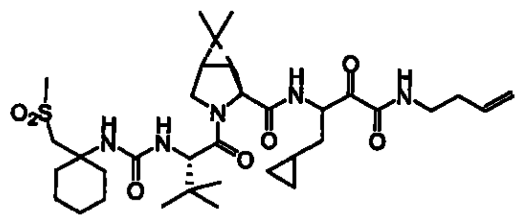
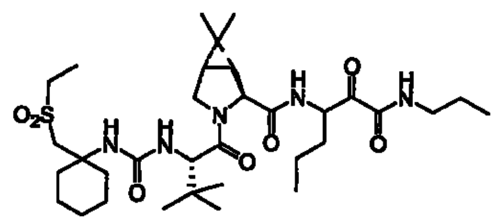
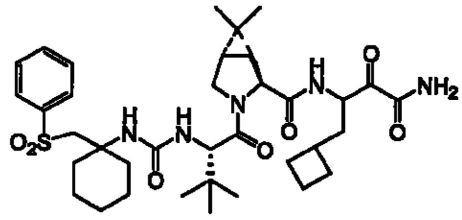
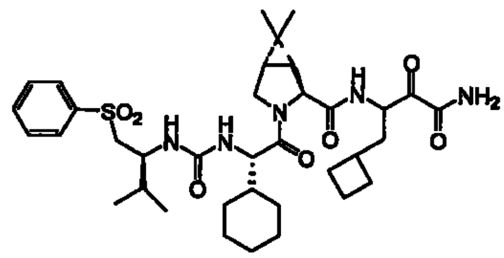
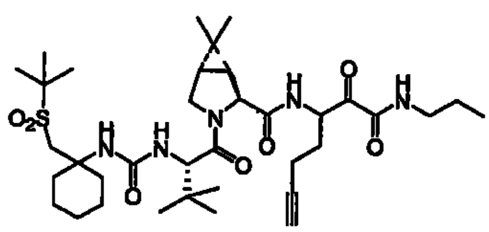
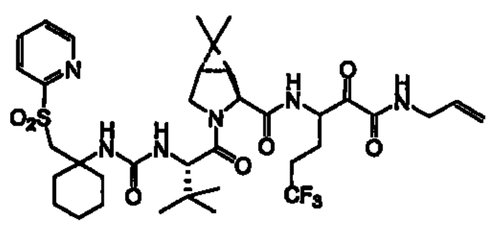


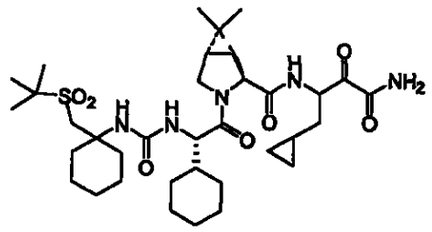


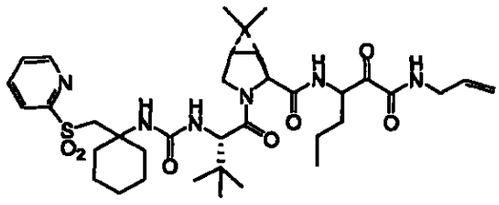


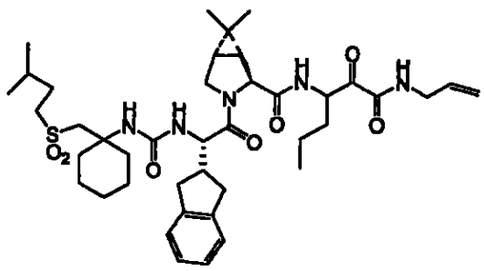


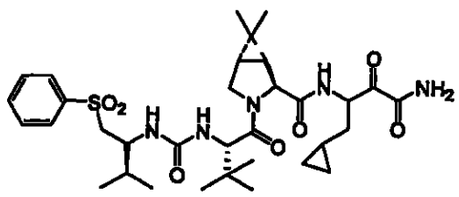
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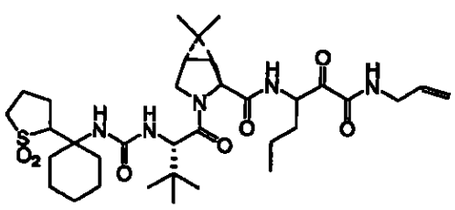











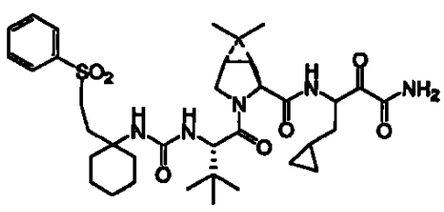


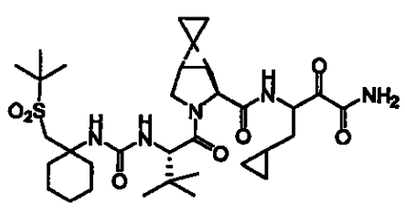


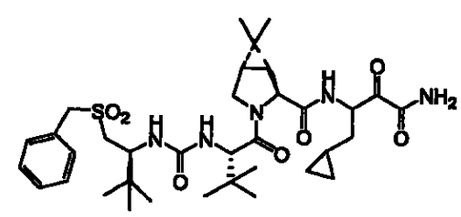


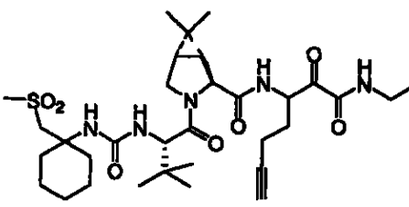


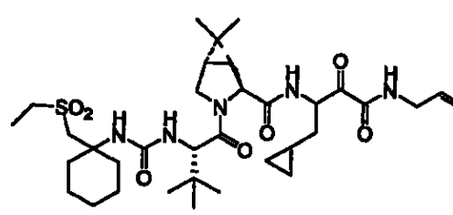


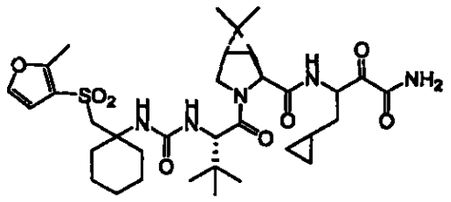


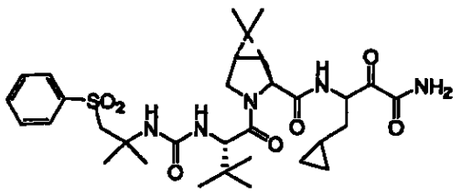


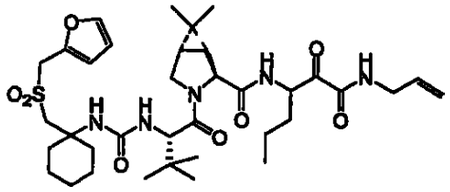


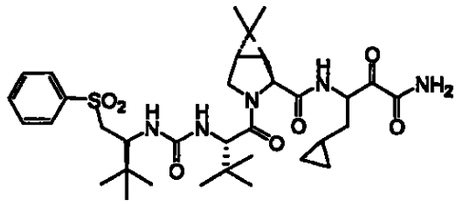


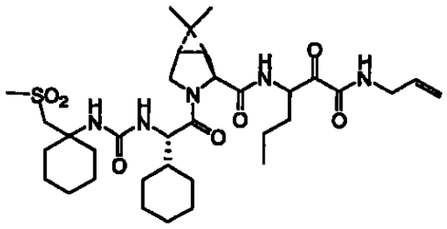


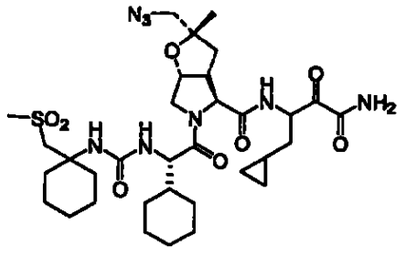


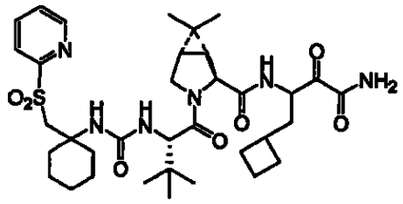


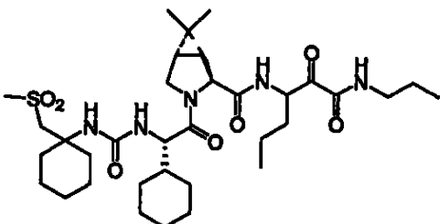


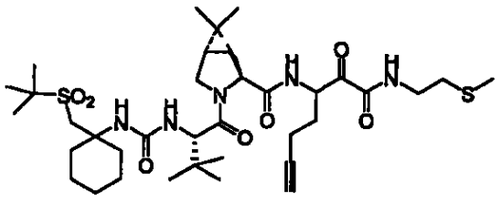


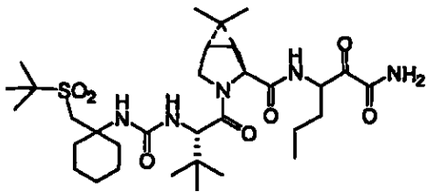


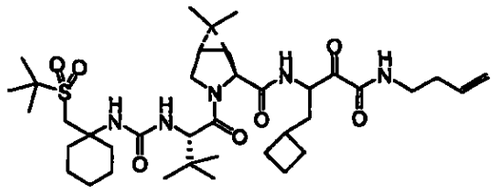


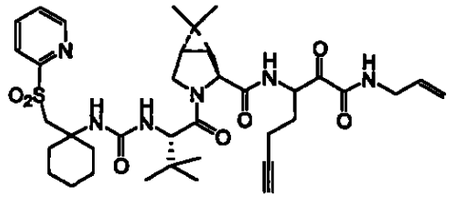


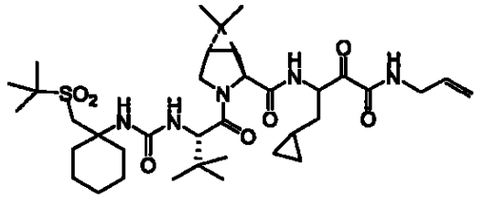


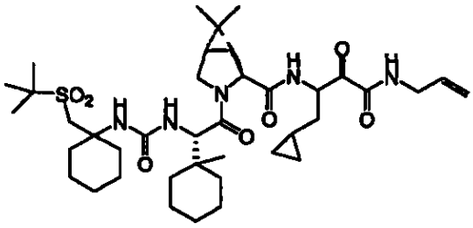


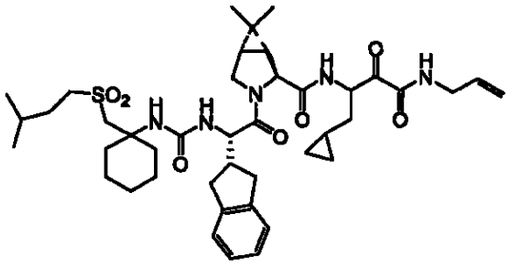


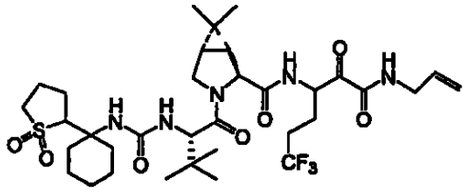


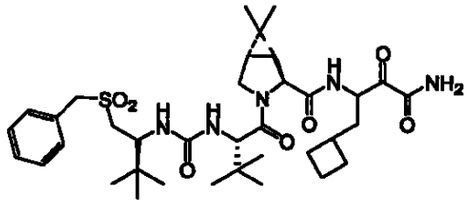


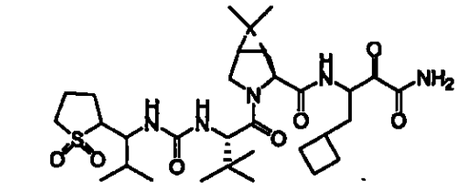


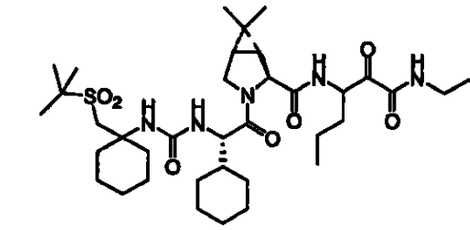


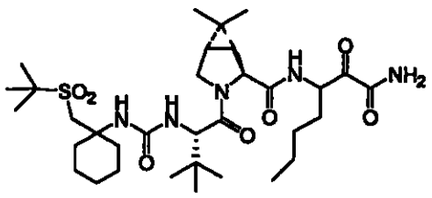


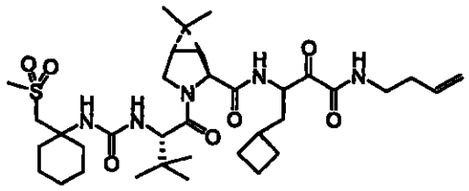


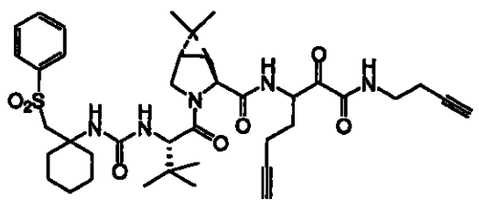


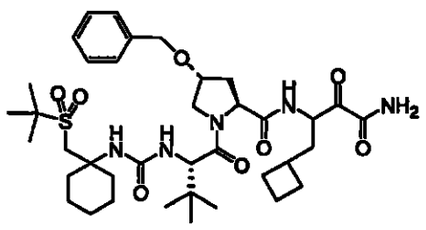


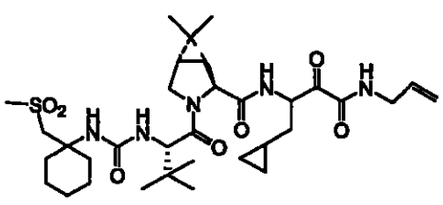


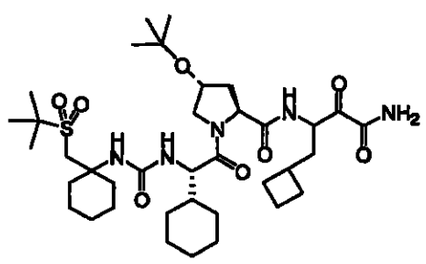


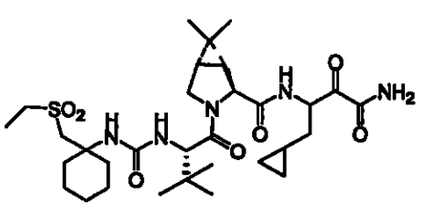


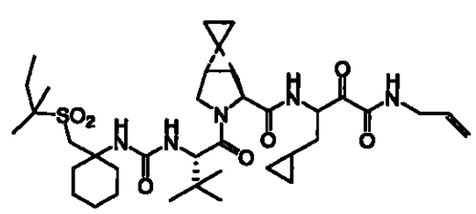


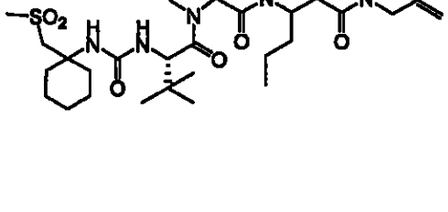


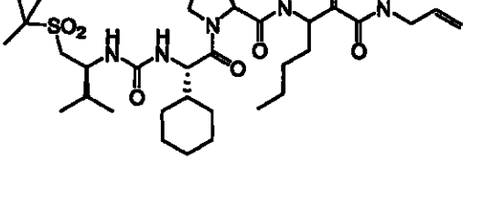




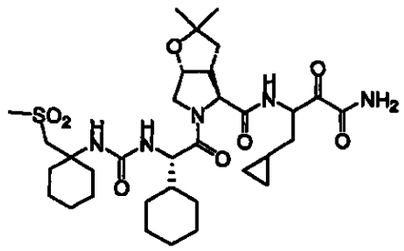


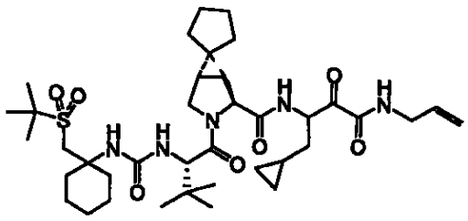


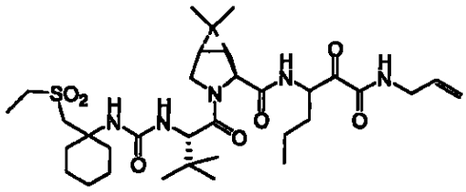


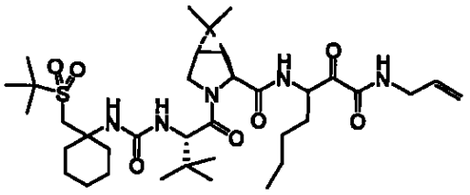


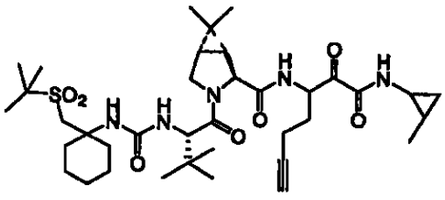
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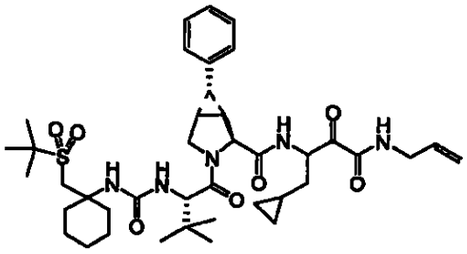


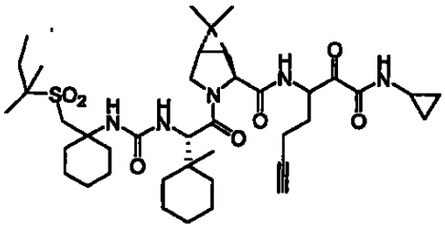


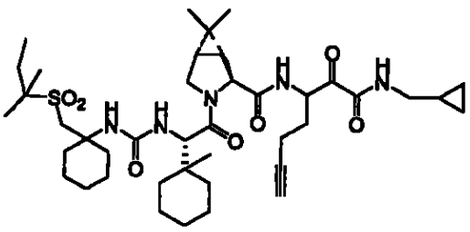


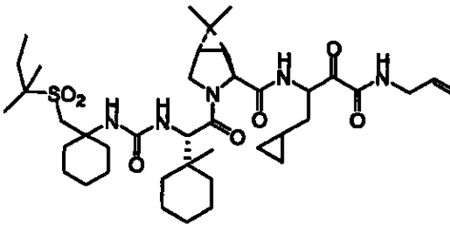


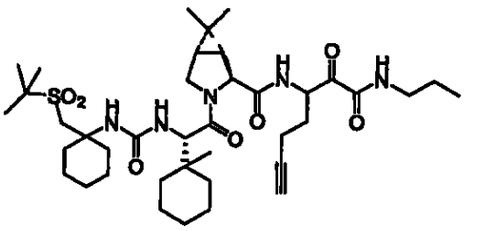


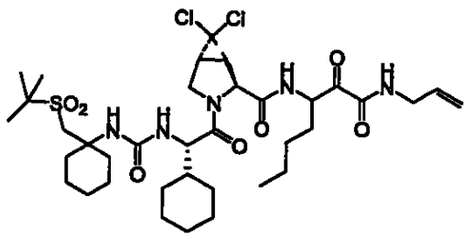


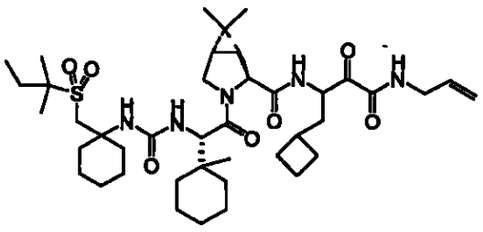


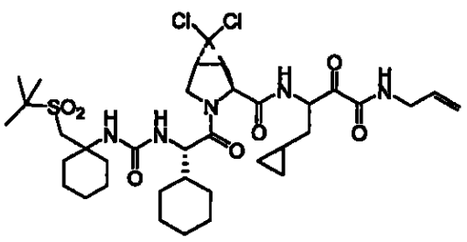


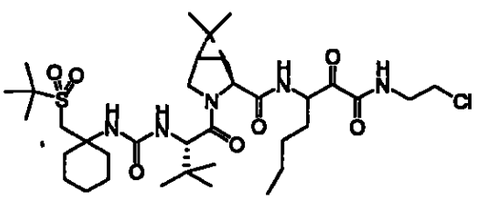


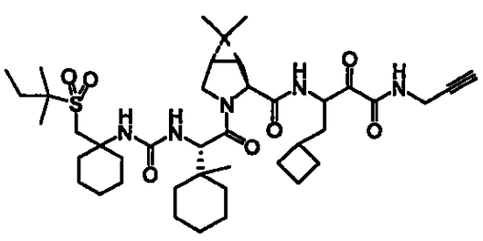


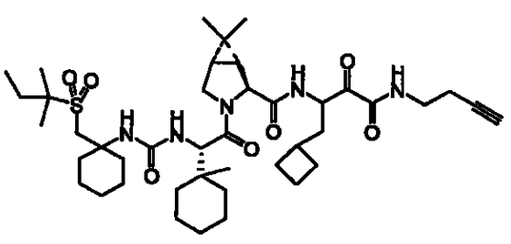


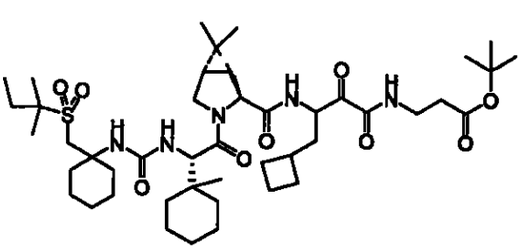


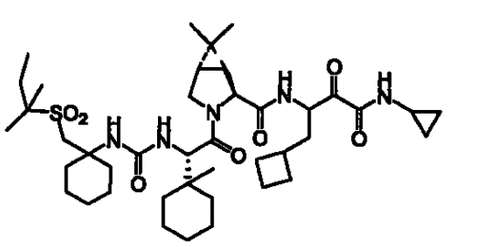


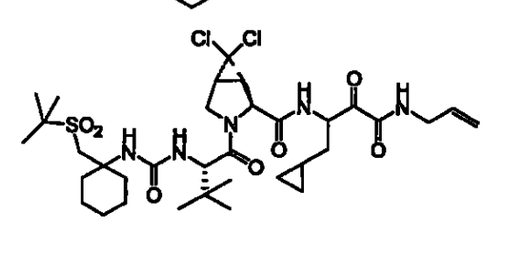


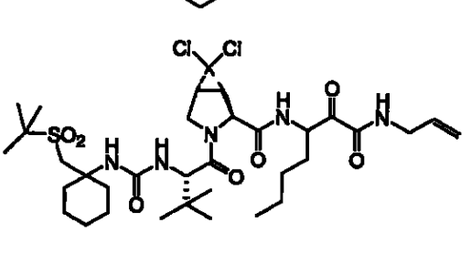


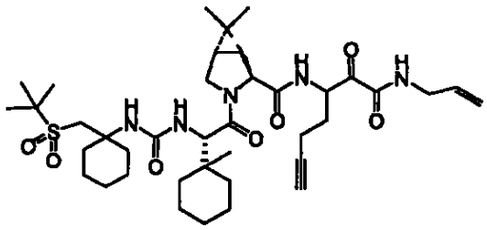


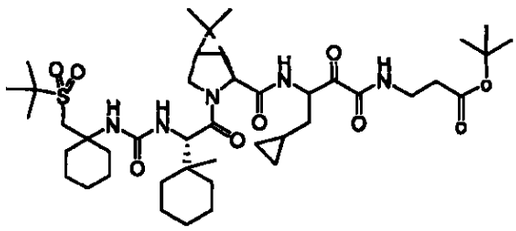


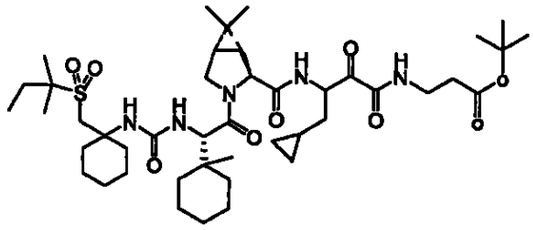


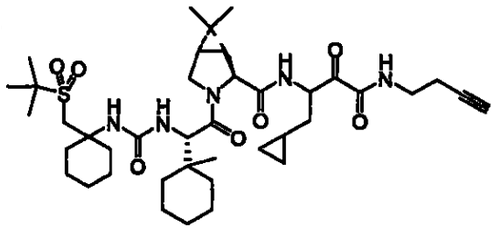


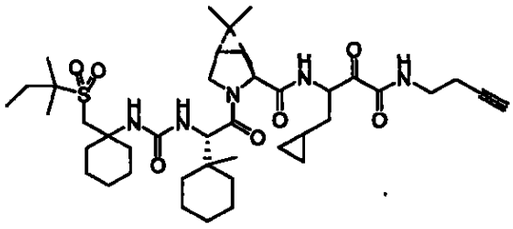


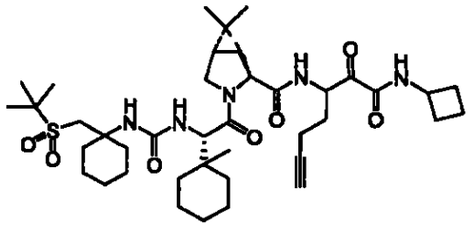


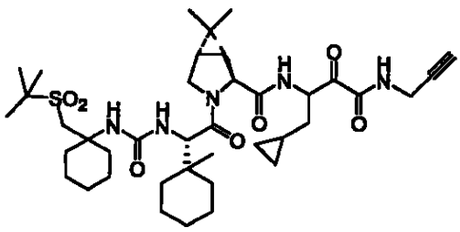


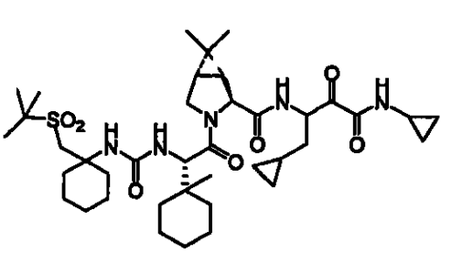


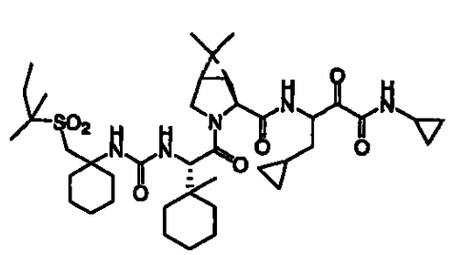


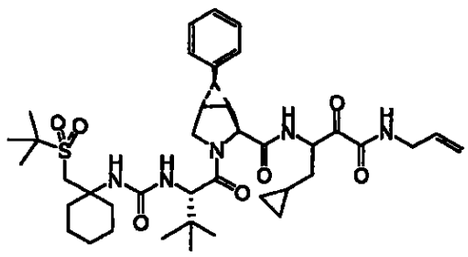


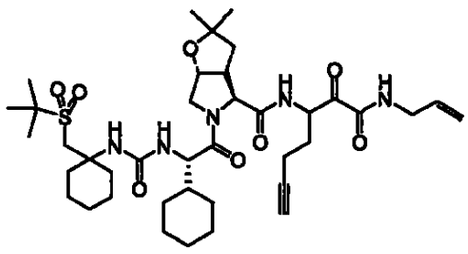


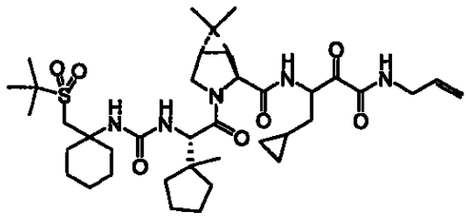


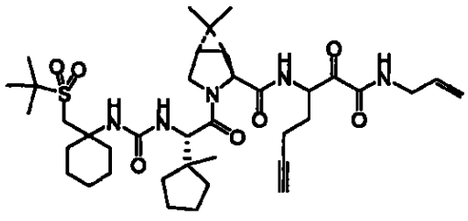


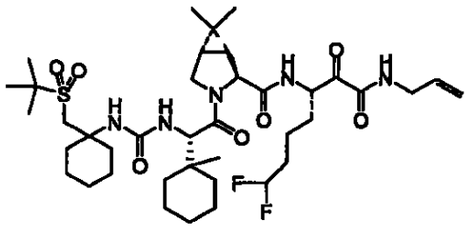


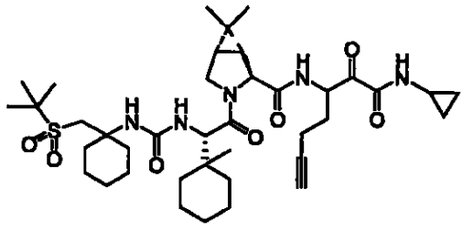


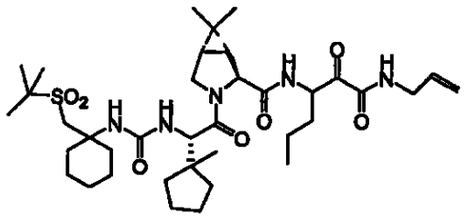


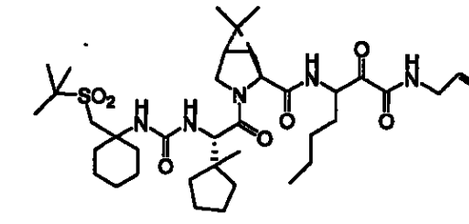


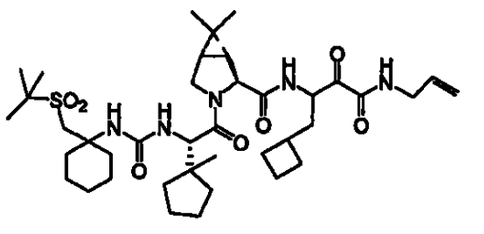


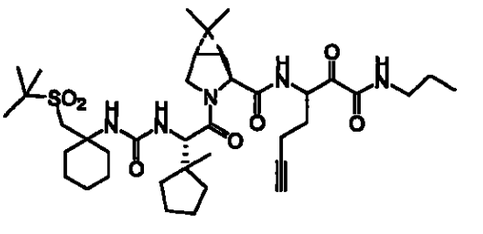


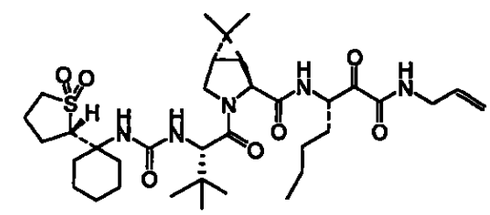


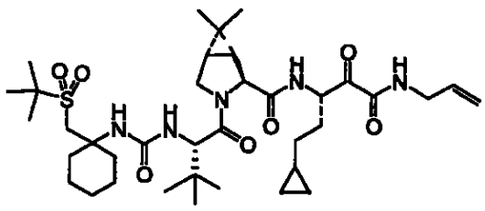


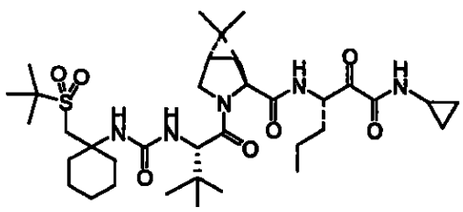


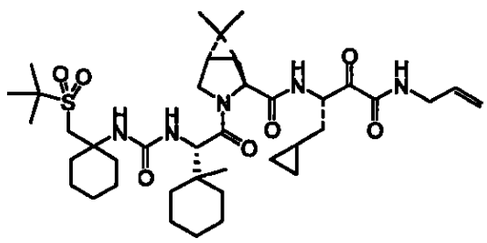


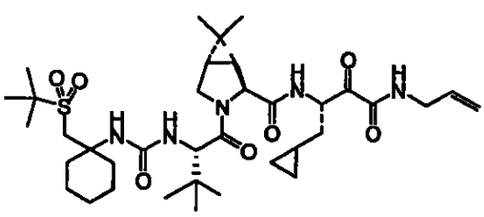


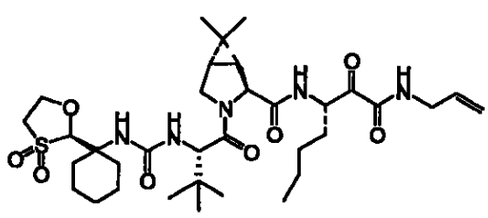


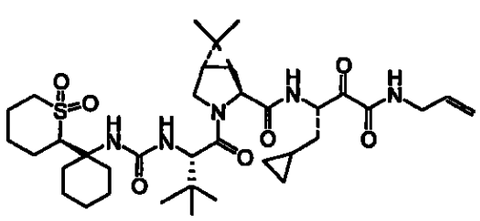


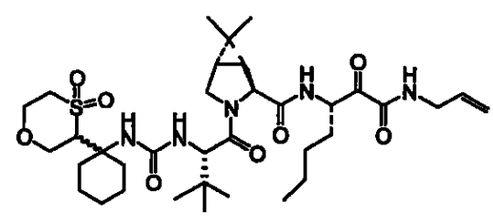


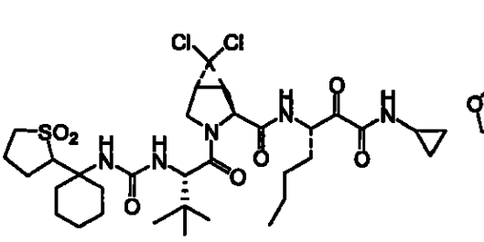


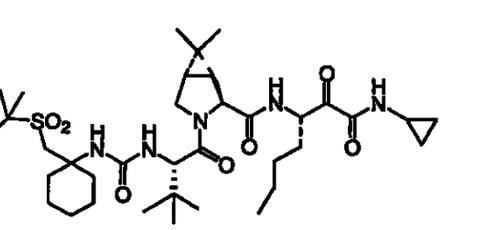




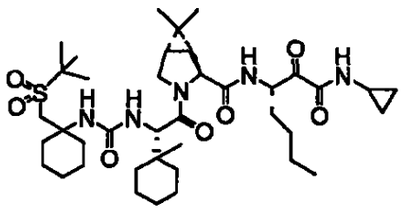


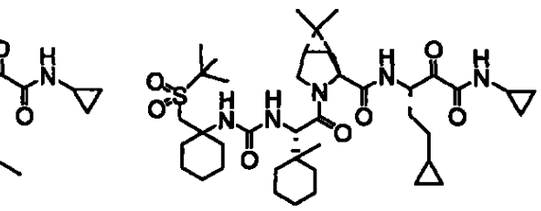


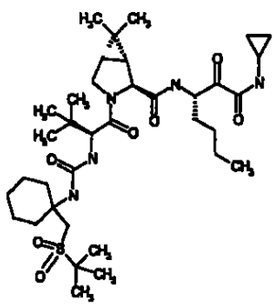


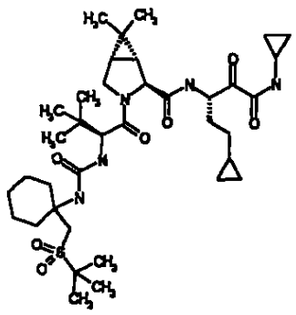


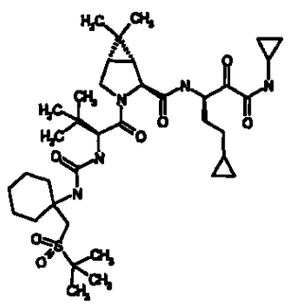
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and .

23. A pharmaceutical composition for treating disorders associated with the HCV, said composition comprising therapeutically effective amount of one or more compounds in claim 22 and a pharmaceutically acceptable carrier.

24. The pharmaceutical composition of claim 23, additionally containing at least one antiviral agent.

25. The pharmaceutical composition of claim 24, still additionally containing at least one interferon or PEG-interferon alpha conjugate.

26. The pharmaceutical composition of claim 25, wherein said at least one antiviral agent is ribavirin and said at least one interferon is α-interferon or pegylated interferon.

27. A method of treatment of a hepatitis C virus associated disorder, comprising administering an effective amount of one or more compounds of claim 22.

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28. A method of modulating the activity of hepatitis C virus (HCV) protease, comprising contacting HCV protease with one or more compounds of claim 22.

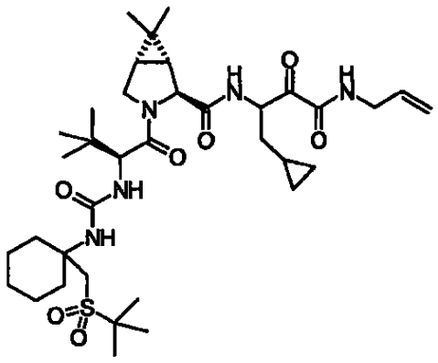
29 A method of treating, preventing, or ameliorating one or more symptoms of hepatitis C, comprising administering a therapeutically effective amount of one or more compounds of claim 22.

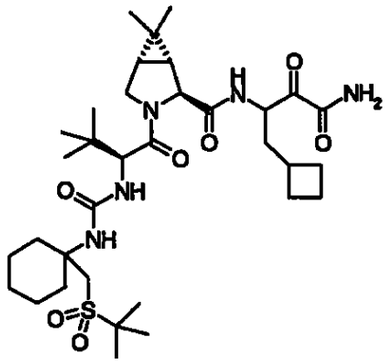
30. The method of claim 29, wherein the HCV protease is the NS3/NS4a protease.

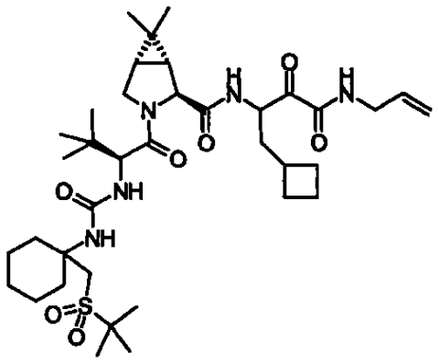
31. The method of claim 30, wherein the compound or compounds inhibit HCV NS3/NS4a protease.

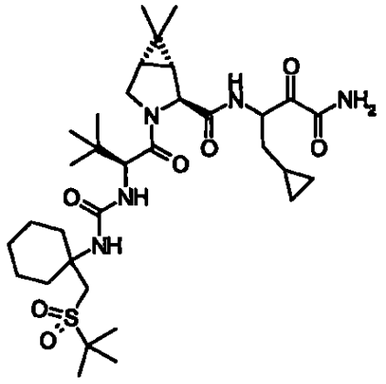
32. A method of modulating the processing of hepatitis C virus (HCV) polypeptide, comprising contacting a composition containing the HCV polypeptide under conditions in which said polypeptide is processed with one or more compounds of claim 22.

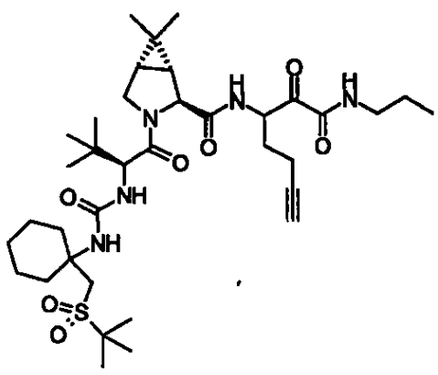
33. A method of treating disorders associated with the HCV, said method comprising administering to a patient in need of such treatment, a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound, or enantiomers, stereoisomers, rotamers, tautomers, and racemates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

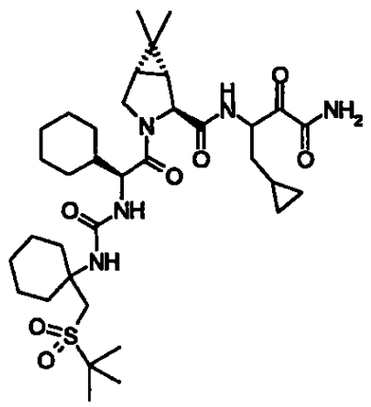


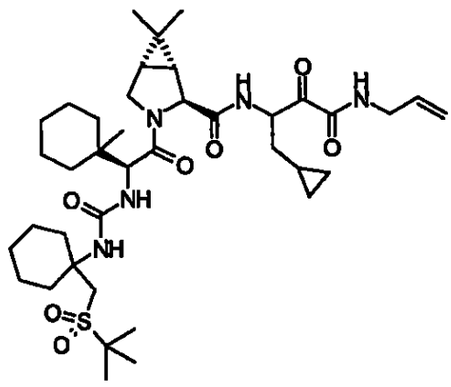


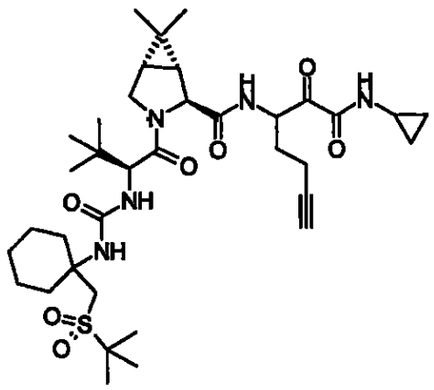


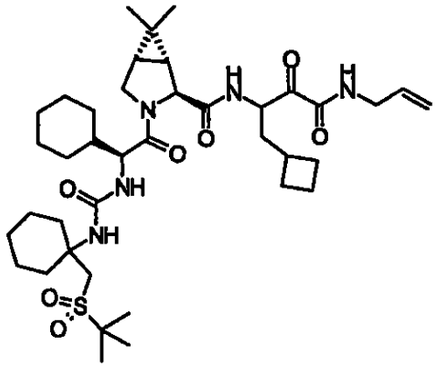


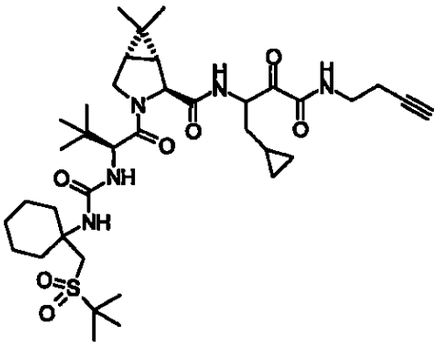


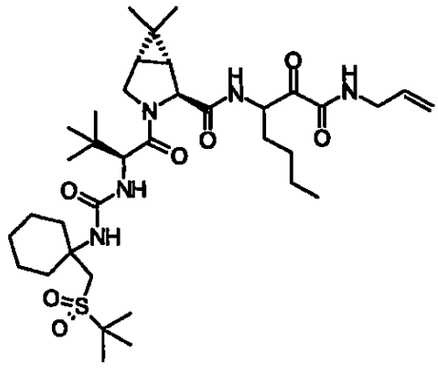


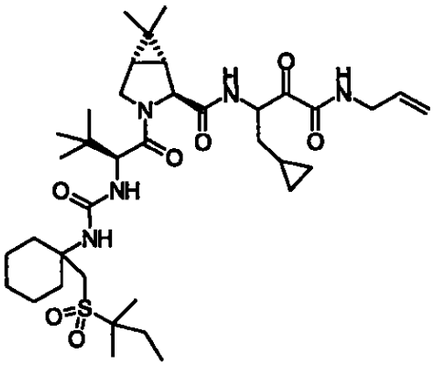


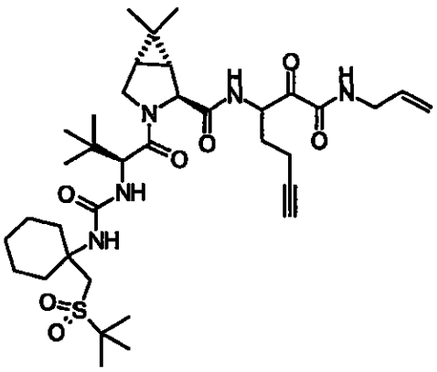


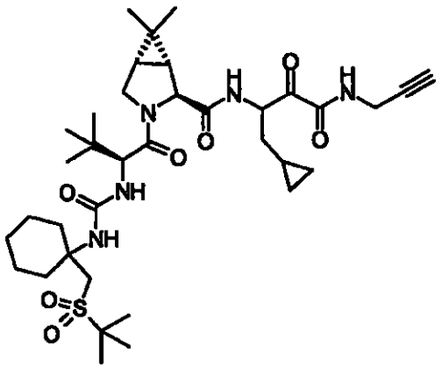


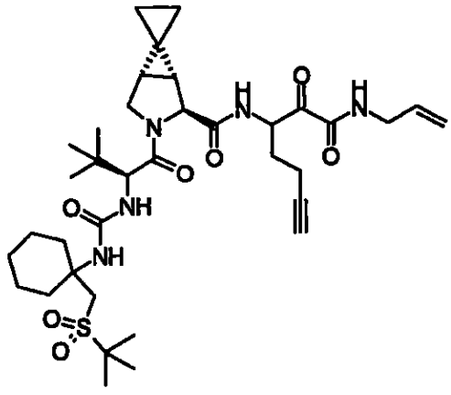


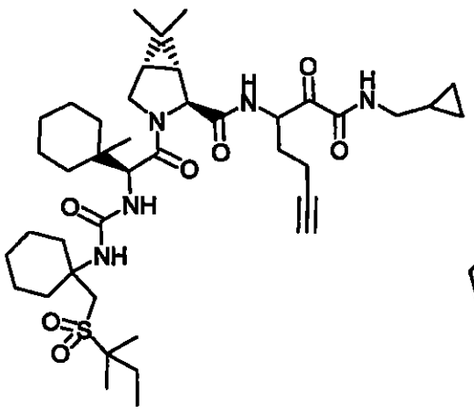


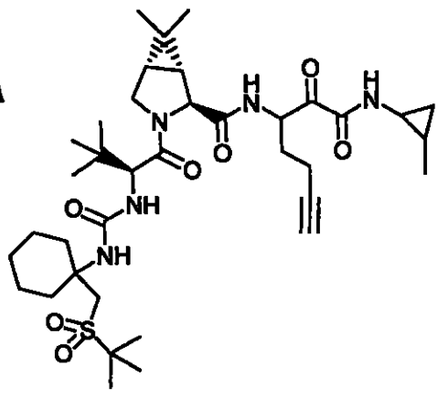


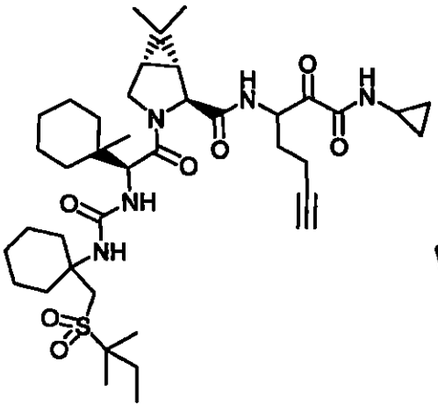


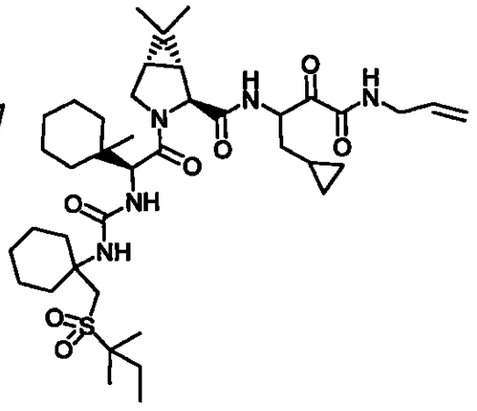


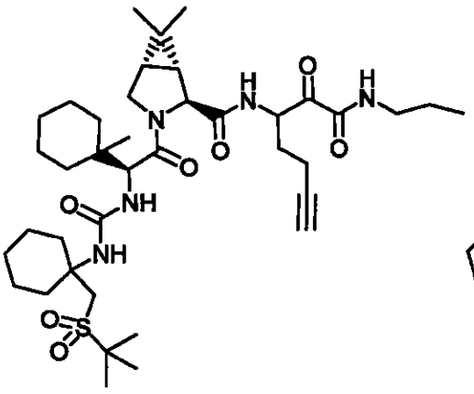


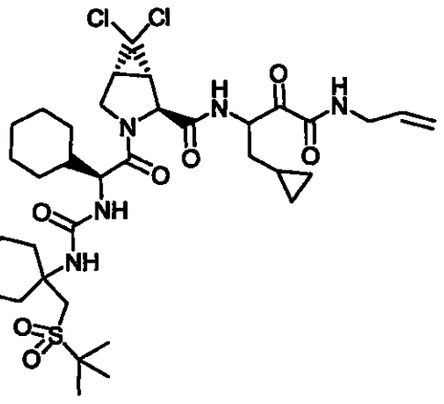


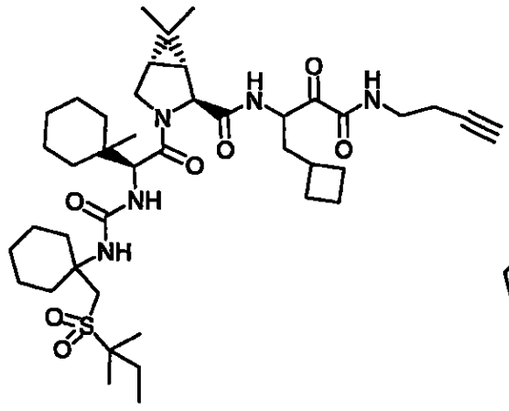


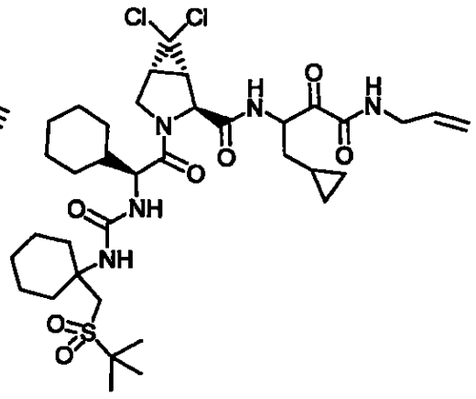


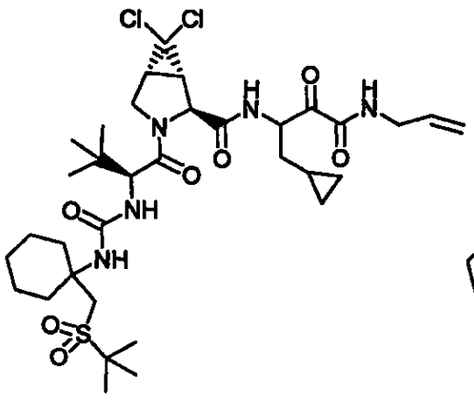


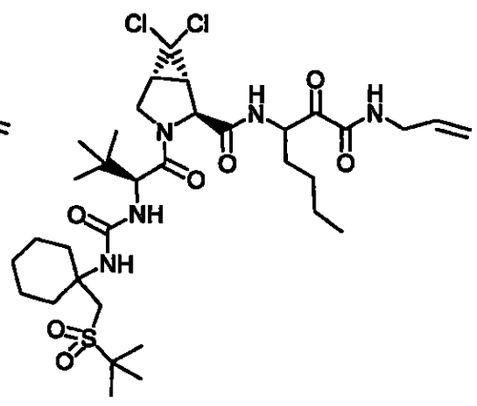


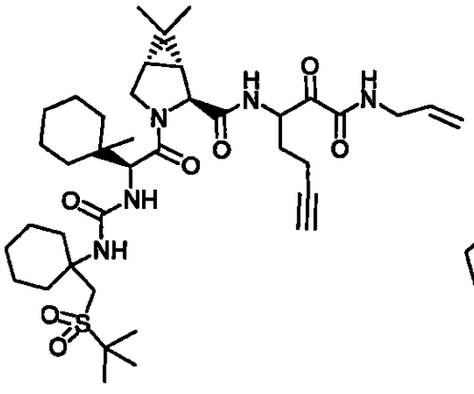


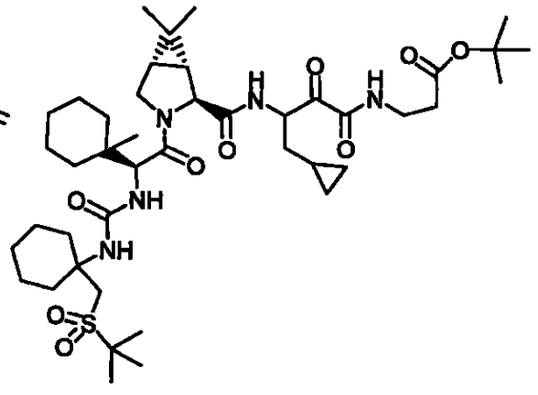


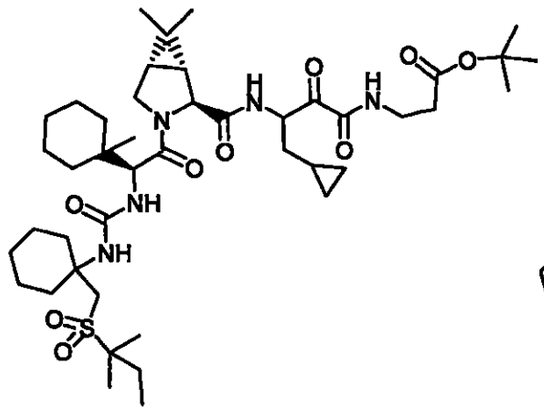


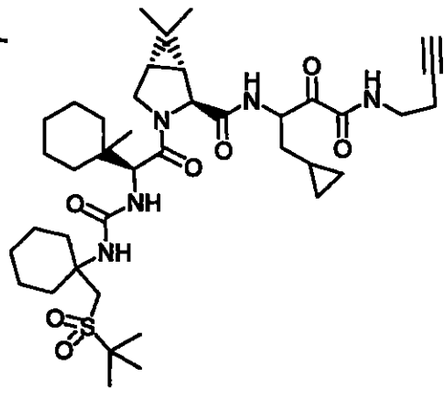


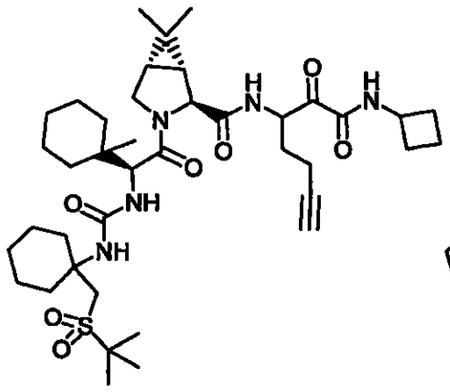


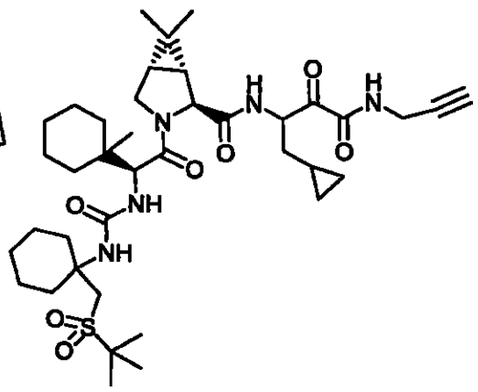


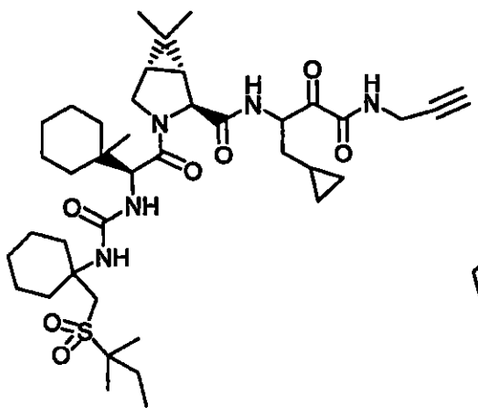


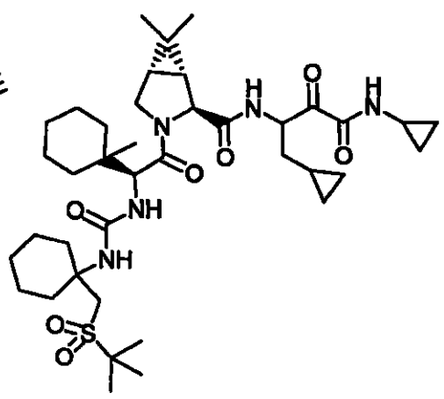


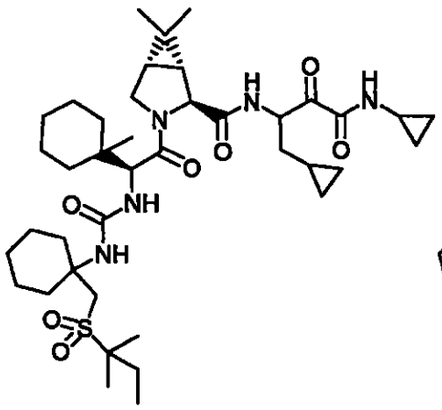


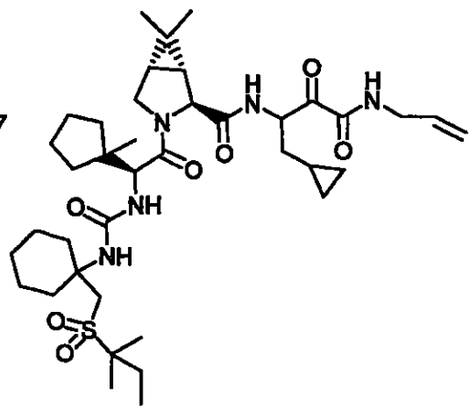


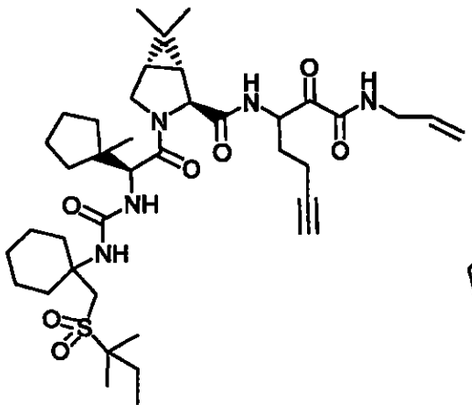


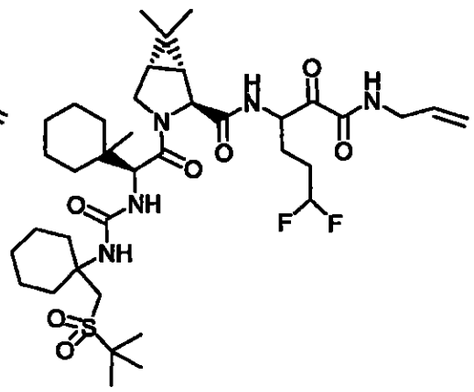


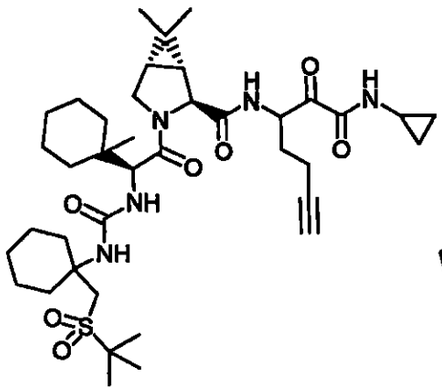


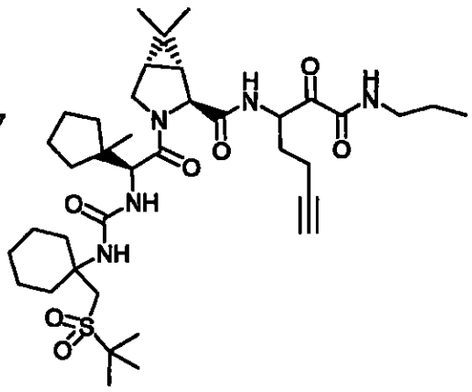


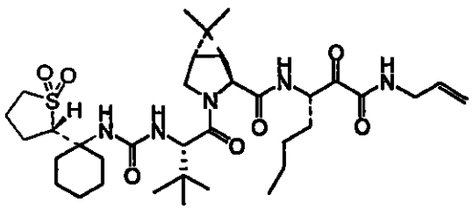


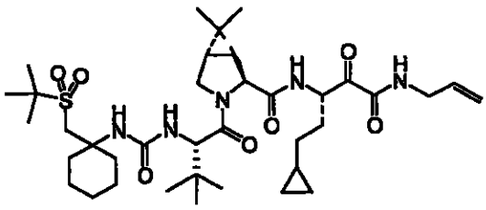


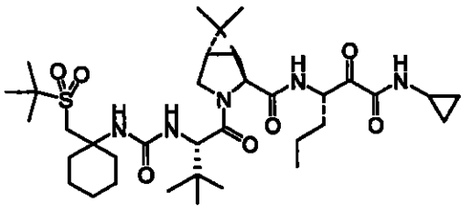


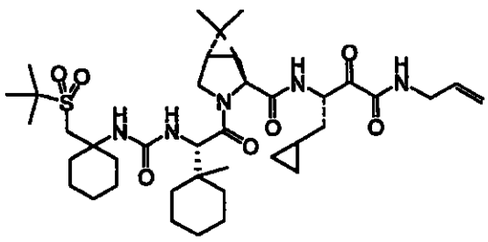


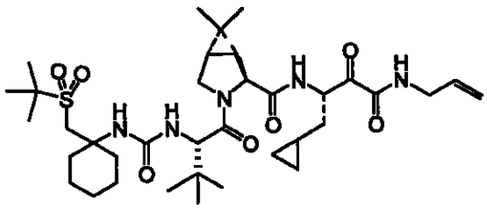


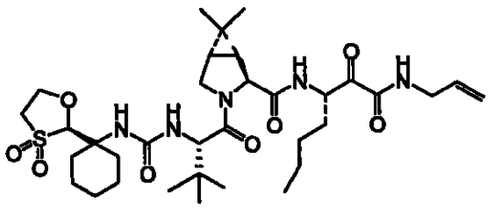


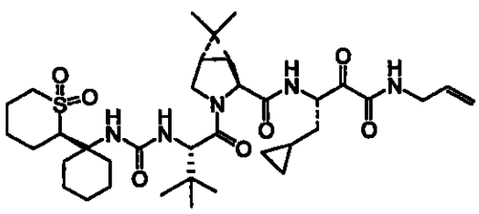


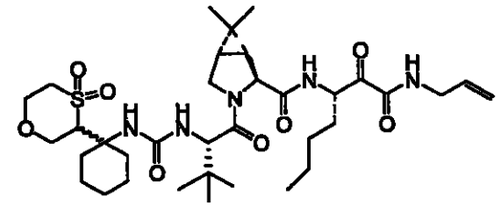


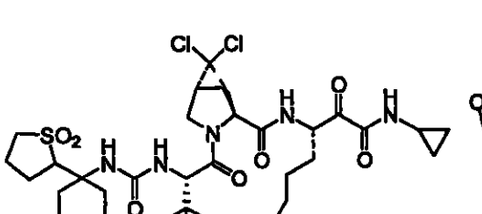


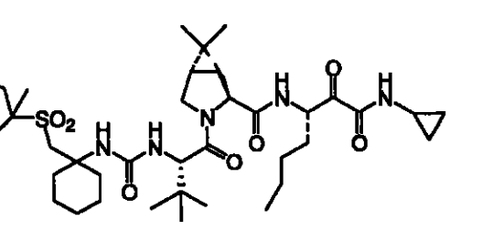






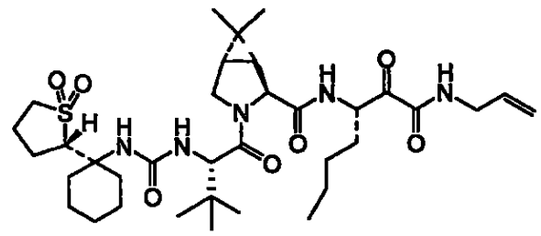




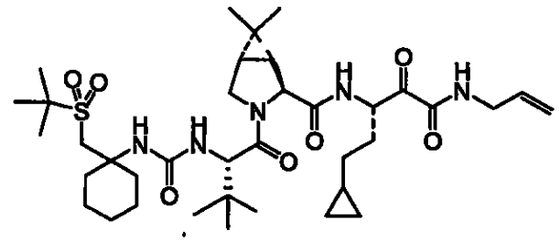


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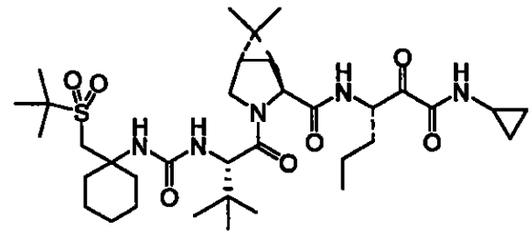
34. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



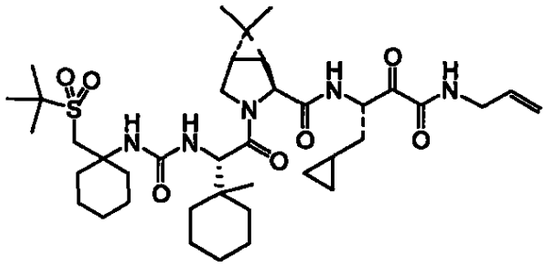
35. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



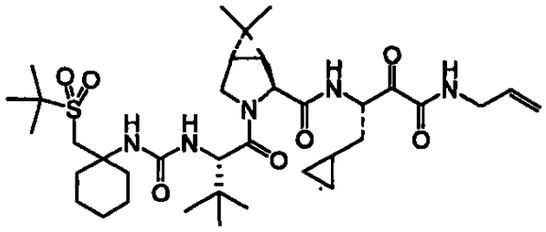
36. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



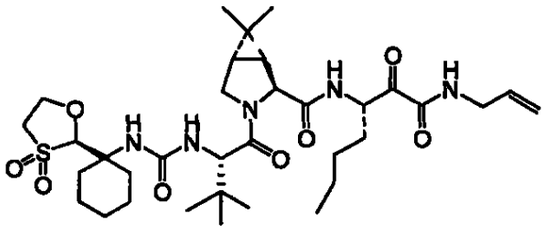
37. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



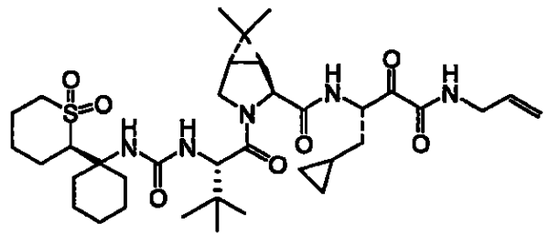
38. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



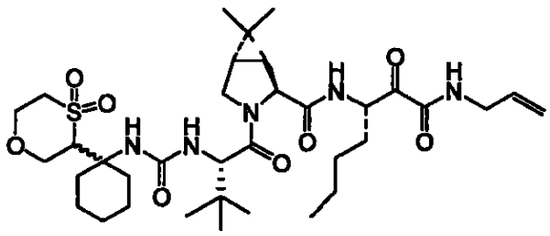
39. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



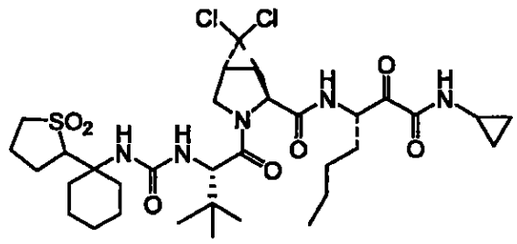
40. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



41. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:

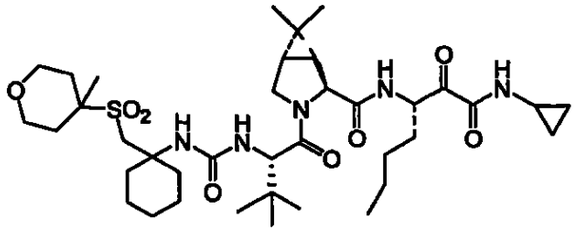


42. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:

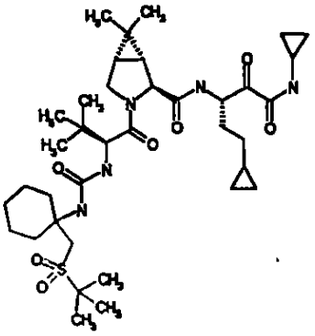


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43. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:

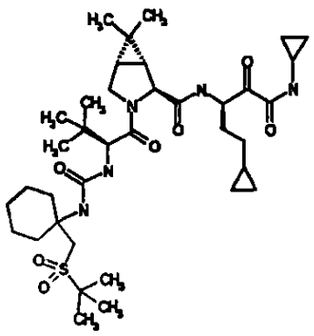


44. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:

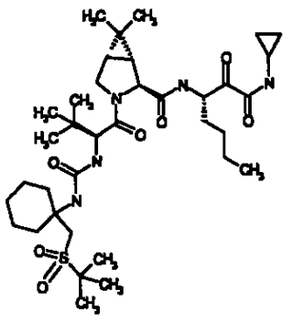


45. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:

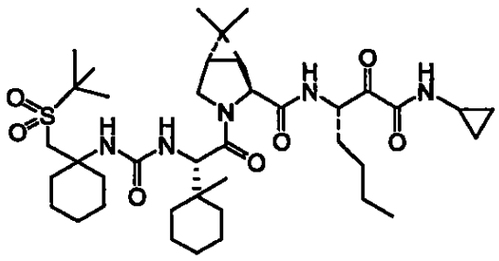
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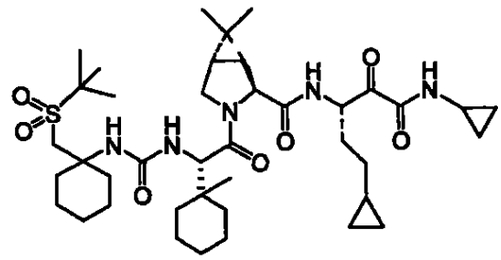
46. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



47. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



48. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



49. A compound of claim 1 in purified form.

INTERNATIONAL SEARCH REPORT

ınal application No.
rCT/US2005/005795

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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 19, 20, 27-33 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

Internal Application No
PCT/US2005/005795

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Form PCT/ISA/210 (patent family annex) (January 2004)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int al Application No
PCT/US2005/005795

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0009543 A		CZ	20010516 A3	15-08-2001
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		EE	200100081 A	15-08-2002
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		US	2002016442 A1	07-02-2002
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/005795

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/52 C07D209/56 C07D491/04 C07K5/08 C07K7/02
A61K31/403 A61K31/407 A61P31/12
//(C07D491/04,307:00,209:00)

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 C07D C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/062265 A (SCHERING CORPORATION; CORVAS INTERNATIONAL, INC; DENDREON CORPORATION) 31 July 2003 (2003-07-31) page 155, last formula; page 156, fifth formula; page 157, second and seventh formula; page 158, fourth formula; page 363, first formula; page 364, sixth formula; page 365, first formula; page 472, third and fourth formula; page 505, first formula; page 567, first formula; claims	1-49

-/--

[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
3 June 2005	13/06/2005

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	Hass, C

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

In ...nal Application No
I..., JS2005/005795 764

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	WO 02/08244 A (SCHERING CORPORATION; CORVAS INTERNATIONAL, INC) 31 January 2002 (2002-01-31) cited in the application page 168, last formula; page 169, fifth formula; page 170, second and seventh formula; page 171, fourth formula; claims	1-49
A	US 2003/216325 A1 (SAKSENA ANIL K ET AL) 20 November 2003 (2003-11-20) page 296, examples 104, 106; page 405, third formula; page 406, first formula; page 408, first and second formula; page 506, first and second formula; claims	1-49
A	WO 02/18369 A (ELI LILLY AND COMPANY; BABINE, ROBERT, EDWARD; CHEN, SHU, HUI; LAMAR,) 7 March 2002 (2002-03-07) page 64, formula EG; page 66, formulae EQ and ER; page 67, formulae EW and EX; claims	1-49
A	WO 00/09543 A (BOEHRINGER INGELHEIM LTD; LLINAS-BRUNET, MONTSE; BAILEY, MURRAY, D; C) 24 February 2000 (2000-02-24) cited in the application page 122, compound 907; claims	1-49

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

06/178 of 765

Memoria Descriptiva

de la

Patente de Invención

Sobre

"COMPUESTOS AZUFRADOS COMO INHIBIDORES DE LA 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

212058
US/JPV

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COMPUESTOS AZUFRADOS COMO INHIBIDORES DE LA 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 ("VHC"), composiciones farmacéuticas que contienen uno o más de dichos inhibidores, métodos para preparar dichos inhibidores y métodos para usar dichos inhibidores para tratar la hepatitis C y trastornos relacionados. Esta invención describe, en forma adicional, nuevos compuestos como inhibidores de la serina proteasa NS3/NS4a del VHC. Esta solicitud reivindica el beneficio de prioridad de la solicitud provisional de los Estados Unidos con Número de Serie 60/548.670 presentada el 27 de febrero de 2004.

Fundamento de la Invención

El virus de la hepatitis C (VHC) es un virus de ARN de hebra simple de sentido (+) que se ha implicado como principal agente causante de la hepatitis no A, no B (HNANB), en particular en la HNANB asociada con la sangre (BB-HNANB) (*ver,* Publicación de Solicitud de Patente Internacional No. WO 89/04669 y Publicación de Solicitud de Patente Europea No. EP 381 216). Debe distinguirse la HNANB de otros tipos de enfermedades hepáticas virales, tales como el virus de la hepatitis A (VHA), el virus de la hepatitis B (VHB), virus de la hepatitis delta (VHD), citomegalovirus (CMV) y virus de Epstein-Barr (VEB), como también de otras formas de enfermedad hepática tal como el alcoholismo y la cirrosis biliar primaria.

Recientemente, se ha identificado, clonado y expresado una proteasa del VHC necesaria para el procesamiento de polipéptidos y replicación viral. (*Ver,* por ej., Patente de los Estados Unidos No. 5 712.145). Esta poliproteína de aprox. 3000 aminoácidos contiene, desde el amino terminal hasta el carboxilo terminal, una proteína nucleocápsida (C), proteínas de envoltura (E1 y E2) y varias

proteínas no estructurales (NS1, 2, 3, 4a, 5a y 5b). NS3 es una proteína de aproximadamente 68 kda, codificada por aproximadamente 1893 nucleótidos del genoma del VHC, y posee dos dominios distintos: (a) un dominio de serina proteasa formado por aproximadamente 200 de los aminoácidos N-terminales, y (b) un dominio de ATPasa dependiente del ARN en el extremo C-terminal de la proteína. La proteasa NS3 se considera miembro de la familia de quimiotripsina debido a las similitudes en la secuencia de la proteína, la estructura tridimensional general y el mecanismo de catálisis. Otra enzimas similares a la quimiotripsina son la elastasa, factor Xa, trombina, tripsina, plasmina, uroquinasa, tPA y PSA La serina proteasa NS3 del VHC es responsable de la proteólisis del polipéptido (poliproteína) en las uniones NS3/NS4a, NS4a/NS4b, NS4b/NS5a y NS5a/NS5b y de este modo es responsable de generar cuatro proteínas virales durante la replicación viral. Esto hizo de la serina proteasa NS3 del VHC un blanco atractivo para la quimioterapia antiviral. Los compuestos de la invención pueden inhibir dicha proteasa También pueden modular el procesamiento del polipéptdo del virus de la hepatitis C (VHC).

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 auto-ruptura de la unión NS3/NS4a producida por la serina proteasa NS3/NS4a ocurre dentro de la molécula (es decir, *cis*) mientras que otros sitios de ruptura se procesan intermolecularmente (es decir, *trans*).

El análisis de los sitios de ruptura natural para la proteasa de VHC reveló la presencia de cisteína en P1 y serina en P1' y que estos residuos se conservan estrictamente en las uniones NS4a/NS4b, NS4b/NS5a y NS5a/NS5b. La unión NS3/NS4a contiene una treonina en P1 y una serina en P1'. La sustitución Cis→Tr en NS3/NS4a se postula como explicación para el requerimiento del procesamiento *cis* en lugar de *trans* en esta unión *Ver,* por ej., Pizzi et al (1994)

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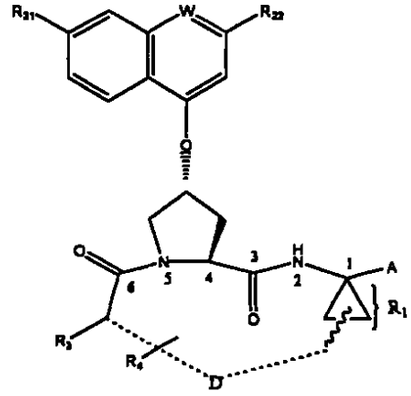
Proc. Natl. Acad. Sci (USA) 91 888-892, Failla et al (1996) Folding & Design 1 35-42 El sitio de ruptura de NS3/NS4a es, además, más resistente a la mutagénesis que otros sitios. *Ver,* por ej., Kollykhalov et al (1994) J Virol 68:7525-7533. Se ha descubierto, además, que los residuos ácidos en la región ascendente del sitio de ruptura son un requerimiento para una ruptura eficiente. *Ver,* por ej., Komoda et al (1994) J. Virol. 68:7351-7357.

Los inhibidores de la proteasa del VHC que se han informado incluyen antioxidantes (*ver,* Publicación de Solicitud de Patente Internacional No. WO 98/14181), ciertos péptidos y análogos de péptidos (*ver,* Publicación de 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 eglin c (Martin et al. (1998) Biochem. 37:11459-11468, inhibidores con afinidad seleccionados entre el inhibidor de la tripsina secretora 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) Proteína Eng. 10:607-614), y α1-antiquimotripsina (ACT) (Elzouki et al.) (1997) J. Hepat. 27:42-28). Recientemente se ha descubierto una ribozima diseñada para destruir selectivamente el ARN del virus de la hepatitis C (*ver, BioWorld Today* 9(217): 4 (10 de noviembre de 1998)).

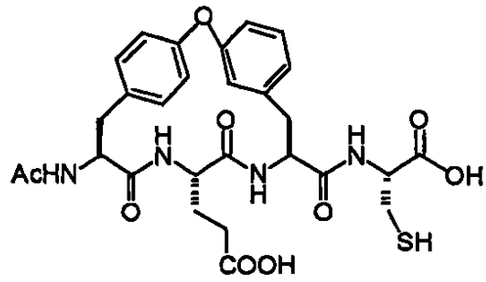
Además, se hace referencia a las publicaciones de PCT No. WO 98/17679, publicada el 30 de abril de 1998 (Vertex Pharmaceuticals Incorporated); WO 98/22496, publicada el 28 de mayo de 1998 (F Hoffmann-La Roche AG); y WO 99/07734, publicada el 18 de febrero de 1999 (Boehringer Ingelheim Canada Ltd)

El VHC se ha vinculado a la cirrosis hepática y a la inducción del carcinoma hepatocelular. El pronóstico para pacientes que sufren de infección por VHC actualmente es pobre La infección por VHC es más difícil de tratar que otras formas de la hepatitis debido a la falta de inmunidad o remisión asociada con la infección por VHC Datos actuales indican un índice de sobrevida inferior al 50% a los cuatro años posteriores al diagnóstico de cirrosis. Los pacientes con diagnóstico de carcinoma hepatocelular extirpable localizado tienen un índice de sobrevida del 10-30%, mientras que aquellos con carcinoma hepatocelular no extirpable localizado tienen un índice de sobrevida a los cinco años inferior al 1%.

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

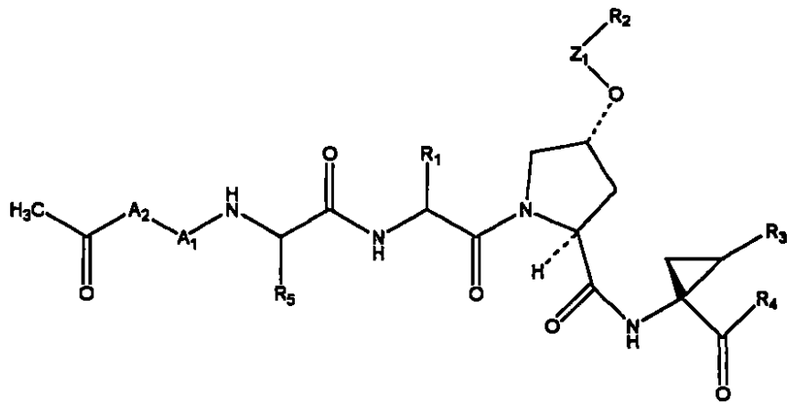


Se hace referencia a A Marchetti *et al*, *Synlett*, S1, 1000-1002 (1999) que describe la síntesis de análogos bicíclicos de un inhibidor de proteasa NS3 del VHC Un compuesto descrito allí tiene la fórmula.

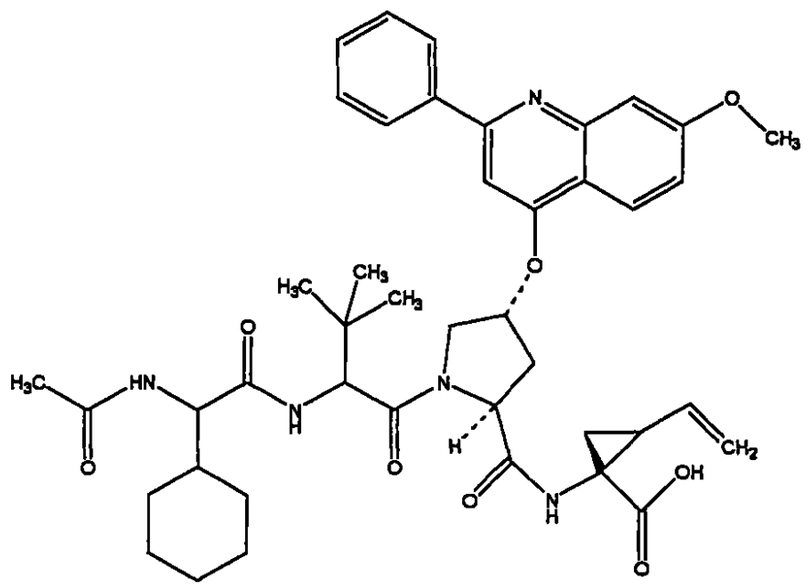


Se hace referencia, además, a W Han *et al*, *Bioorganic & Medicinal Chem. Lett,* (2000) 10, 711-713, que describe la preparación de ciertas α-cetoamidas, α-cetoésteres y α-dicetonas que contienen grupos funcionales alilo y etilo.

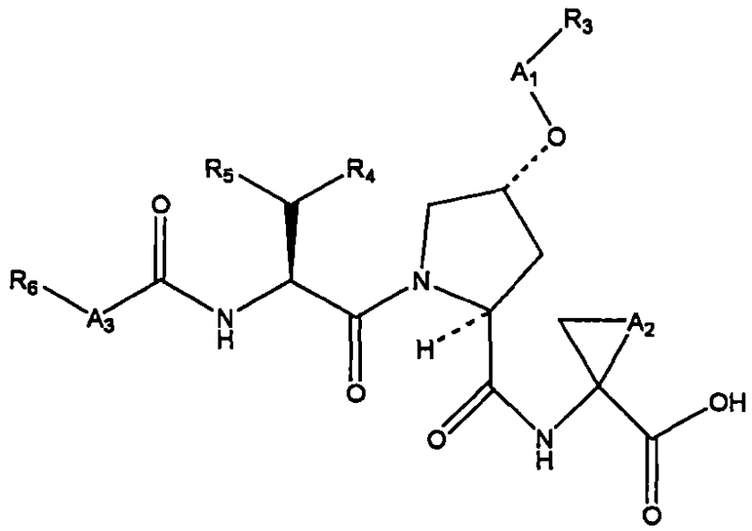
Se hace referencia, además, a la WO 00/09558 (Cesionario: Boehringer Ingelheim Limited, Publicada el 24 de febrero de 2000) que describe derivados peptídicos de fórmula



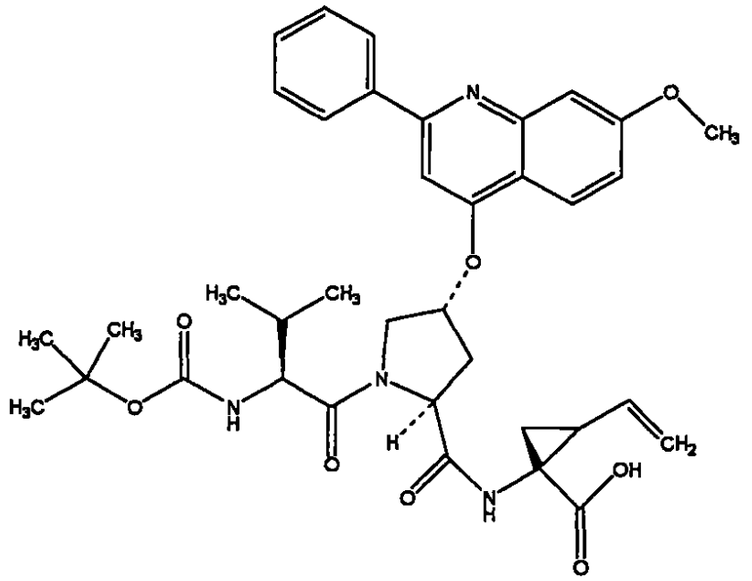
donde los diferentes elementos se definen en ella. Un compuesto ilustrativo de esa serie es:



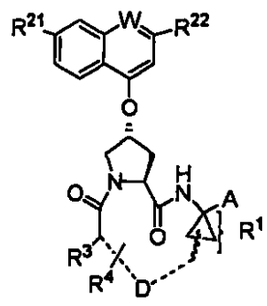
Se hace referencia, además, a la WO 00/09543 (Cesionario: Boehringer Ingelheim Limited; Publicada el 24 de febrero 2000) que describe derivados peptídicos de fórmula.



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



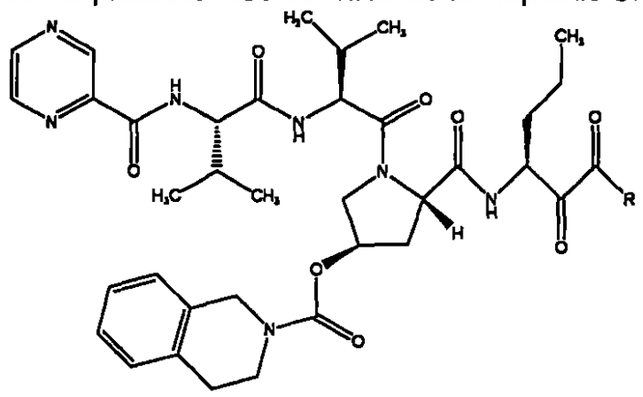
Se hace referencia, además, a la U.S. 6.608 027 (Boehringer Ingelheim, Canada) que describe inhibidores de la proteasa NS3 del tipo



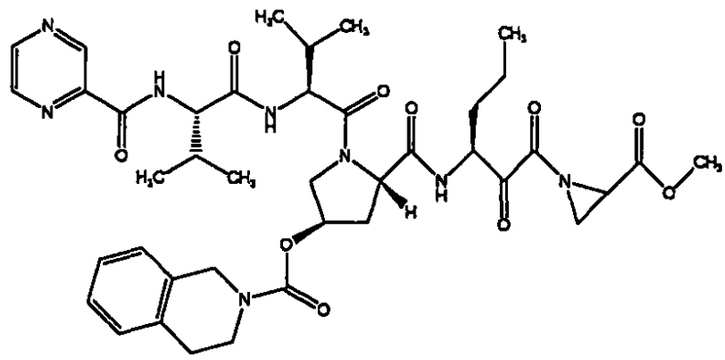
en los cuales los diferentes restos se definen allí

Los tratamientos actuales para la hepatitis C incluyen tratamiento con interferón-α (INF_{α}) y tratamiento combinado con ribavirina e interferón. *Ver,* por ej., Beremguer et al. (1998) Proc. Assoc Am. Physicians 110(2).98-112. Estos tratamientos adolecen de un índice bajo de respuesta prolongada y frecuentes efectos colaterales *Ver,* por ej., Hoofnagle et al (1997) N. Engl J. Med. 336:347. Actualmente, no se encuentra vacuna disponible para la infección por VHC

Se hace referencia, en forma adicional, a la WO 01/74768 (Cesionario: 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 revelado en la antes mencionada WO 01/74768 tiene la siguiente fórmula



Las publicaciones por 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, La solicitud pendiente de Patente de los Estados Unidos, No de Serie 10/052.386, presentada el 18 de enero de 2002, describe varios tipos de péptidos y/u otros compuestos como inhibidores de la serina proteasa NS-3 del virus de la hepatitis C Las revelaciones de esas solicitudes se incorporan aquí a modo de referencia.

Existe la necesidad de lograr nuevos tratamientos y nuevas terapias para la infección por VHC. Existe la necesidad de obtener compuestos útiles en el tratamiento o la prevención o la atenuación de uno o más síntomas de la hepatitis C.

Existe la necesidad de lograr métodos para tratamiento o prevención o atenuación de uno o más síntomas de la hepatitis C

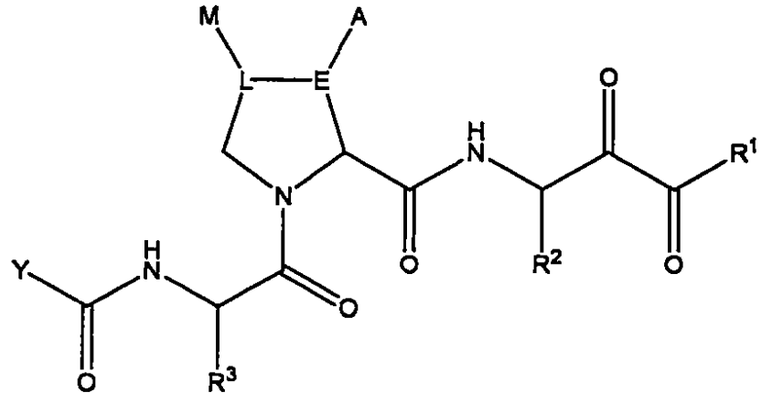
Existe la necesidad de lograr métodos para modular la actividad de las serina proteasas, en particular la serina proteasa NS3/NS4a del VHC, usando los compuestos provistos aquí

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

Breve Descripción de la Invención

En sus muchas realizaciones, la presente invención provee una nueva clase de inhibidores de la proteasa del VHC, composiciones farmacéuticas que contienen uno o más de los compuestos, métodos para preparar formulaciones

farmacéuticas que comprenden uno o más de dichos compuestos, y métodos para tratamiento o prevención del VHC o la atenuación de uno o más de los síntomas de la hepatitis C usando uno o más dichos compuestos o una o más dichas formulaciones. Se proveen, además, métodos para modular la interacción de un polipéptido del VHC con la proteasa de VHC. Entre los compuestos provistos aquí, los compuestos que inhiben la actividad de la serina proteasa NS3/NS4a del VHC son los preferidos La presente invención revela compuestos, como también sales, solvatos o ésteres aceptables desde el punto de vista farmacéutico de dichos compuestos, dichos compuestos tienen la estructura general que se muestra en la Fórmula estructural I:

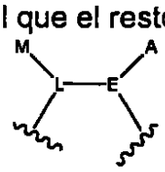


Fórmula I

en la cual

R^1 es H, OR^8, NR^9R^{10}, o CHR^9R^{10}, en los cuales R^8, R^9 y R^{10} pueden ser iguales o diferentes, seleccionándose cada uno en forma independiente del grupo formado por H, alquilo-, alquenilo-, alquinilo-, arilo-, heteroalquilo-, heteroarilo-, cicloalquilo-, heterociclilo-, arilalquilo-, y heteroarilalquilo;

A y M pueden ser iguales o diferentes, seleccionándose cada uno en forma independiente de R, OR, NHR, NRR', SR, SO_2R, y halo; o A y M están conectados uno al otro de modo tal que el resto:



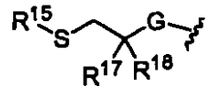
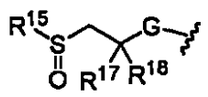
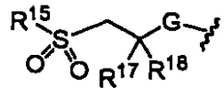
que se mostró anteriormente en la Fórmula I forma tanto un cicloalquilo de tres, cuatro, seis, siete y ocho miembros, un heterociclilo de cuatro a ocho miembros, un arilo de seis a diez miembros, o un heteroarilo de cinco a diez miembros;

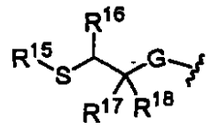
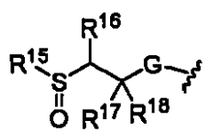
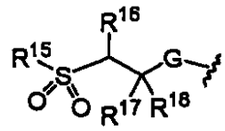
E es C(H) o C(R),

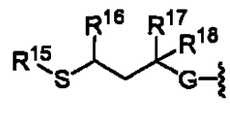
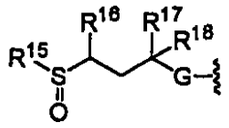
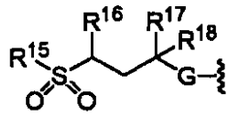
L es C(H), C(R), $CH_2C(R)$, o $C(R)CH_2$;

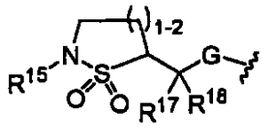
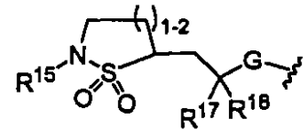
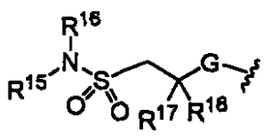
R, R', R^2, y R^3 pueden ser iguales o diferentes, seleccionándose cada uno en forma independiente del grupo formado por H, alquilo-, alquenilo-, alquinilo-, cicloalquilo-, heteroalquilo-, heterociclilo-, arilo-, heteroarilo-, (cicloalquil)alquilo-, (heterociclil)alquilo-, aril-alquilo-, y heteroaril-alquilo-; o alternativamente R y R' en NRR' están conectados uno al otro de manera tal que NRR' forma un heterociclilo de cuatro a ocho miembros;

e Y se selecciona de los siguientes restos:


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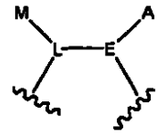
en los cuales G es NH o O, y R^{15}, R^{16}, R^{17} y R^{18} pueden ser iguales o diferentes, seleccionándose cada uno en forma independiente del grupo formado por H, alquilo, heteroalquilo, alquenilo, heteroalquenilo, alquinilo, heteroalquinilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, o alternativamente, (i) R^{15} y R^{16} están conectados entre sí para formar una

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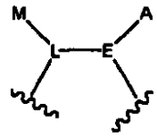
estructura cíclica de cuatro a ocho miembros, y (ii) del mismo modo, en forma independiente R^{17} y R^{18} están conectados uno al otro para formar un cicloalquilo o heterociclilo de tres a ocho miembros;

donde cada uno de dichos alquilo, arilo, heteroarilo, cicloalquilo o heterociclilo pueden no estar sustituidos o estar sustituidos en forma opcional e independiente con uno o más restos seleccionados del grupo formado por: 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

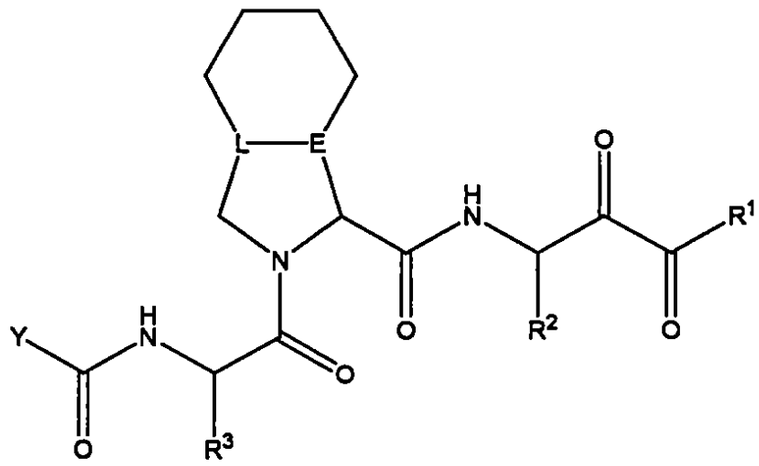
La afirnación anterior "A y M están conectados uno al otro de modo tal que el resto:



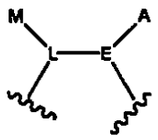
que se mostró anteriormente en la Fórmula I forma tanto un cicloalquilo de tres, cuatro, seis, siete y ocho miembros, un heterociclilo de cuatro a ocho miembros, un arilo de seis a diez miembros, o un heteroarilo de cinco a diez miembros" puede ilustrarse en un modo no limitativo del siguiente modo. Así, por ejemplo, en el caso en el cual A y M están conectados de modo tal que el resto·



que se mostró anteriormente en la Fórmula I forma un cicloalquilo de seis miembros (ciclohexilo), la Fórmula I puede mostrarse como:



Una persona con experiencia usual en el arte apreciará que puede llegarse a presentaciones similares para la Fórmula I cuando A y M que se mostró anteriormente en el resto·



(M-L-E-A tomados juntos) 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 afirmación "alternativamente, (i) R^{15} y R^{16} están conectados uno al otro para formar una estructura cíclica de cuatro a ocho miembros, y (ii) del mismo modo, en forma independiente R^{17} y R^{18} están conectados para formar un cicloalquilo o heterociclilo de tres a ocho miembros" se refiere a las siguientes posibilidades· (i) R^{15} y R^{16} están conectados para formar una estructura cíclica mientras que R^{17} y R^{18} no lo están; (ii) R^{17} y R^{18} están conectados para formar una estructura cíclica mientras que R^{15} y R^{16} no lo están; y (iii) R^{15} y R^{16} están conectados para formar una estructura cíclica, y R^{17} y R^{18} están conectados además para formar una estructura cíclica. Estas posibilidades pueden ocurrir de manera independiente unas de otras.

En las definiciones mencionadas con anterioridad de R, R', R^2 y R^3, el alquilo preferido está formado por uno a diez átomos de carbono, el alquenilo o alquinilo preferido está formado por dos a diez átomos de carbono, el cicloalquilo preferido está formado por tres a ocho átomos de carbono; y el heteroalquilo, heteroarilo o heterocicloalquilo preferido tiene uno a seis átomos de oxígeno, nitrógeno, azufre o fósforo.

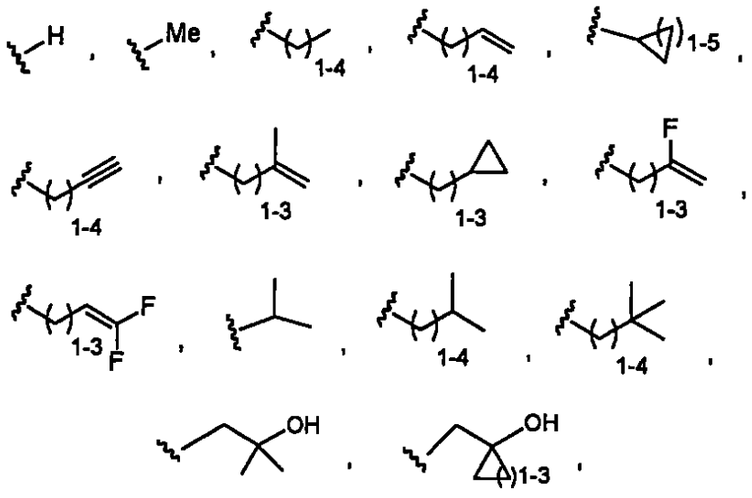
Los compuestos representados por la Fórmula I, sólos o combinados con uno o más agentes adicionales descritos aquí, pueden ser útiles para tratar enfermedades tales como, por ejemplo, VHC, VIH, (SIDA, Síndrome de Inmuno Deficiencia Adquirida), y trastornos relacionados, como también para modular la actividad de la proteasa del virus de la hepatitis C (VHC), prevenir el VHC, o atenuar uno o más síntomas de la hepatitis C. Dicha modulación, tratamiento, prevención o alivio pueden realizarse con los compuestos de la invención, como también con las composiciones farmacéuticas o formulaciones que comprenden dichos compuestos. Sin limitarse a la teoría, se considera que la proteasa del VHC puede ser la proteasa NS3 o NS4a. Los compuestos de la invención pueden inhibir dicha proteasa. Además, pueden modular el procesamiento del polipéptido del virus de la hepatitis C (VHC).

Descripción Detallada

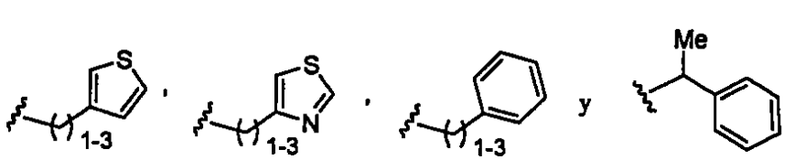
En una realización, la presente invención revela compuestos que están representados por la Fórmula estructural I o una de sus sales o solvatos o ésteres aceptables desde el punto de vista farmacéutico, en los cuales los diferentes restos son como se los definió con anterioridad

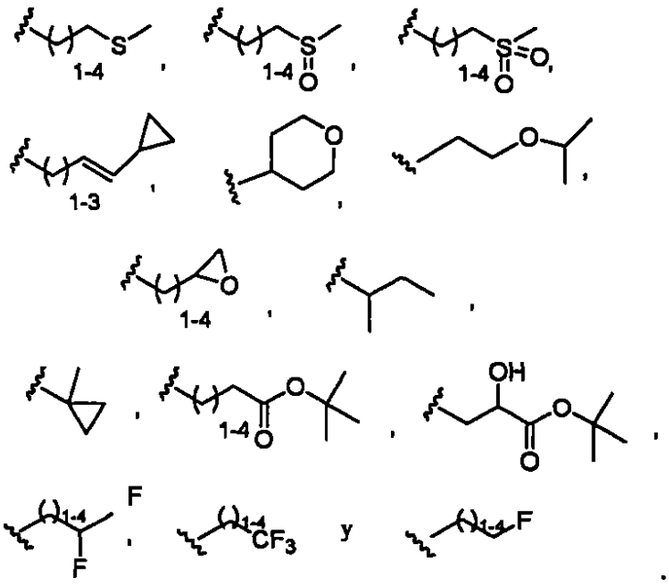
En otra realización, R^1 es NR^9R^{10}, y R^9 es H, R^{10} es H, o R^{14} en los cuales R^{14} es H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, alquil-arilo, alquil-heteroarilo, aril-alquilo, alquenilo, alquinilo o heteroaril-alquilo.

En otra realización, R^{14} se selecciona del grupo formado por:

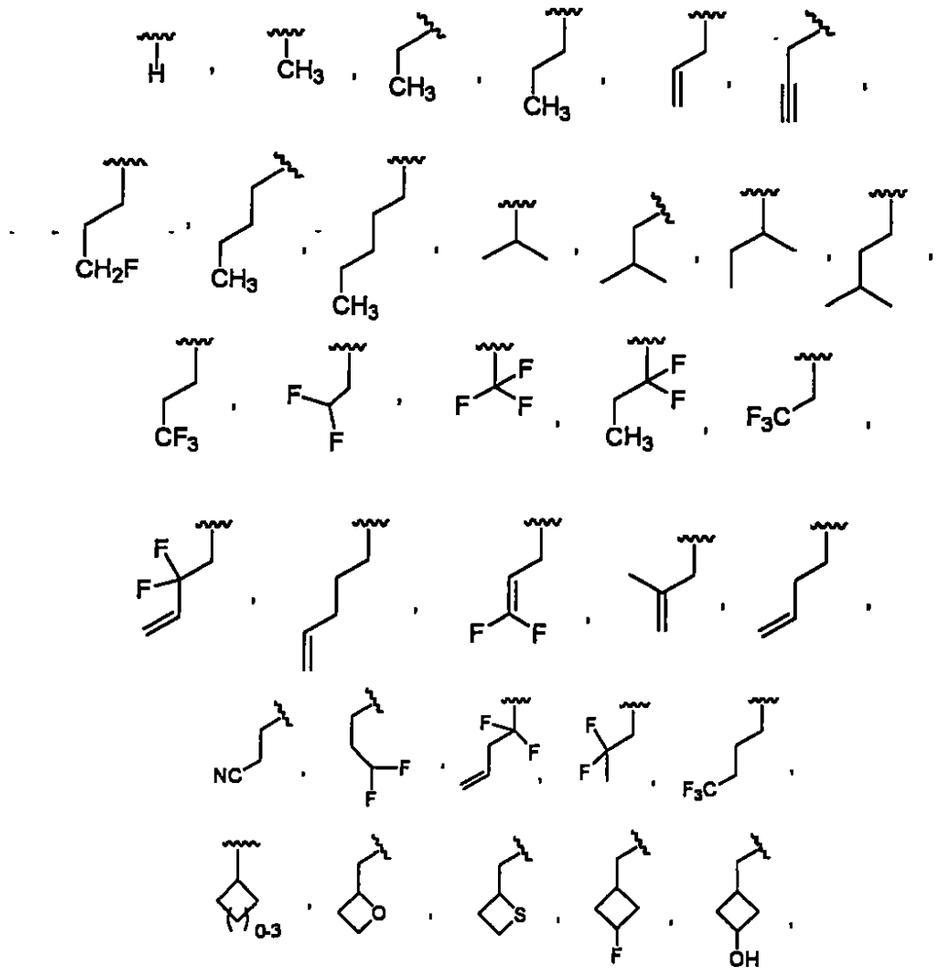


y

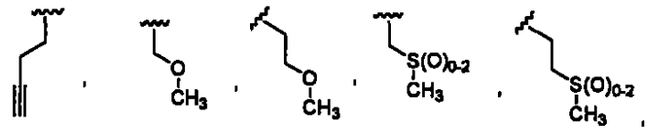


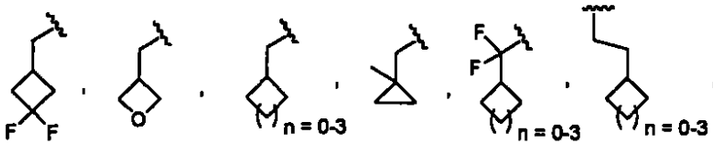


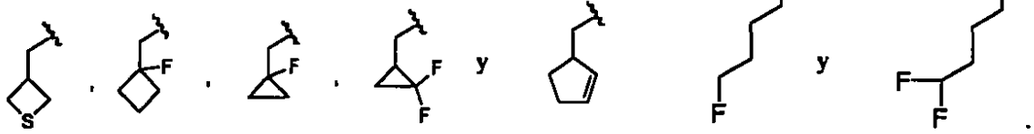
En otra realización, R^2 se selecciona del grupo formado por los siguientes restos:



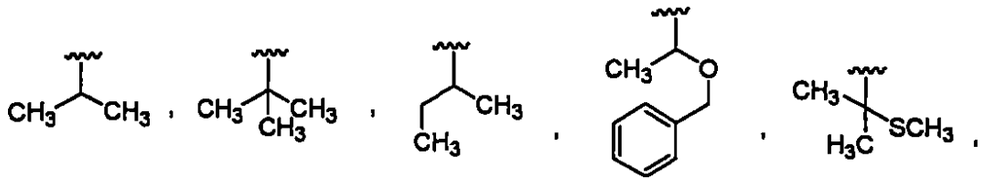
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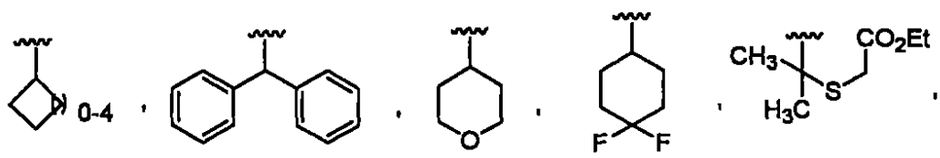


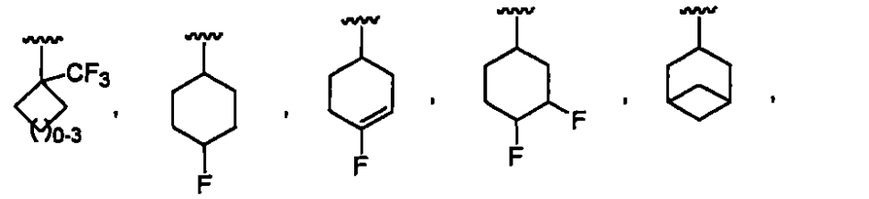


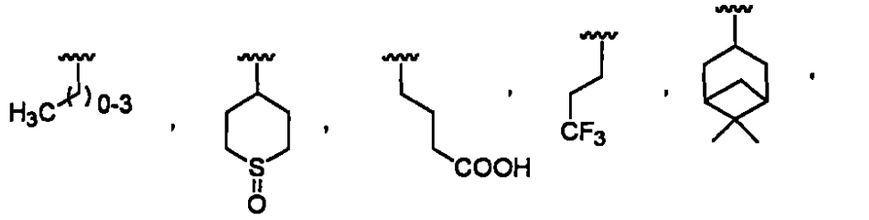


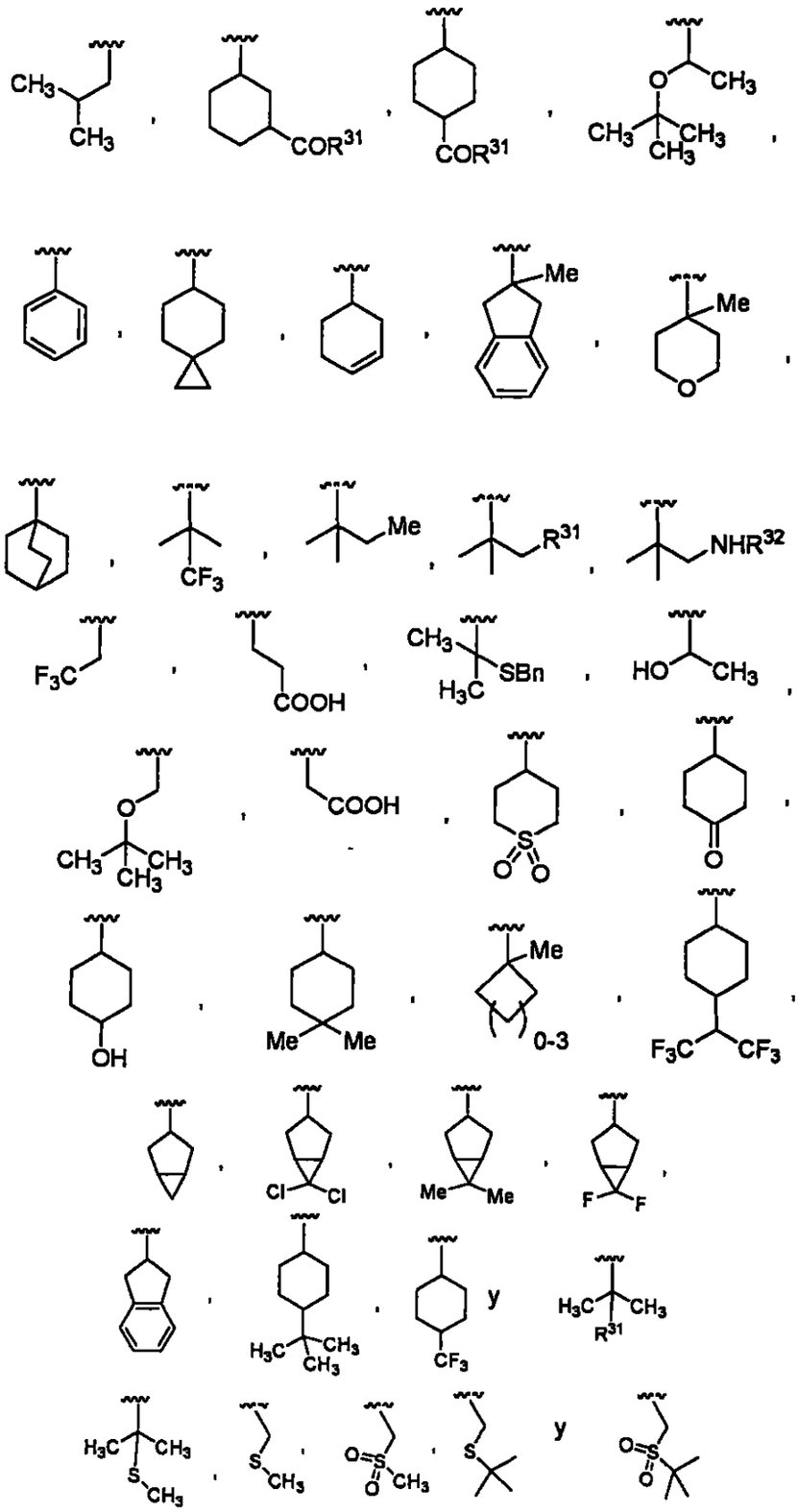
En otra realización, R^3 se selecciona del grupo formado por:







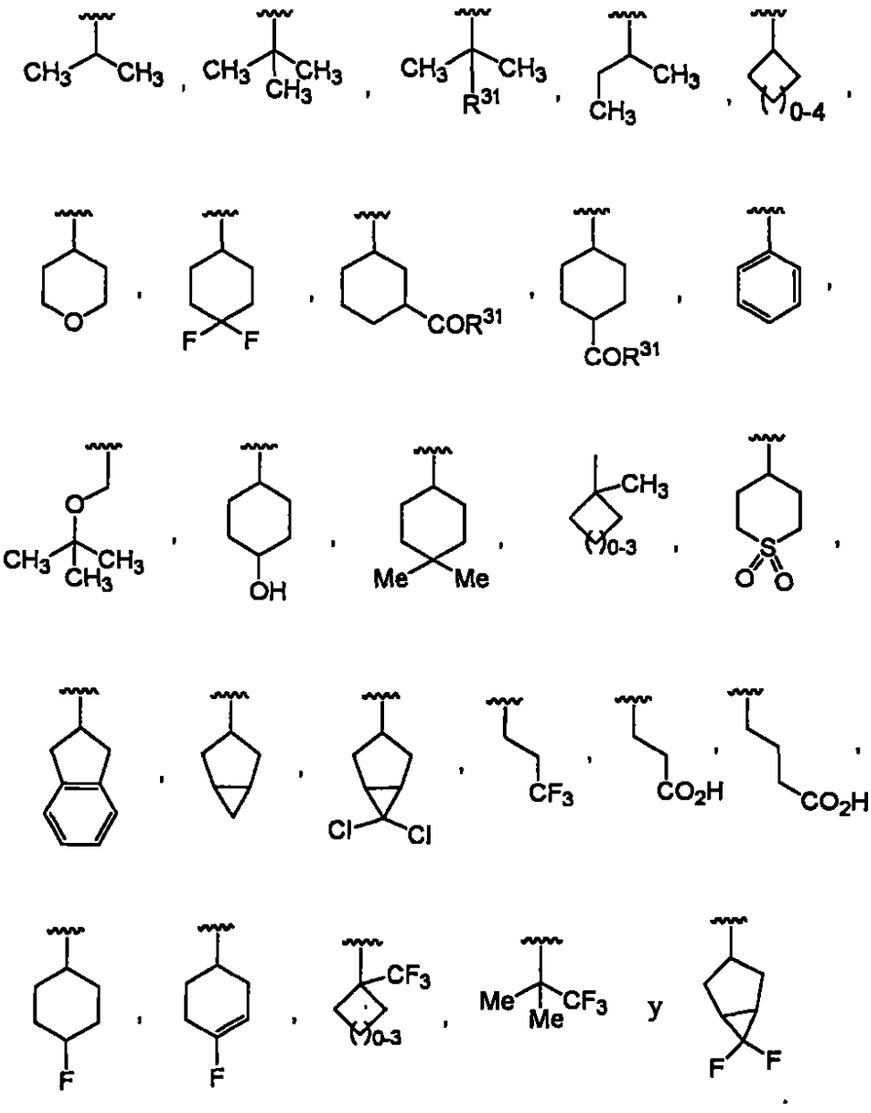




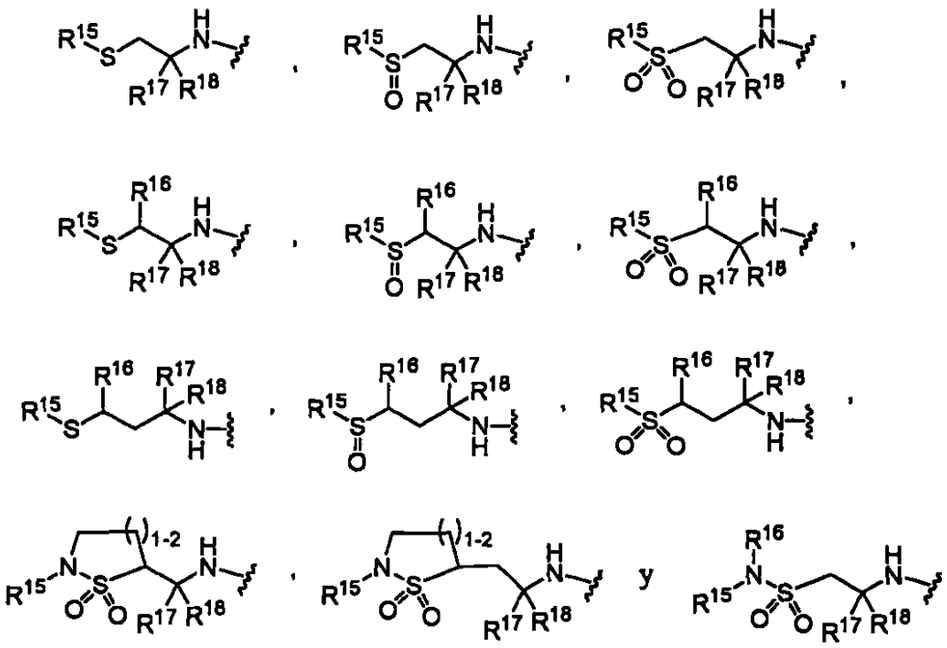
en los cuales R^{31} es OH u O-alquilo, y

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

En una realización adicional, R^3 se selecciona del grupo formado por los siguientes restos:

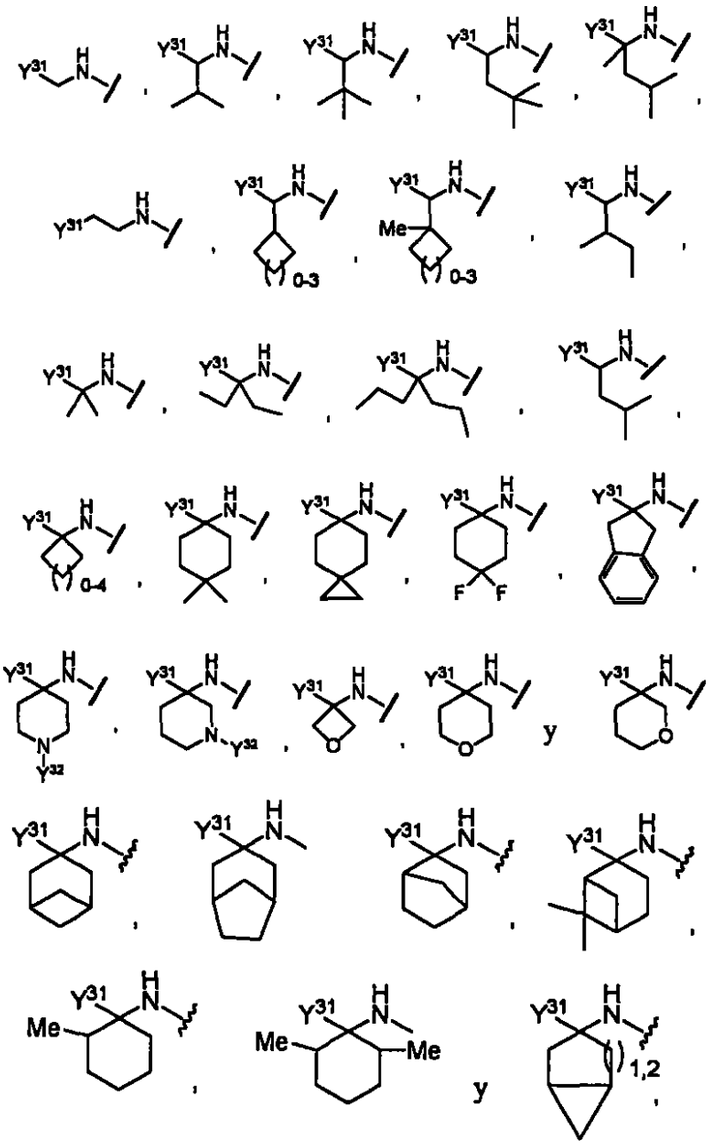


En otra realización, Y se selecciona de los siguientes restos:

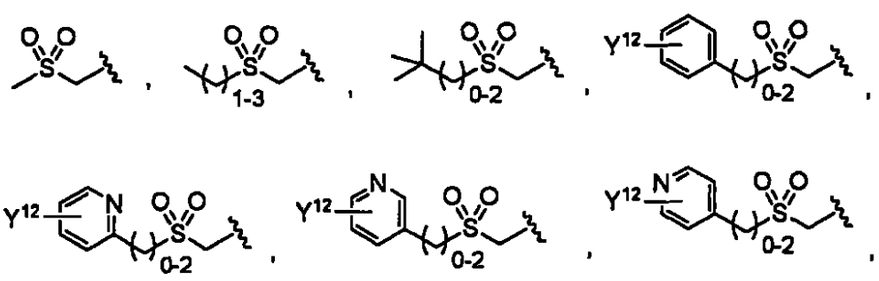


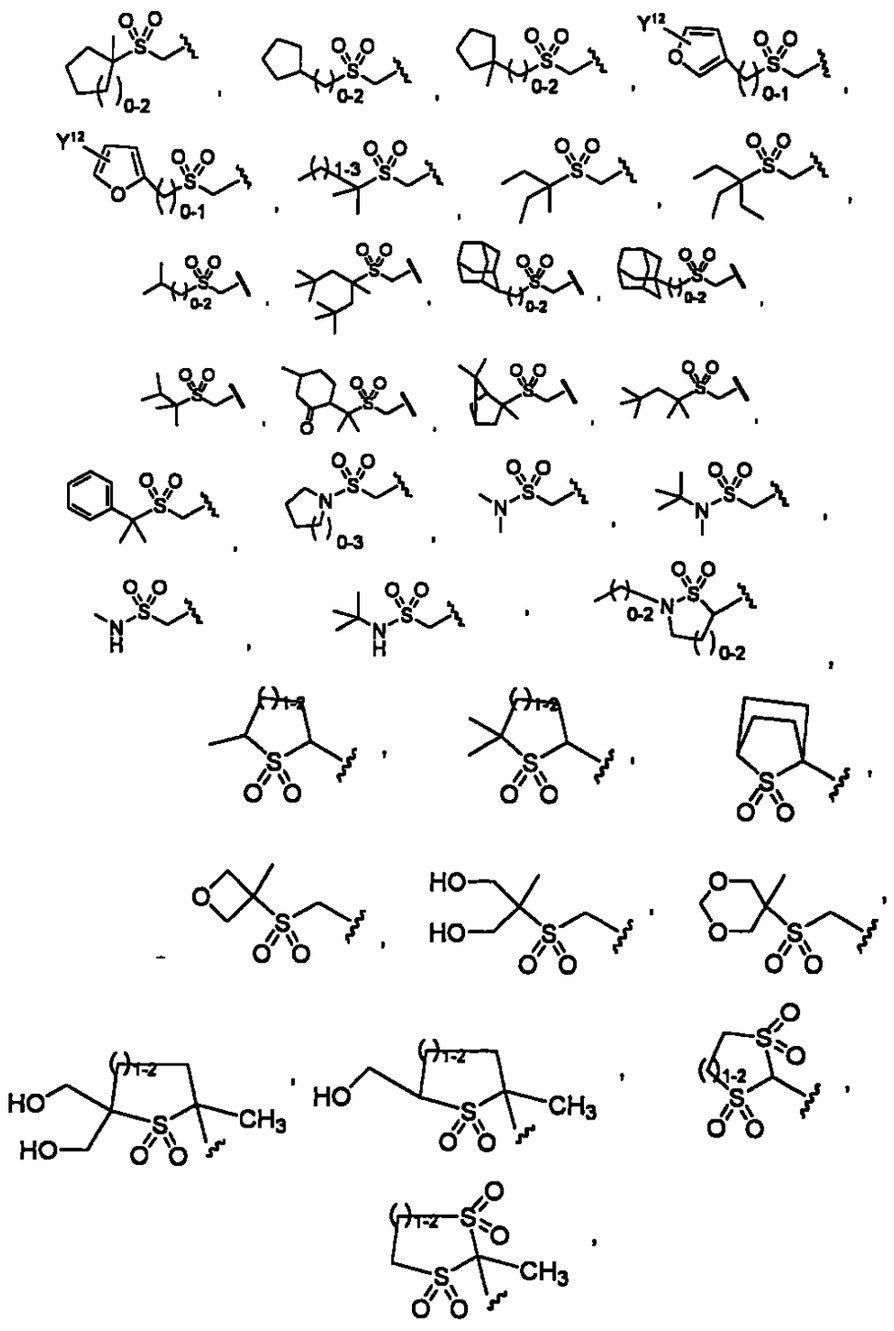
en los cuales R^{15}, R^{16}, R^{17} y R^{18} pueden ser iguales o diferentes, cada uno seleccionado en forma independiente del grupo formado por H, alquilo, heteroalquilo, alquenilo, heteroalquenilo, alquinilo, heteroalquinilo, cicloalquilo, heterociclilo, arilo, y heteroarilo, o alternativamente, R^{15} y R^{16} están conectados uno al otro para formar una estructura cicloalquílica o heterocíclica de cuatro a ocho miembros, y/o R^{17} y R^{18} están conectados uno al otro para formar un cicloalquilo o heterociclilo de tres a ocho miembros, en el cual cada uno de dicho arilo, heteroarilo, cicloalquilo o heterociclilo pueden no estar sustituidos o o estar sustituidos en forma opcional e independiente con uno o más restos seleccionados del grupo formado por: hidroxi, alcoxi, ariloxi, tio, alquiltio, ariltio, amino, amido, alquilamino, arilamino, alquilsulfonilo, arilsulfonilo, sulfonamido, alquilsulfonamido, arilsulfonamido, carboxi, carbalcoxi, carboxamido, alcoxicarbonilamino, alcoxicarboniloxi, alquilureido, arilureido, halo, ciano, y nitro.

En una realización adicional, Y se selecciona del grupo formado por

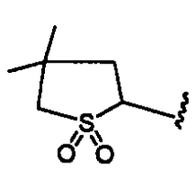
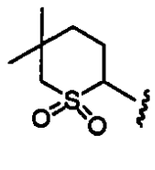
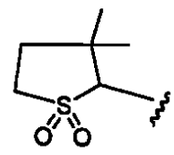
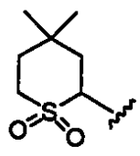
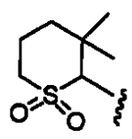
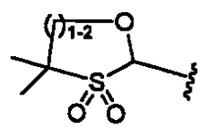
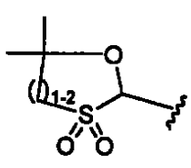
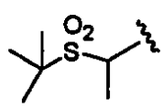
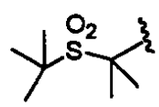


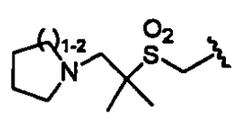
en los cuales Y^{31} se selecciona del grupo formado por

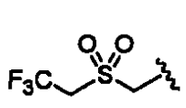
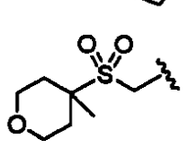
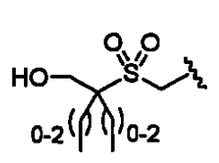
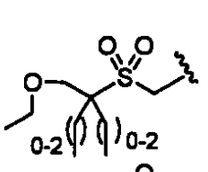
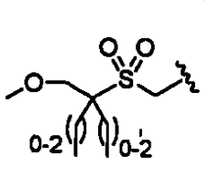
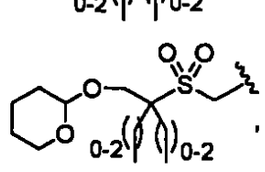
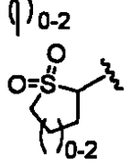
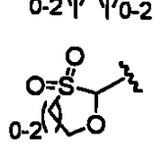
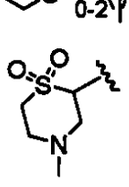
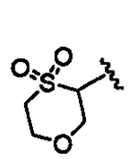
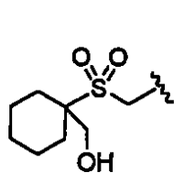
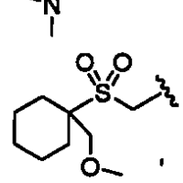
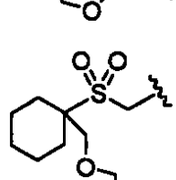
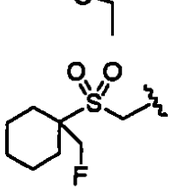
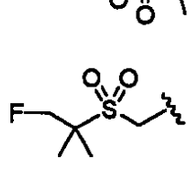
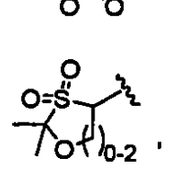




787

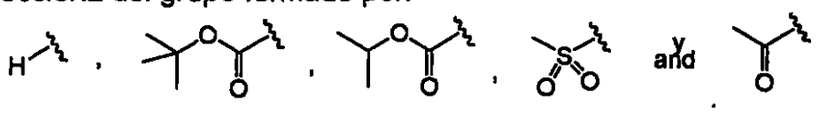












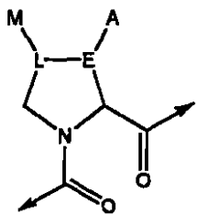
y

Y^{32} se selecciona del grupo formado por.

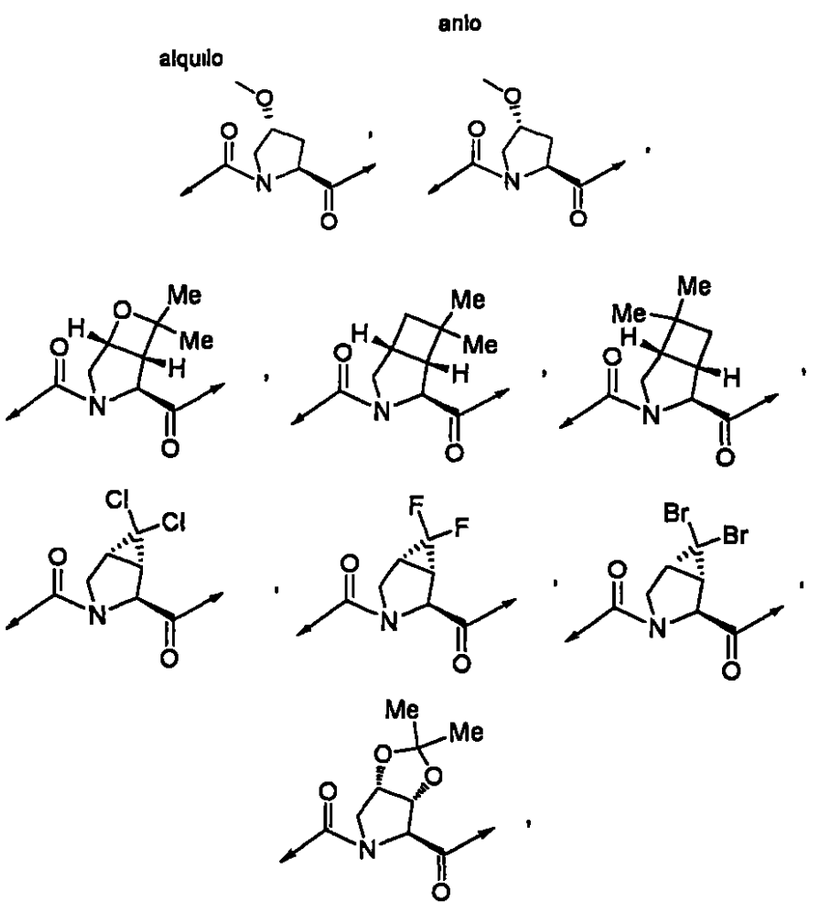


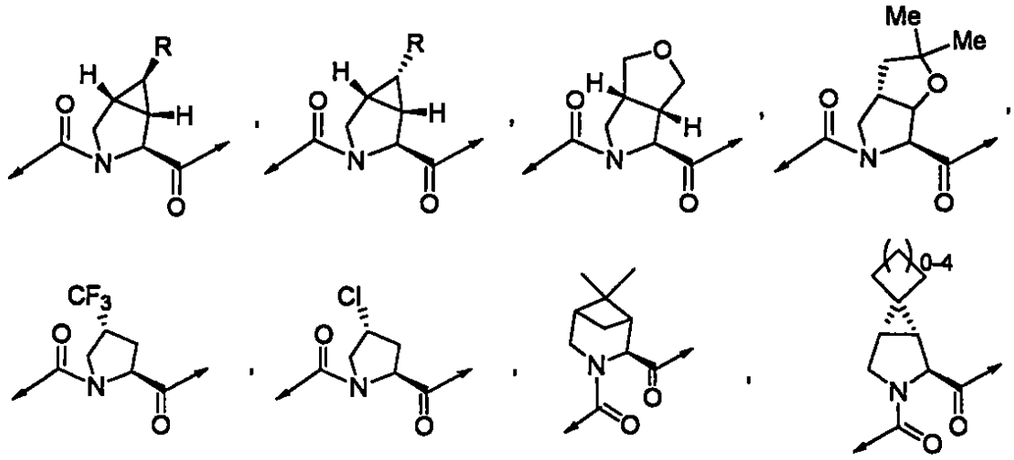
e Y^{12} se selecciona del grupo formado por H, CO_2H, CO_2Me, OMe, F, Cl, Br, NH_2, $N(H)S(O_2)CH_3$, $N(H)C(O)CH_3$, NO_2, $S(O_2)NH_2$, CF_3, Me, OH, OCF_3, y $C(O)NH_2$

En otra realización, el resto:

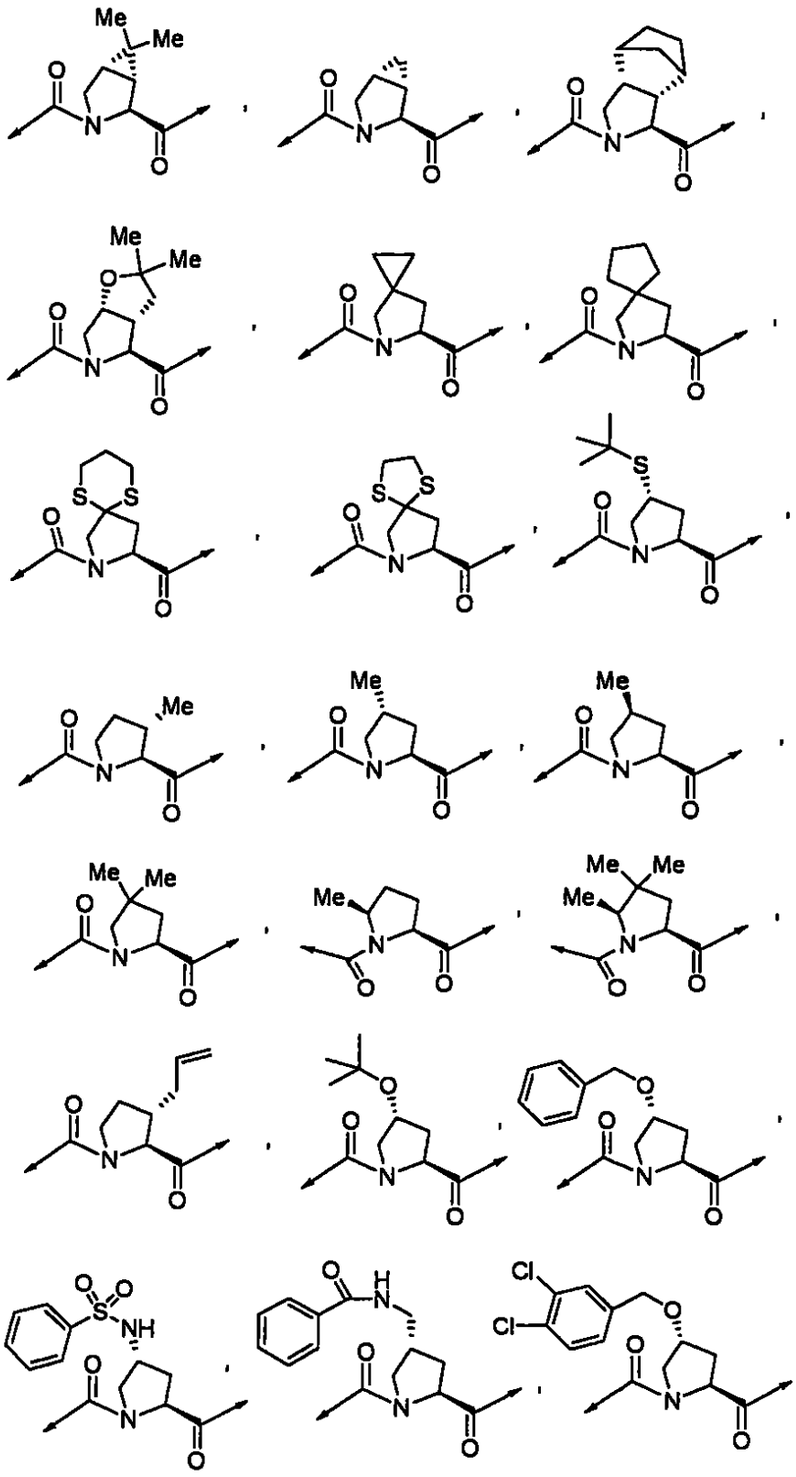


se selecciona de las siguientes estructuras:

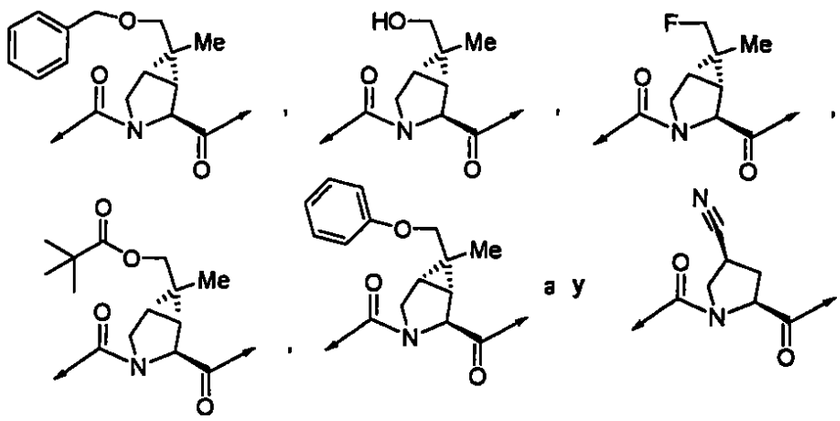



R
H
H
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N
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Me
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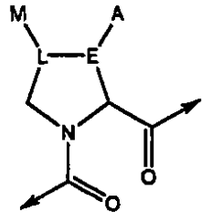
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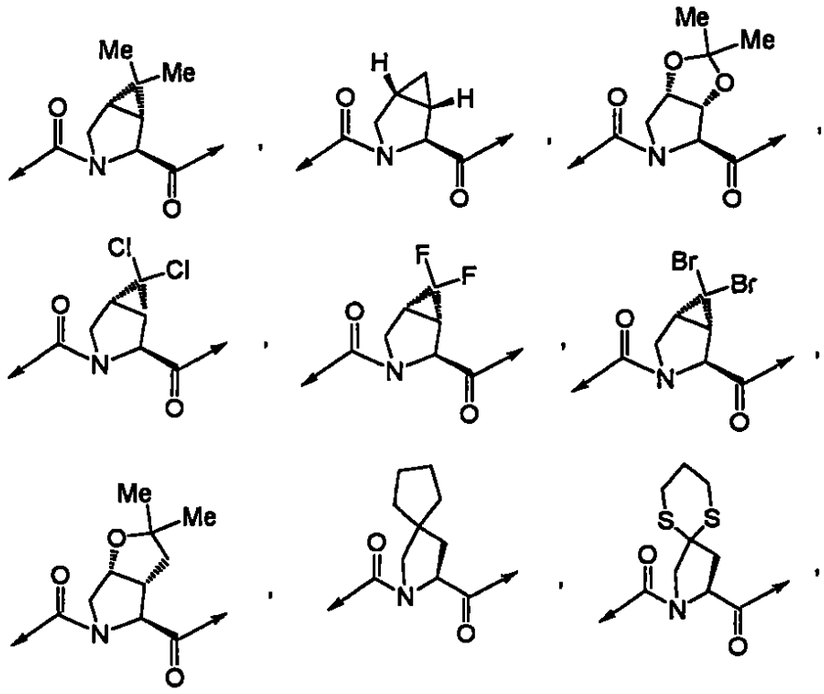
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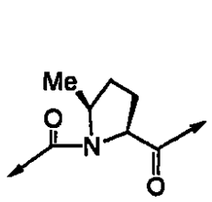
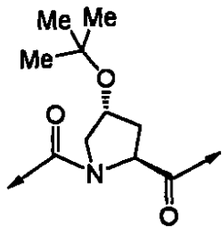
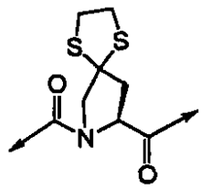
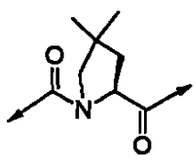
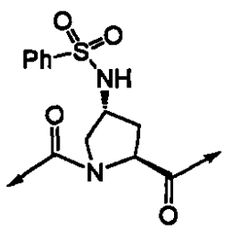
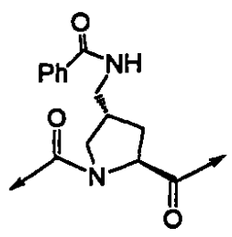
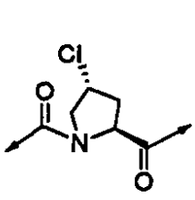
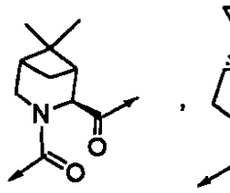
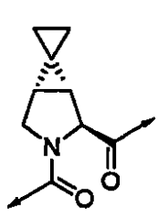
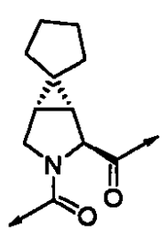
En una realización adicional, el resto:

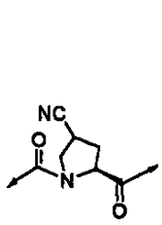
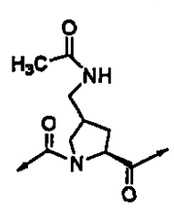


se selecciona de las siguientes estructuras:

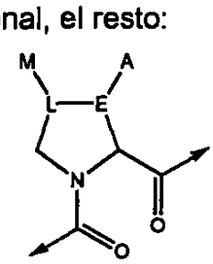


792

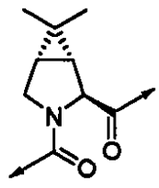
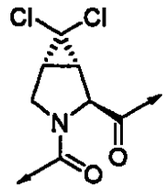
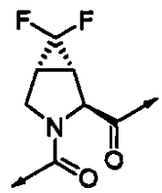



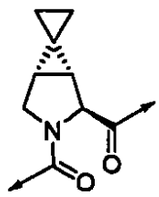
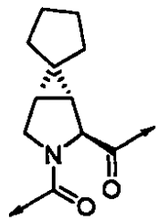
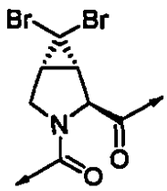
En una realización adicional, el resto:



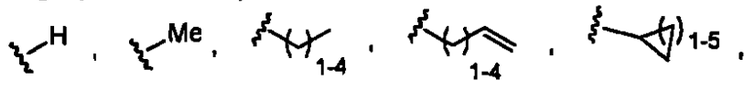
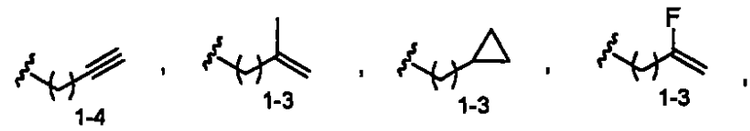
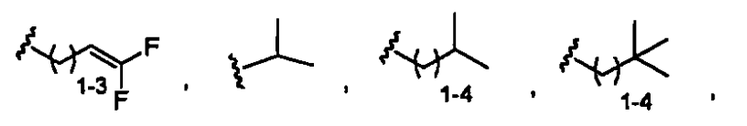
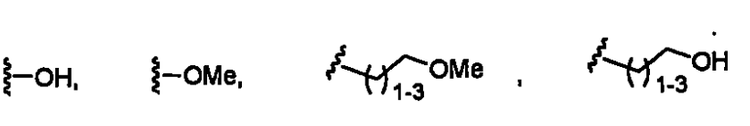
se selecciona de las siguientes estructuras:

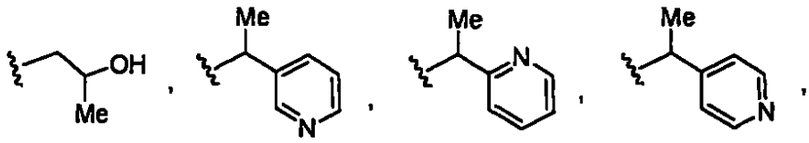
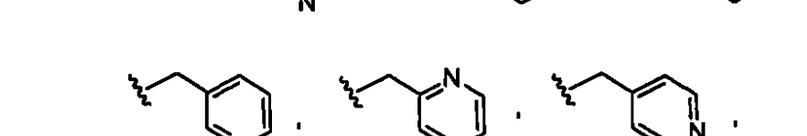
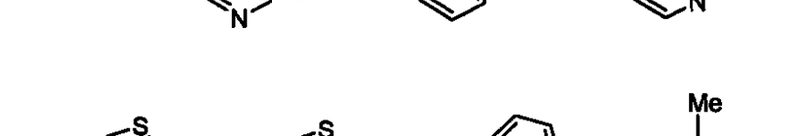
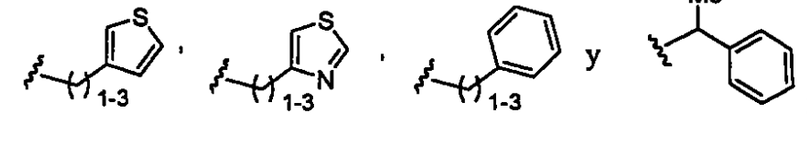
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y

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Incluso en otra realización adicional, R^1 es NHR^{14}, donde R^{14} se selecciona del grupo formado por


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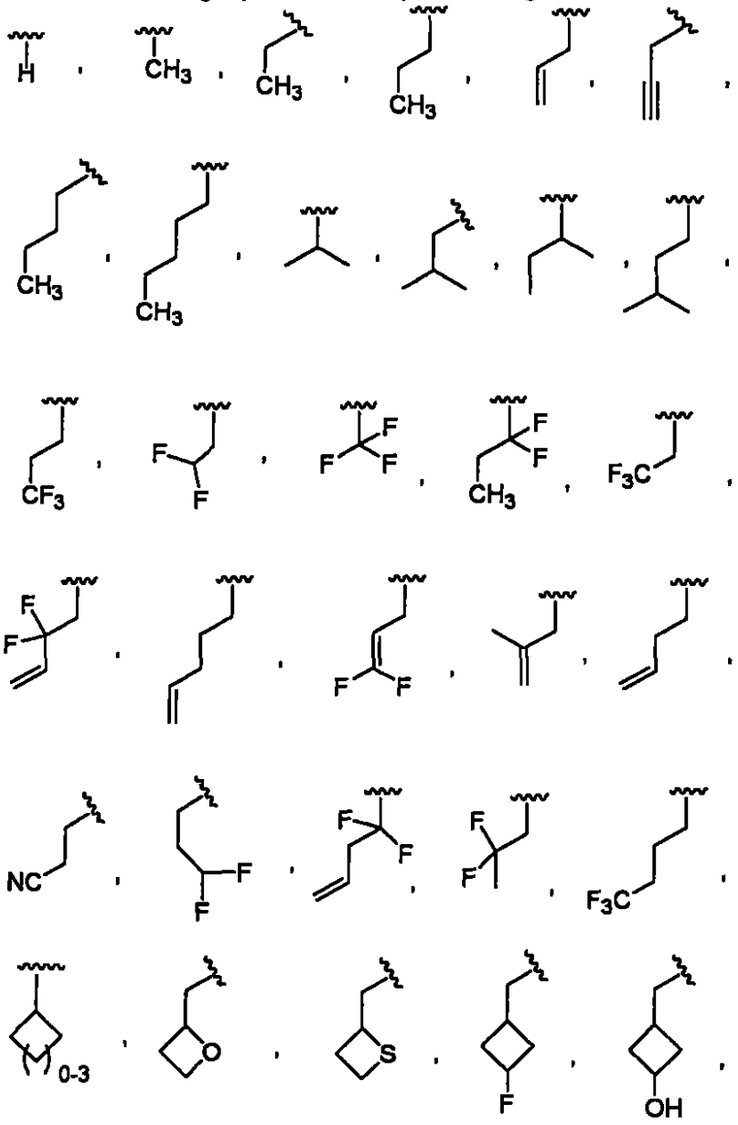
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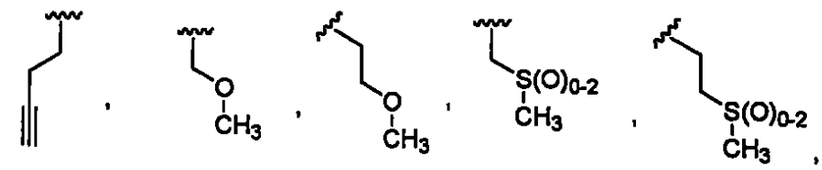
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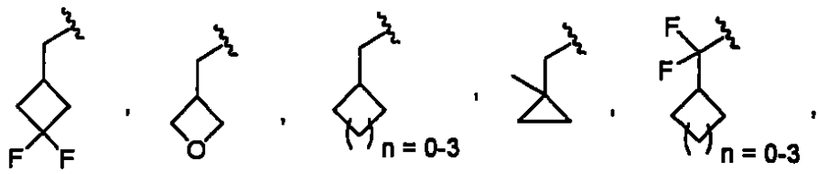
794

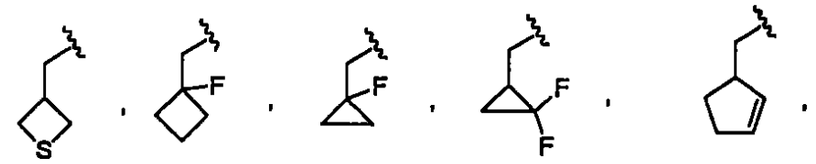
R^2 se selecciona del grupo formado por los siguientes restos:

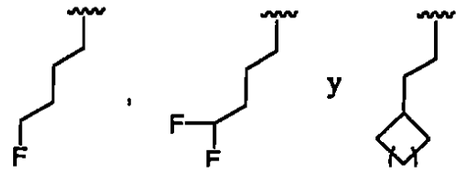


795



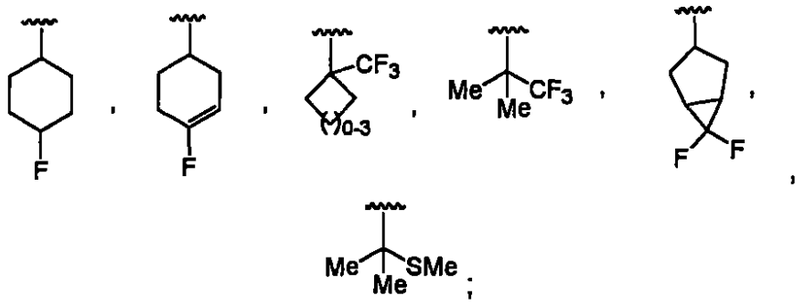




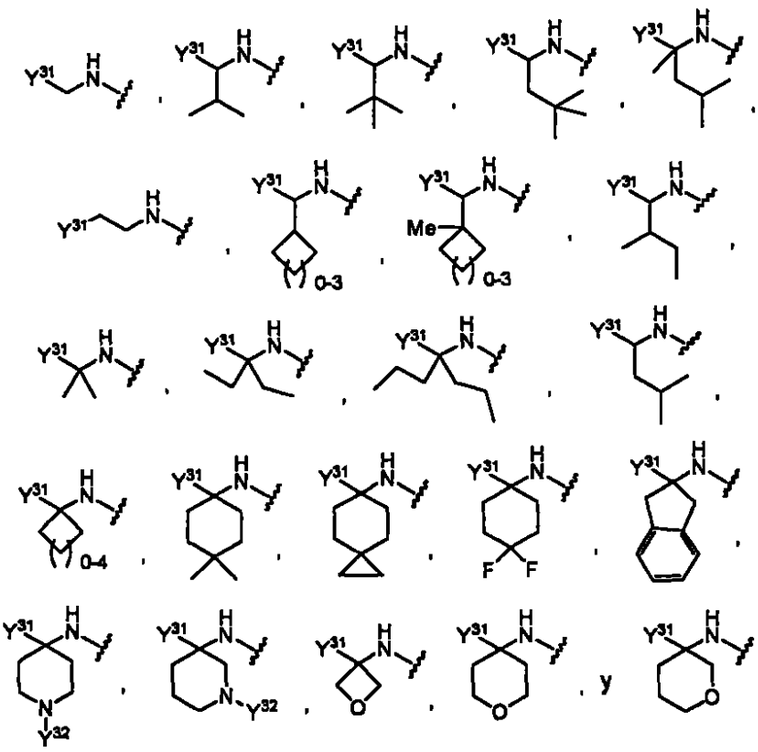


y

796

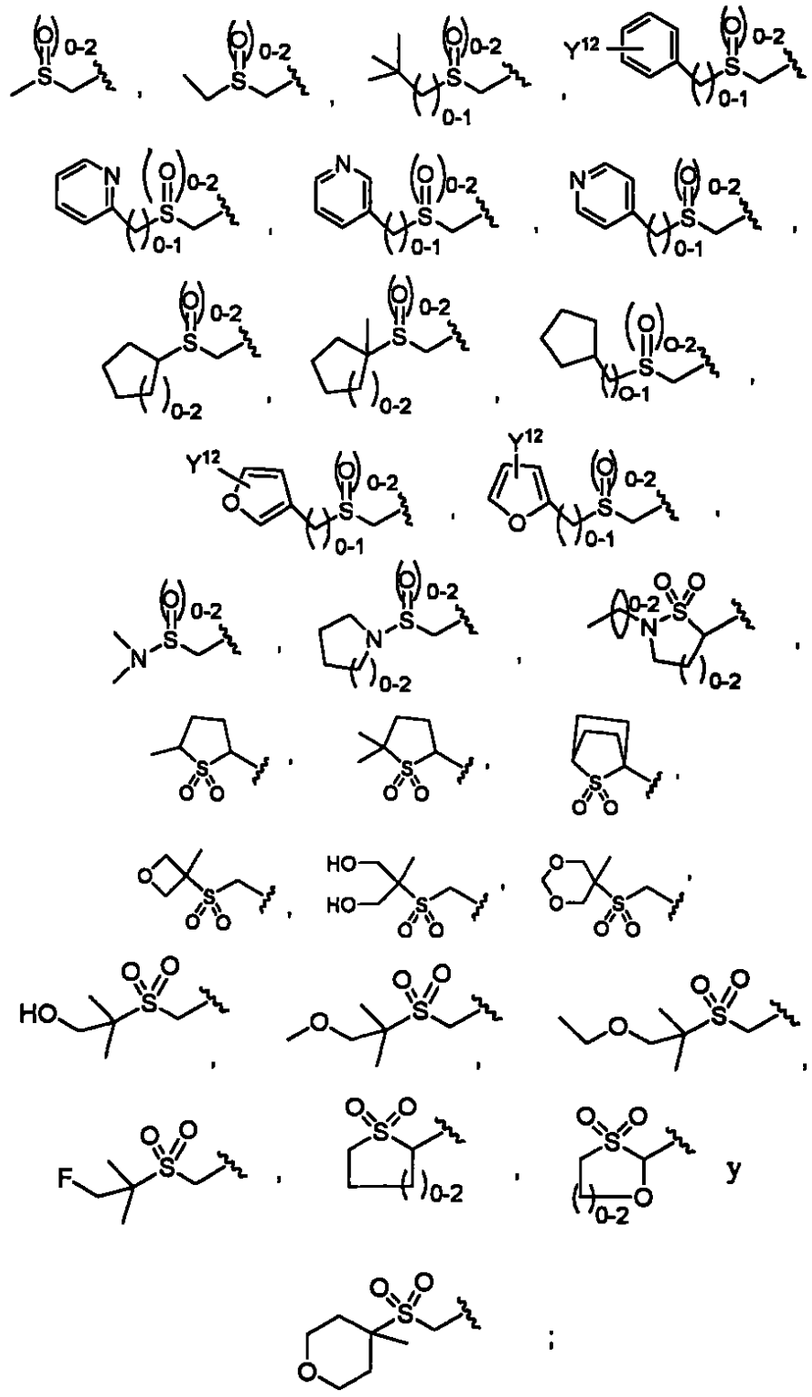


Y se selecciona del grupo formado por:

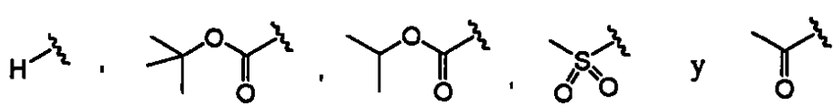


en los cuales Y^{31} se selecciona del grupo formado por

797

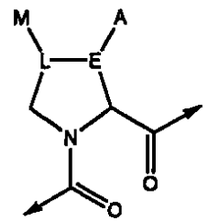


Y^{32} se selecciona del grupo formado por.

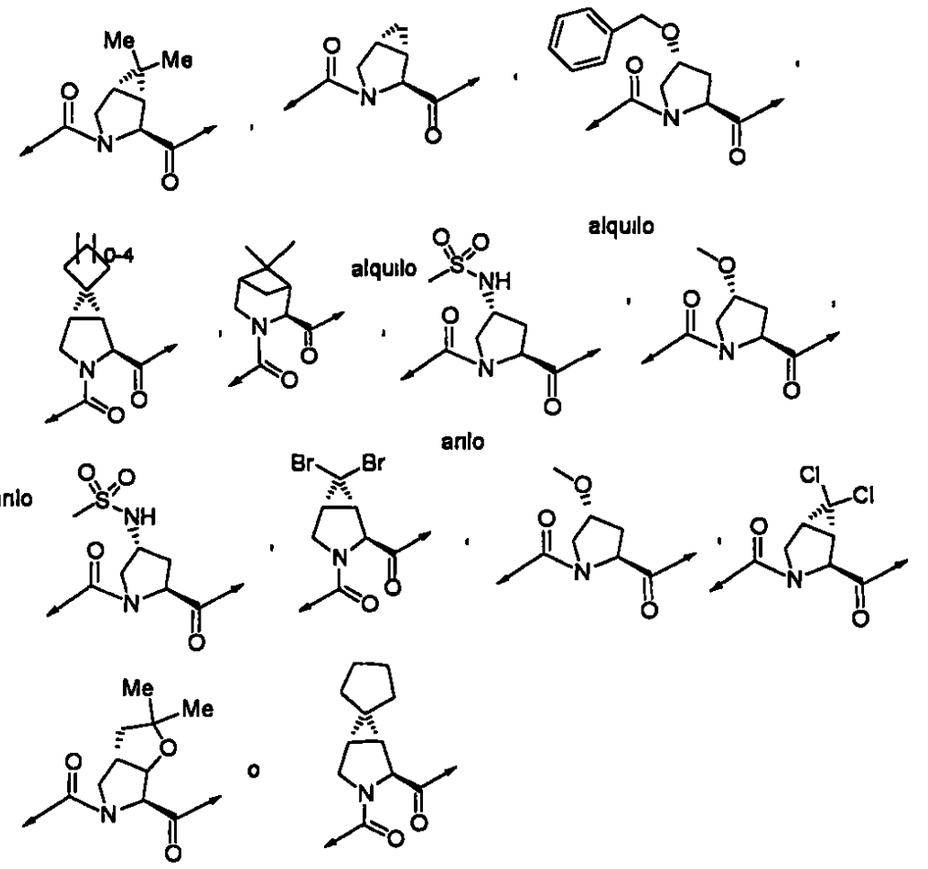


798

e Y^{12} se selecciona del grupo formado por H, CO_2H, CO_2Me, OMe, F, Cl, Br, NH_2, $N(H)S(O_2)CH_3$, $N(H)C(O)CH_3$, NO_2, $S(O_2)NH_2$, CF_3, Me, OH, OCF_3 y $C(O)NH_2$, y el resto:



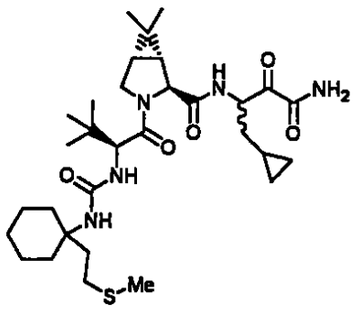
es:

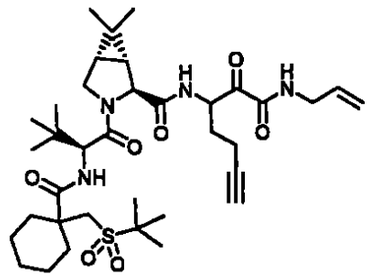


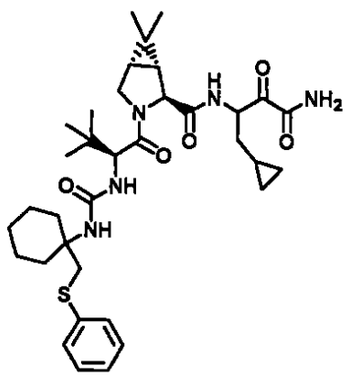
Aun otra realización de la invención revela compuestos en la **Tabla 1** a continuación, como así también se muestran más adelante en la **Tabla 1, Tabla 3, Tabla 3A, Tabla 4, Tabla 4A** y **Tabla 5:**

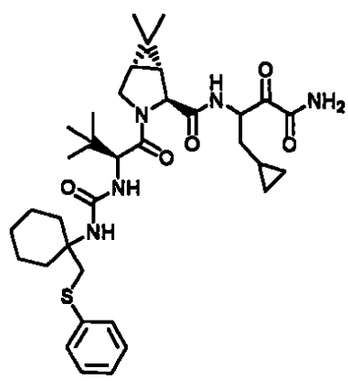
799 816

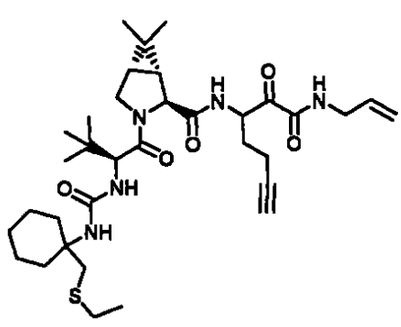
Tabla 1

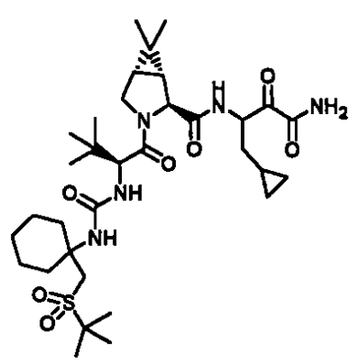


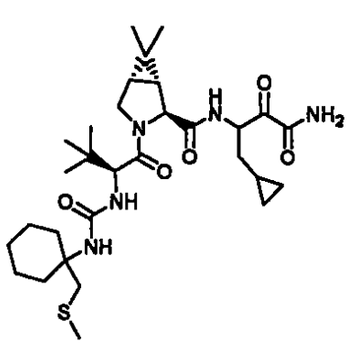


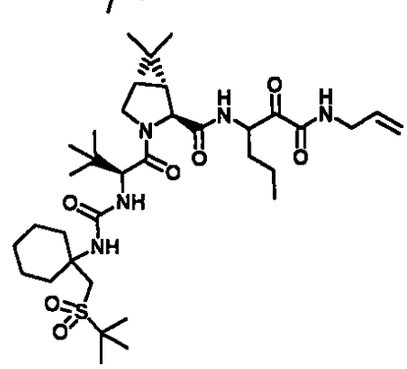


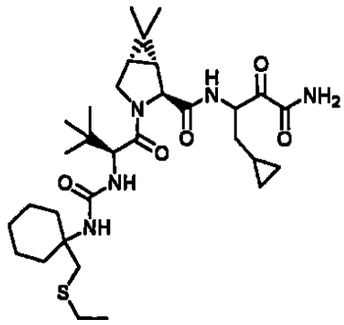


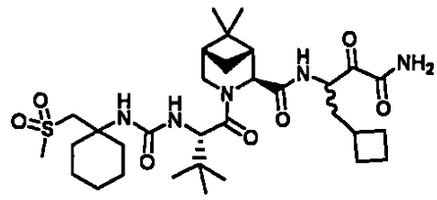


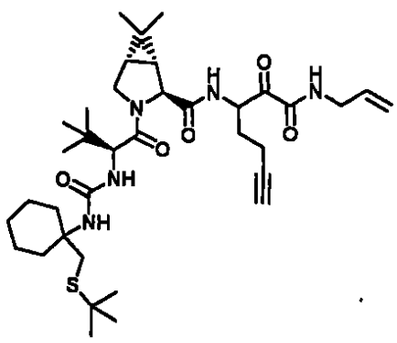


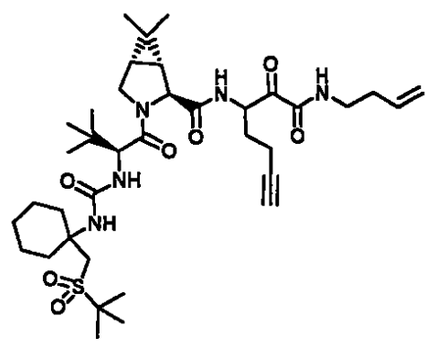


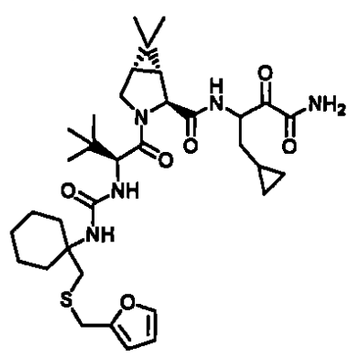


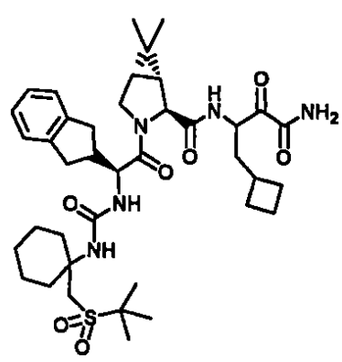


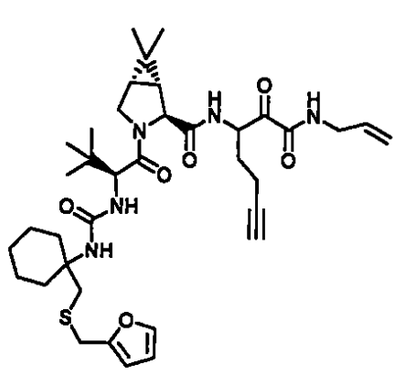


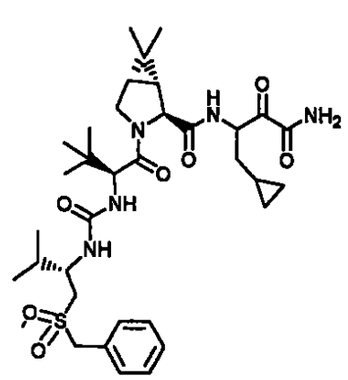




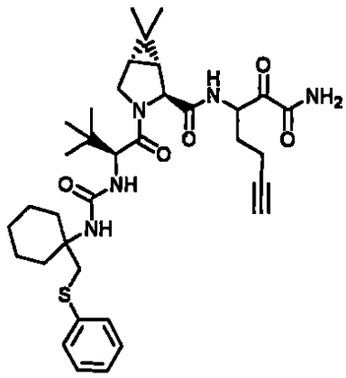


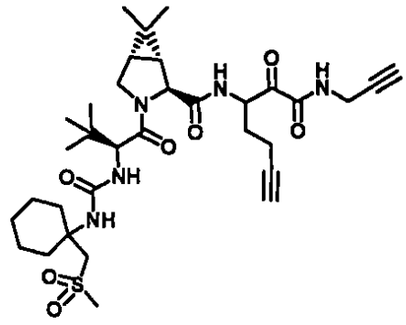


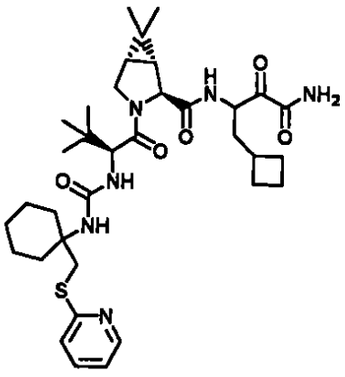


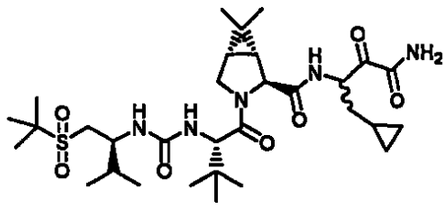


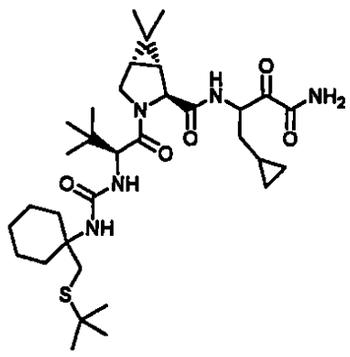
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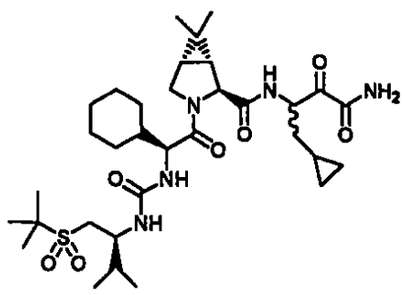


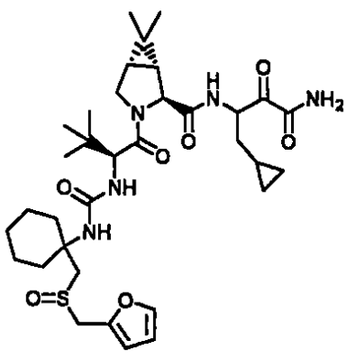


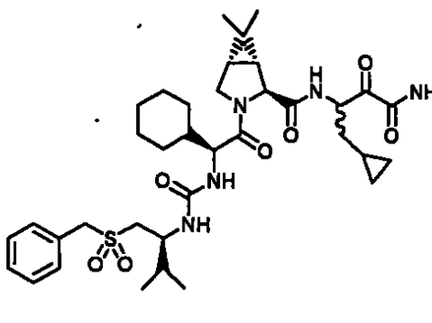


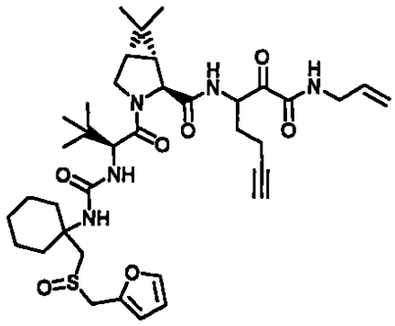


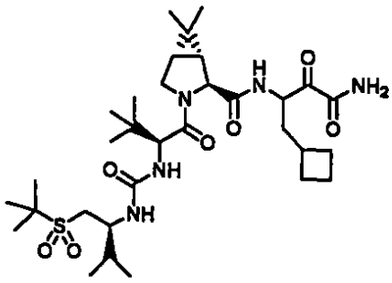


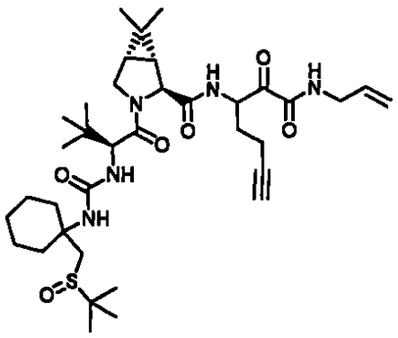


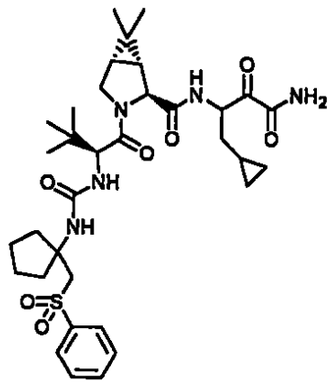


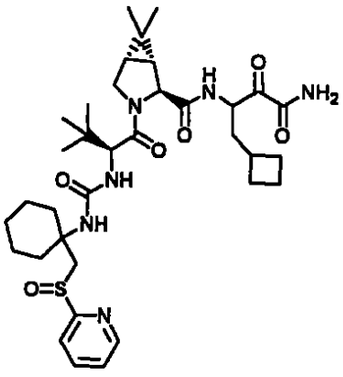


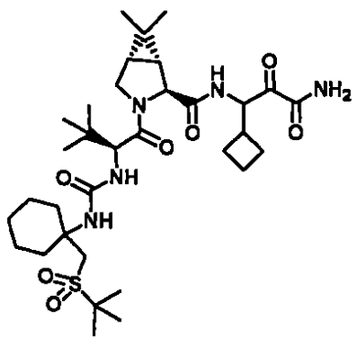


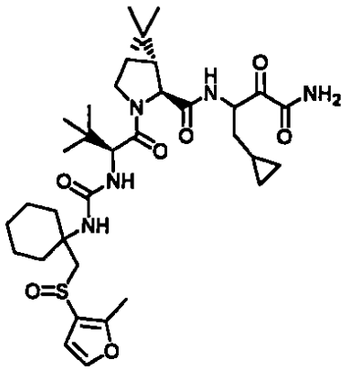


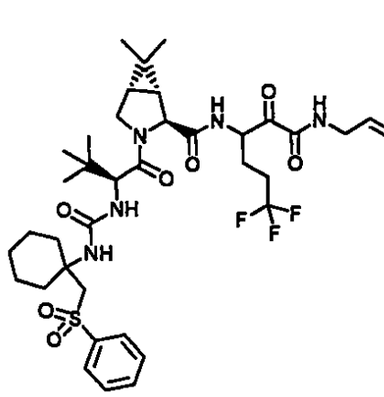




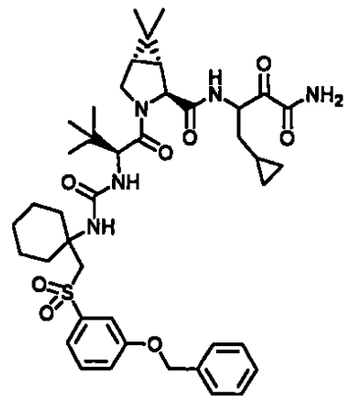


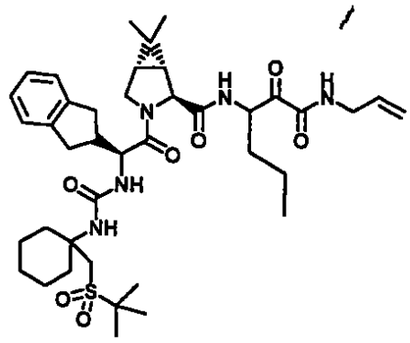


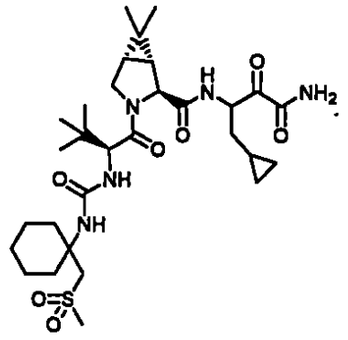


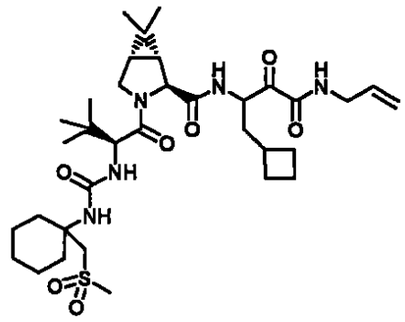


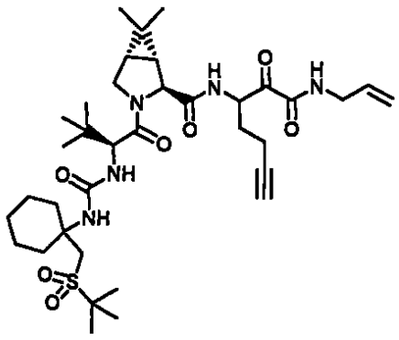
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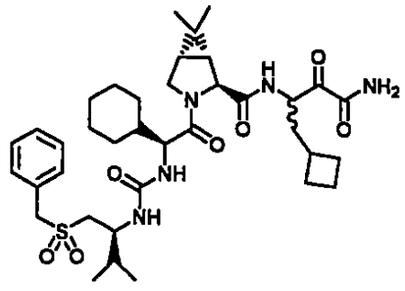


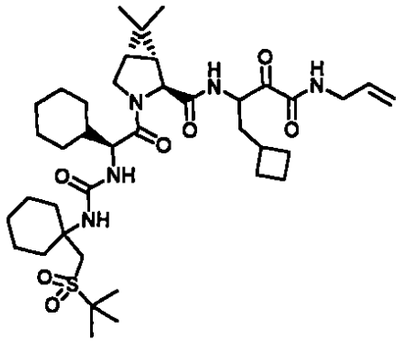




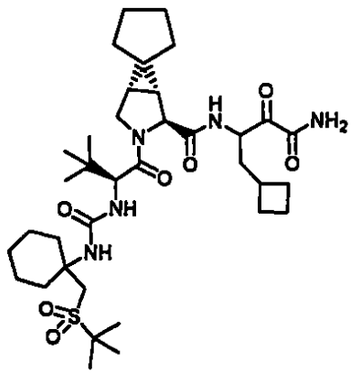


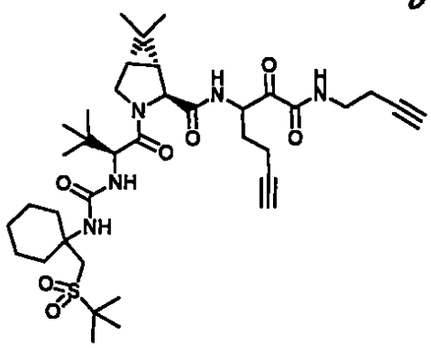


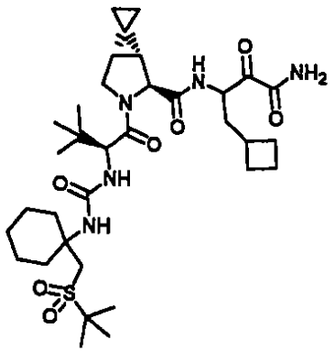


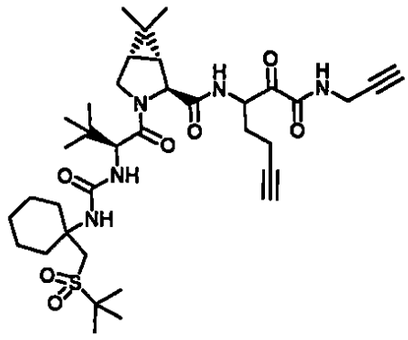


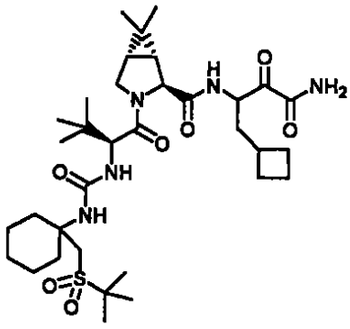
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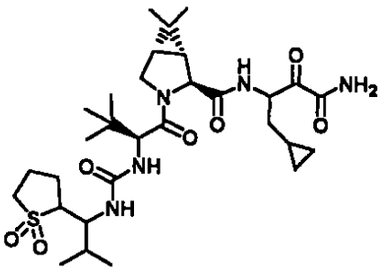


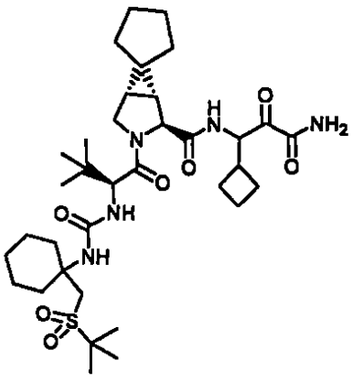


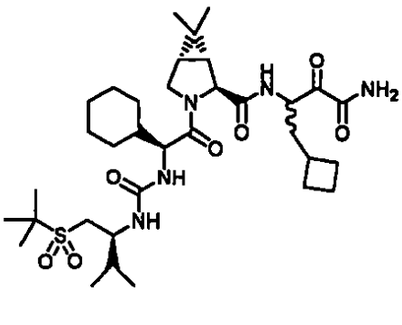


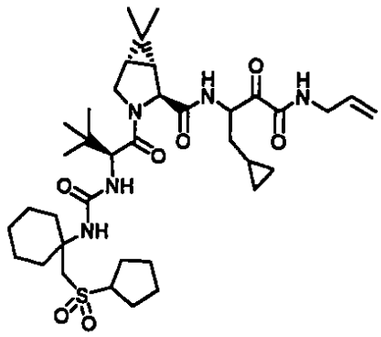


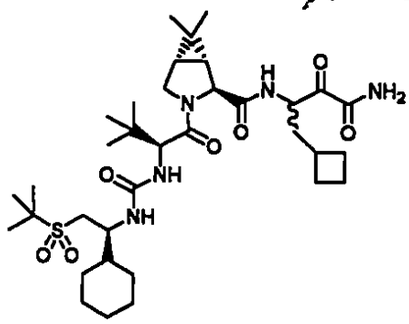


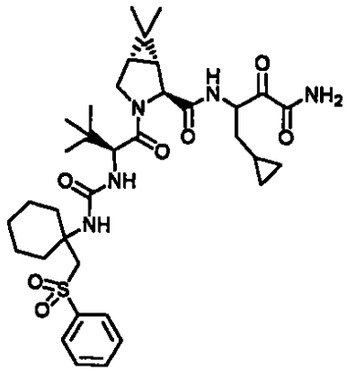


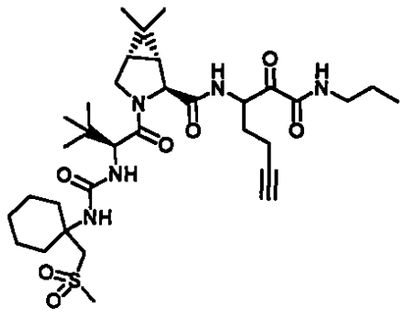


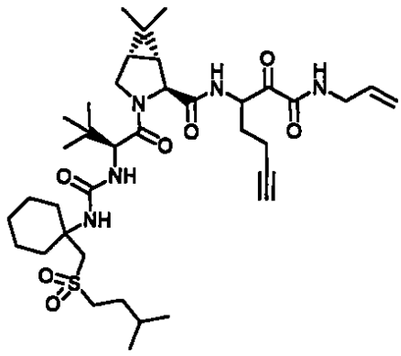


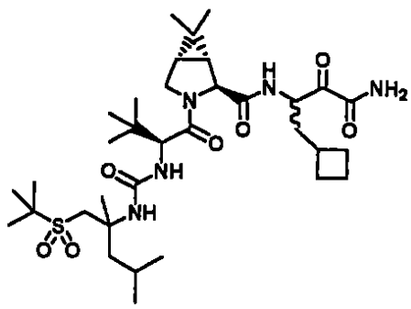


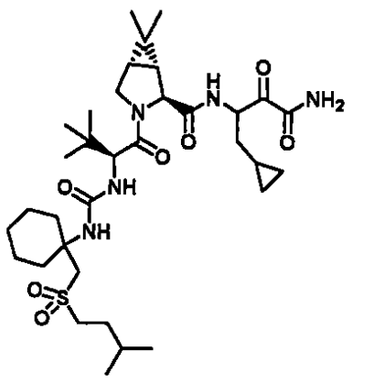


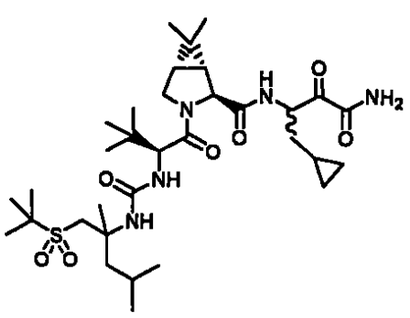


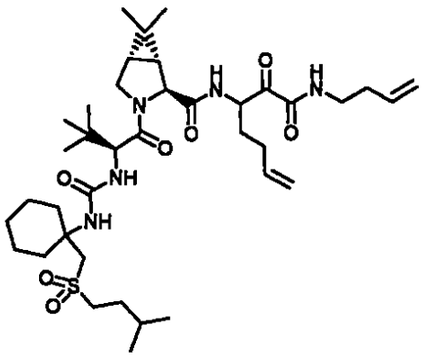


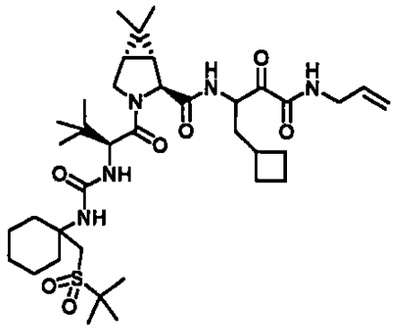


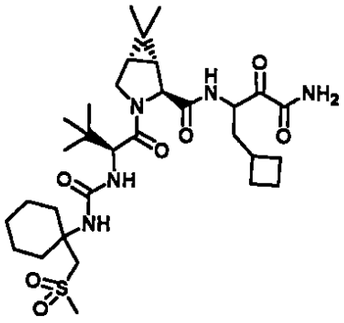


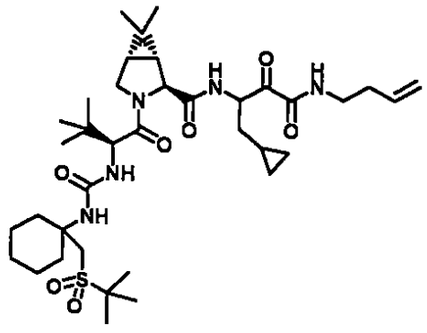


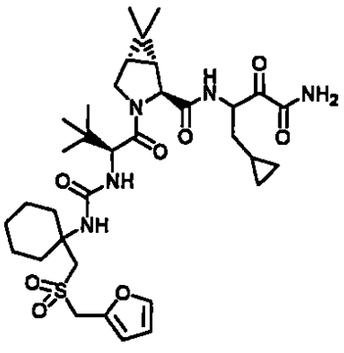


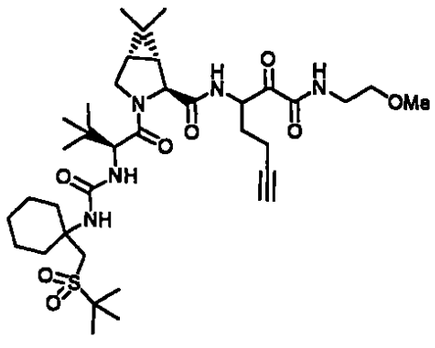


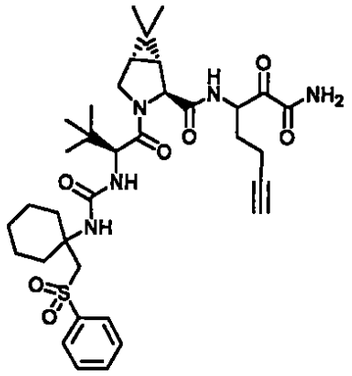


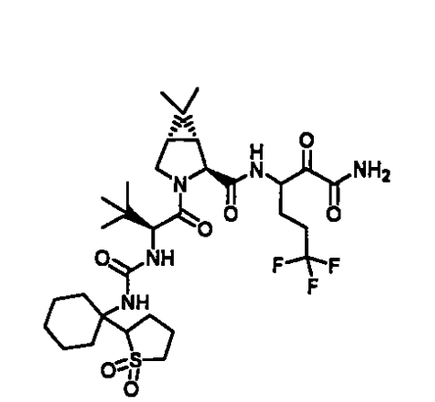


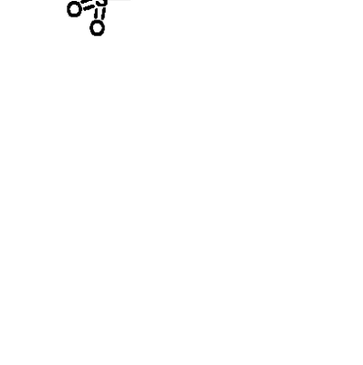




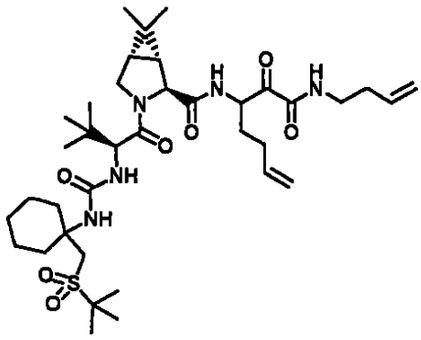


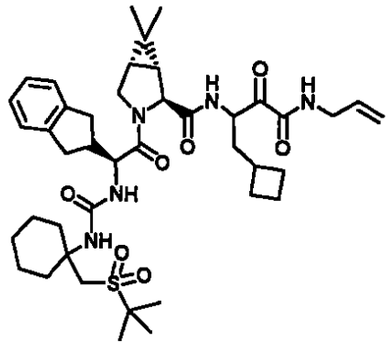


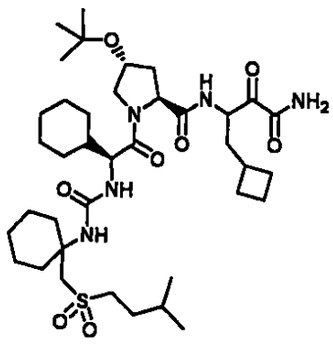


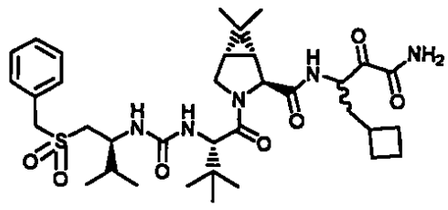


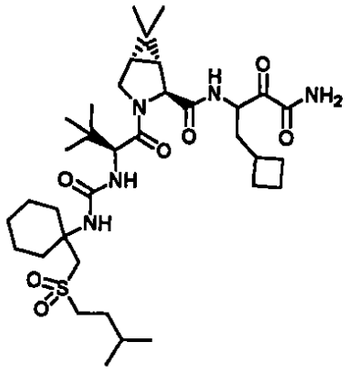
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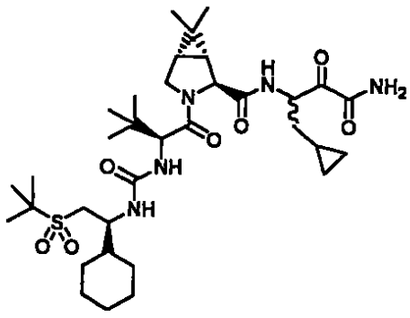


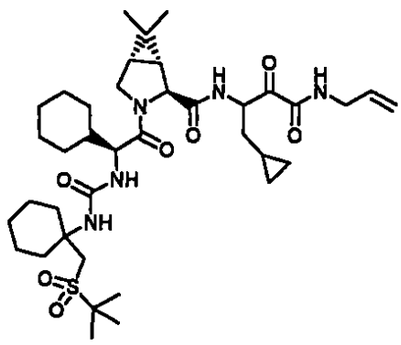


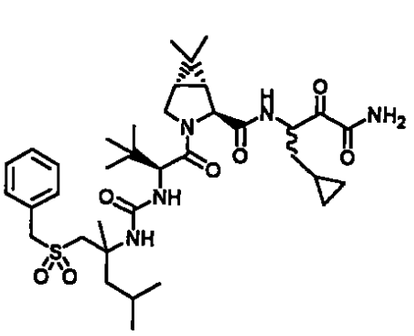




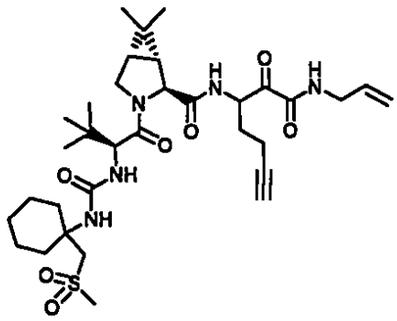


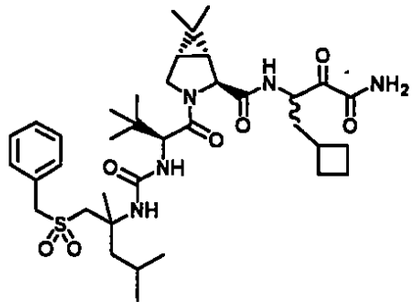


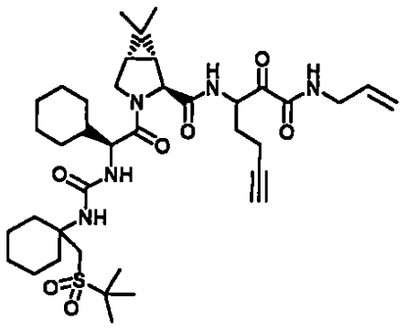


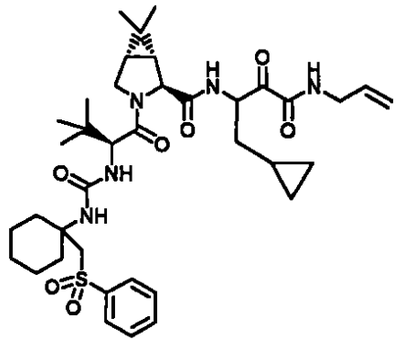


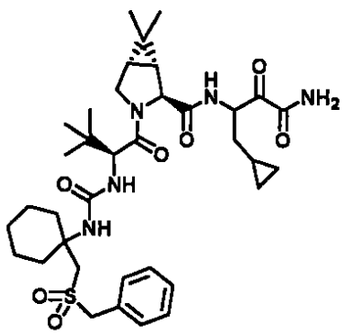
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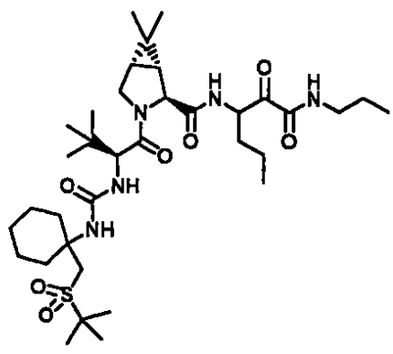


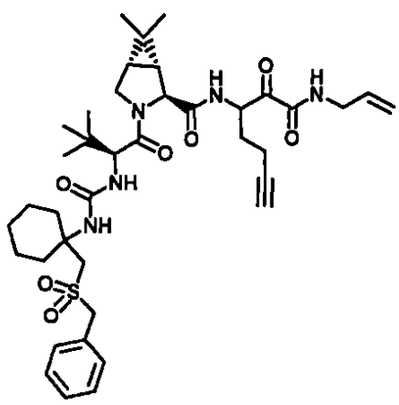


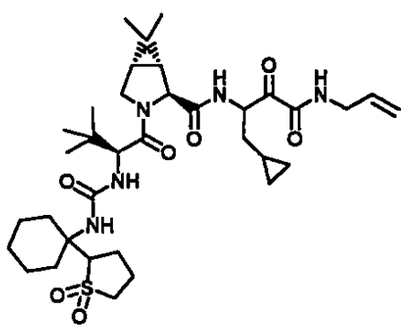




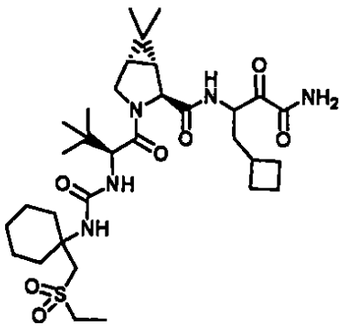


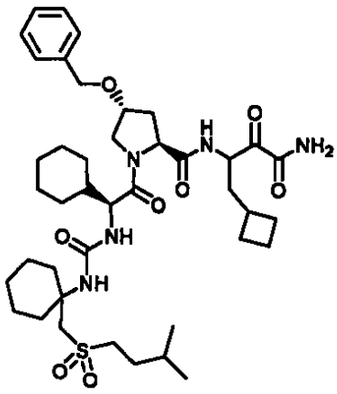


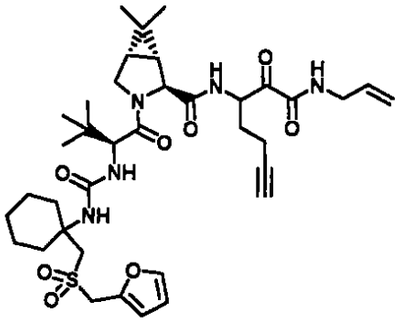


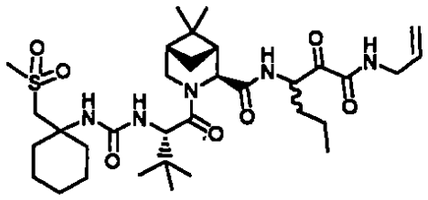


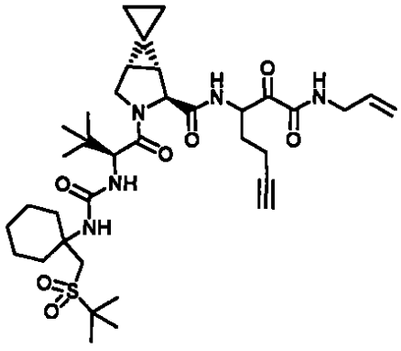
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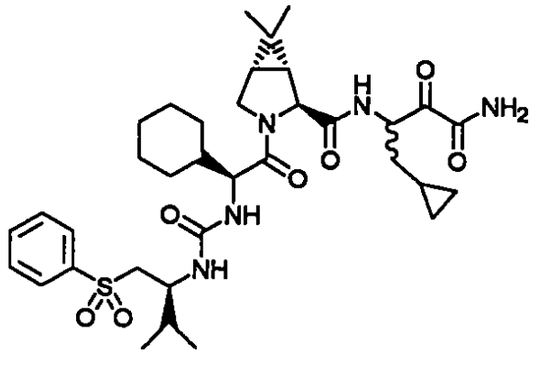


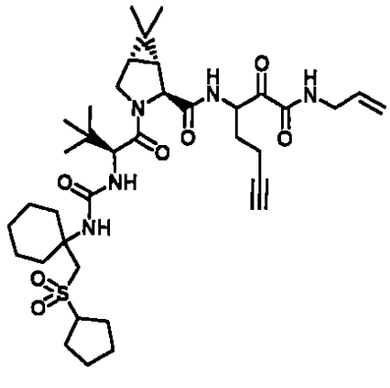


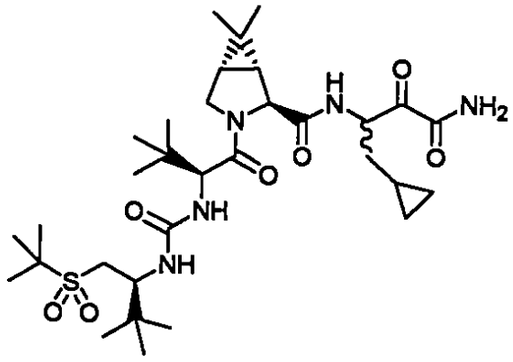




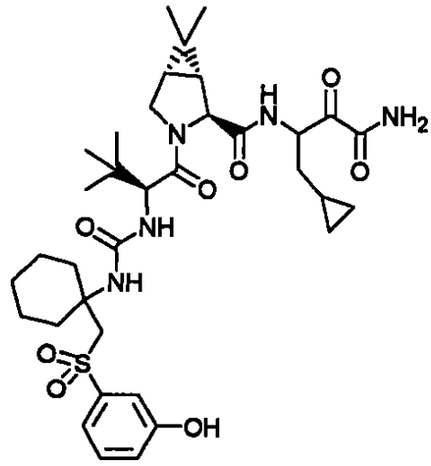


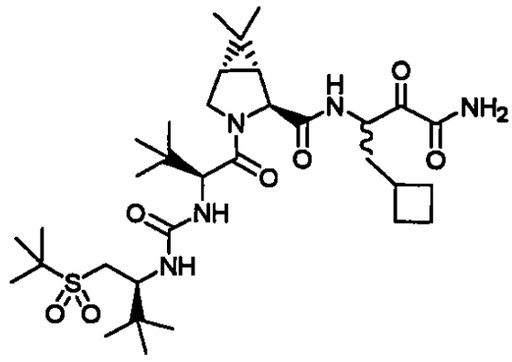


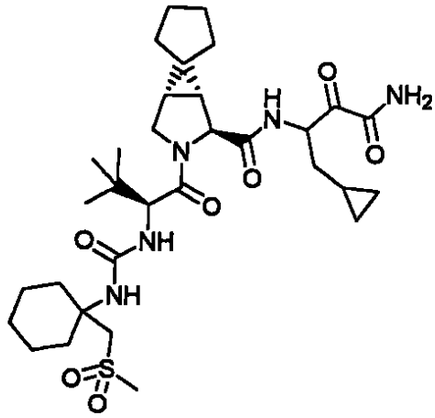


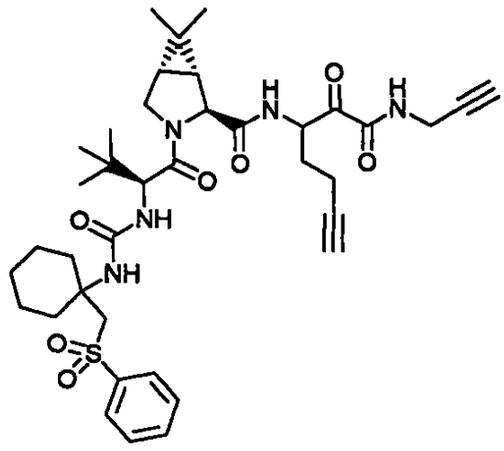


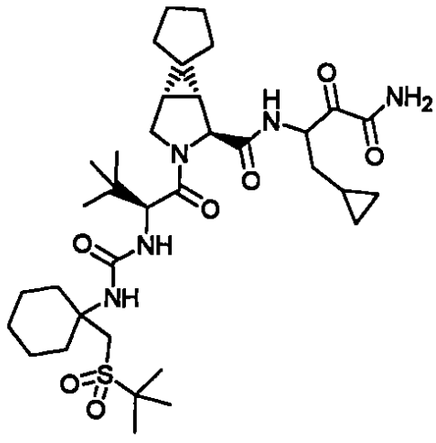
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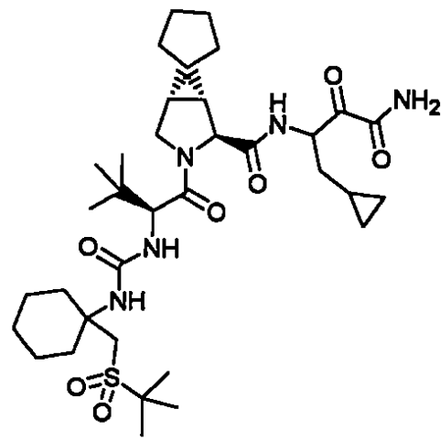




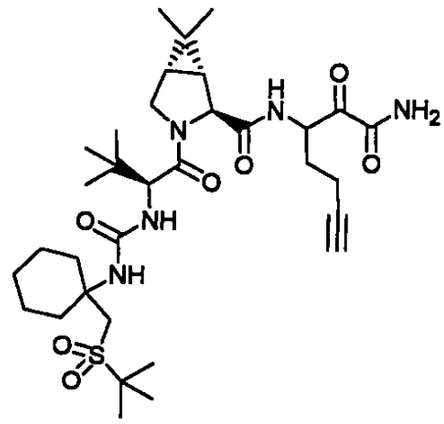


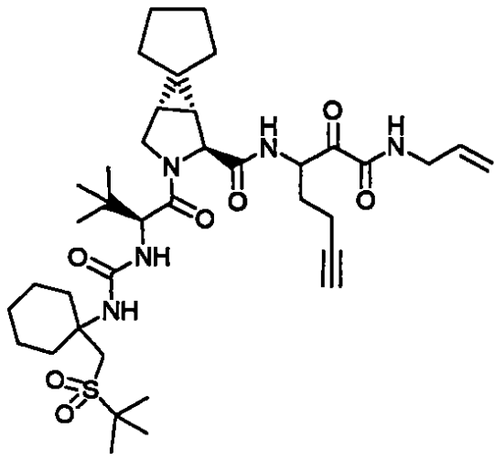


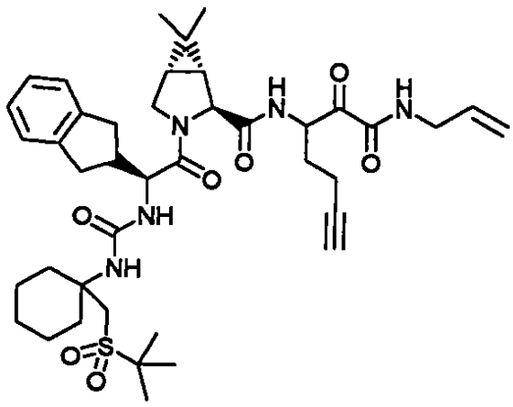


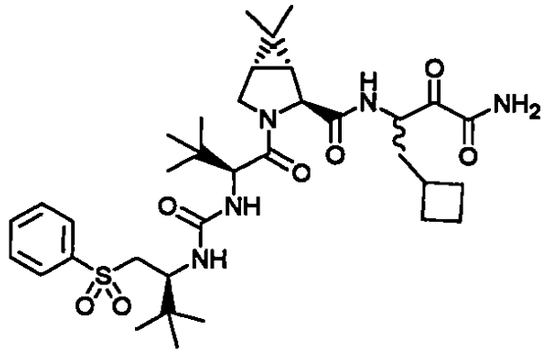


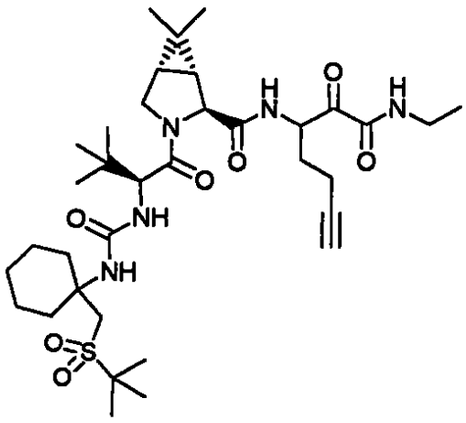
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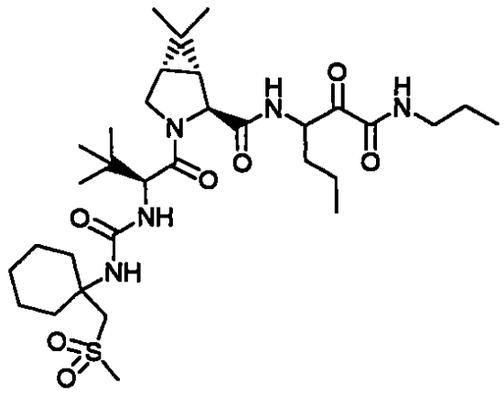




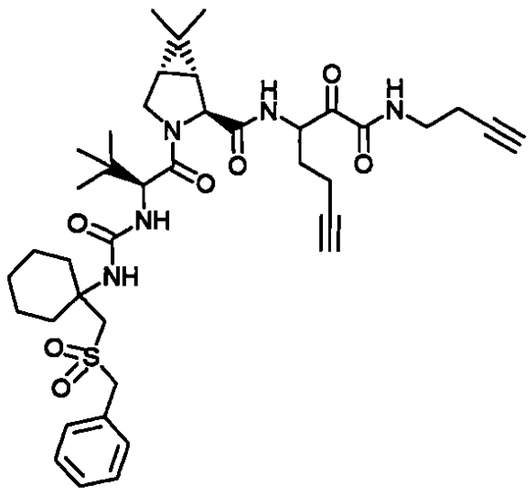


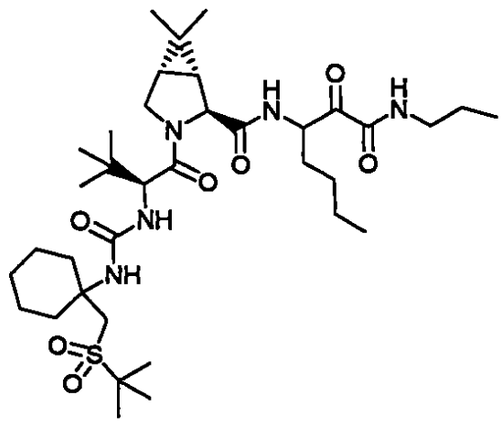


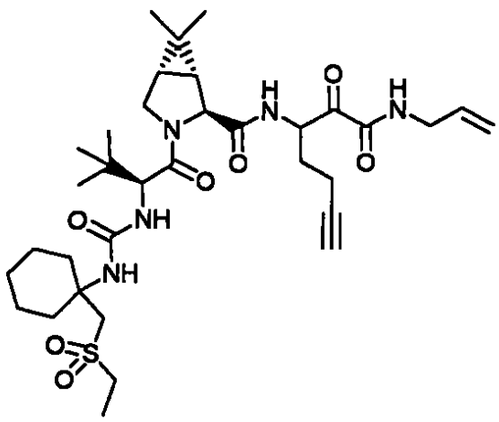


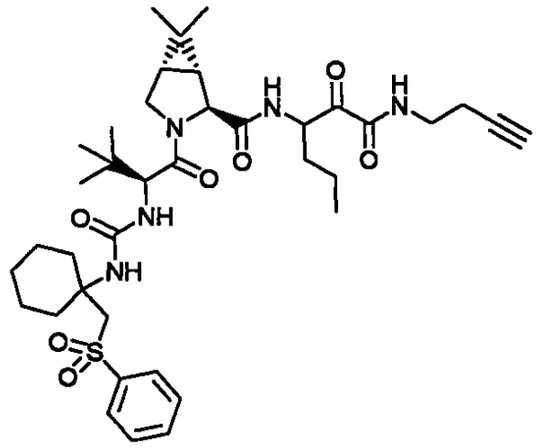


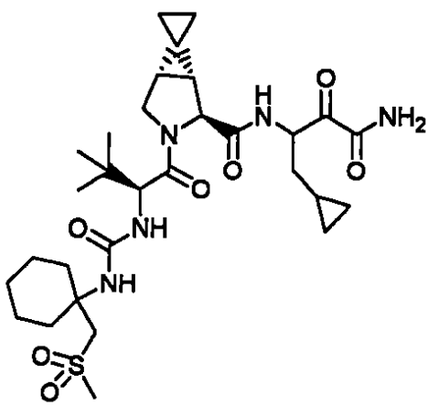
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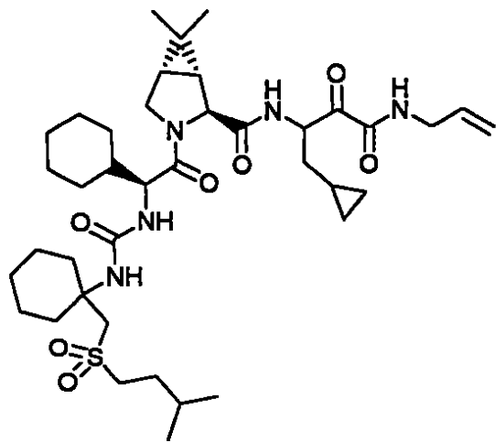




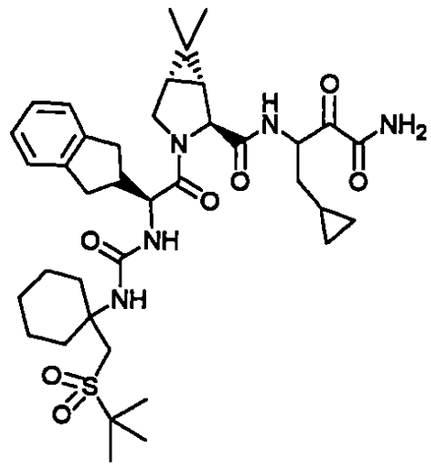


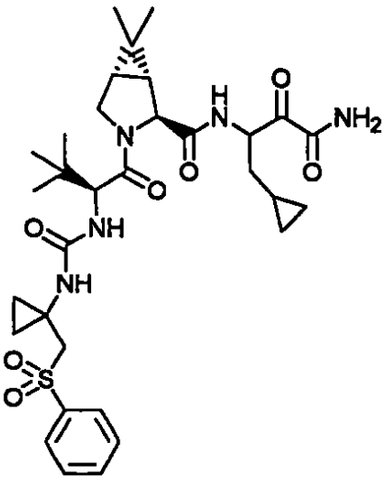


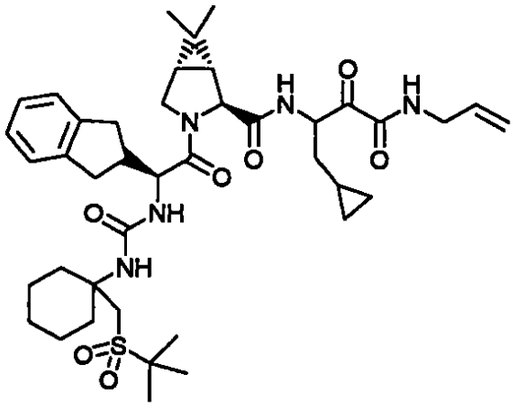


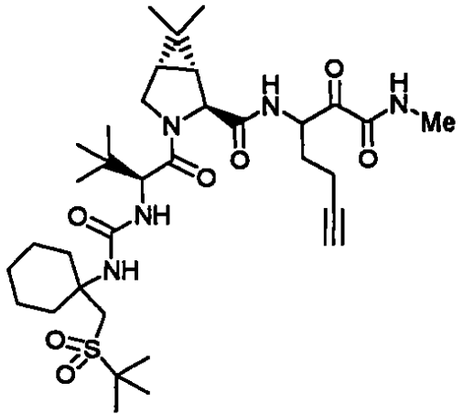


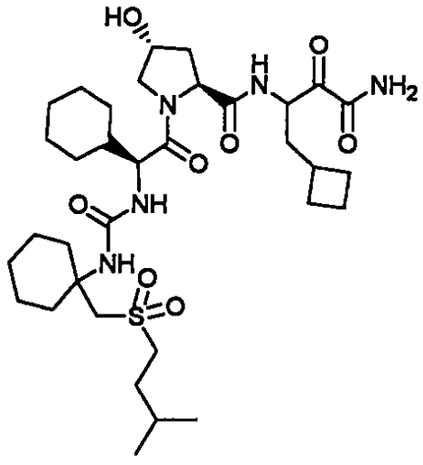
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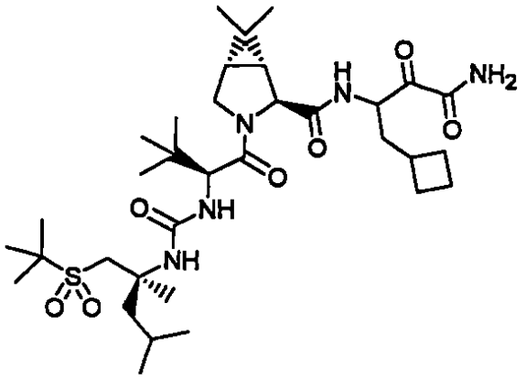




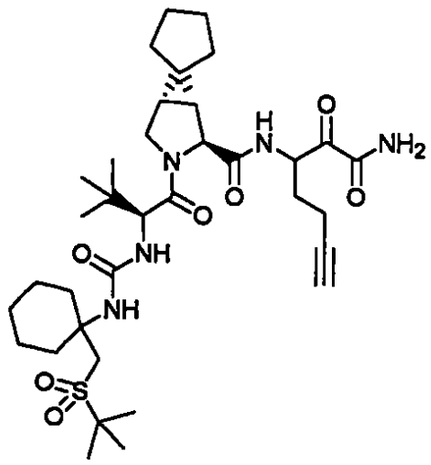


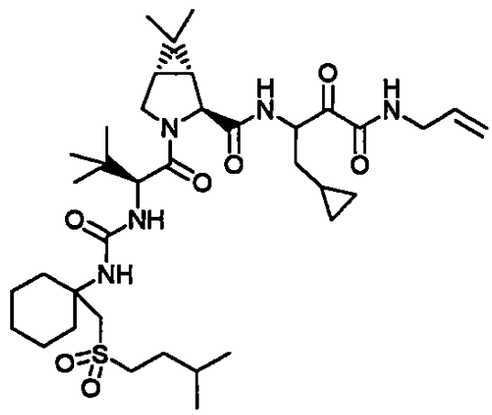


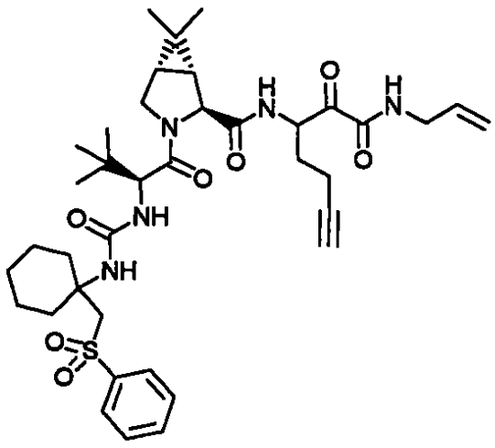


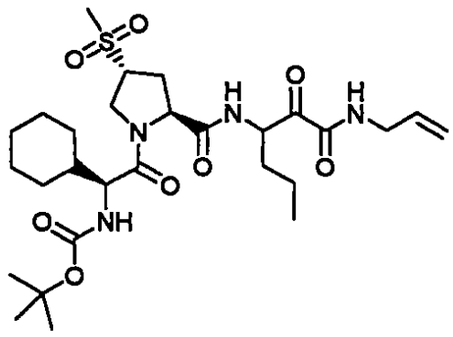


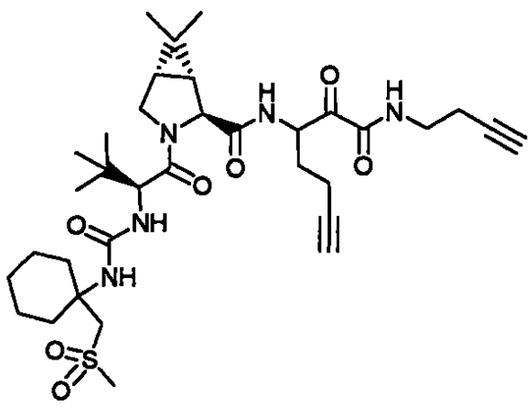
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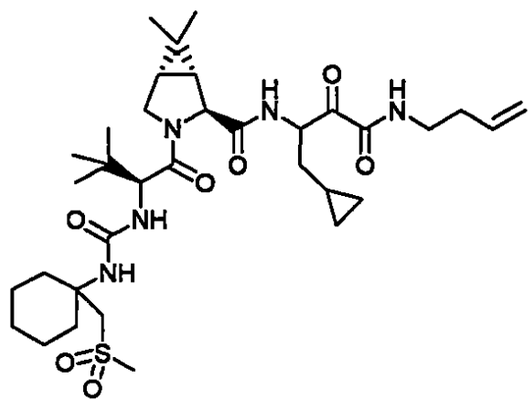




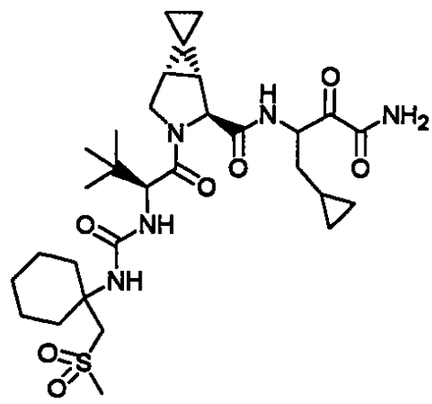


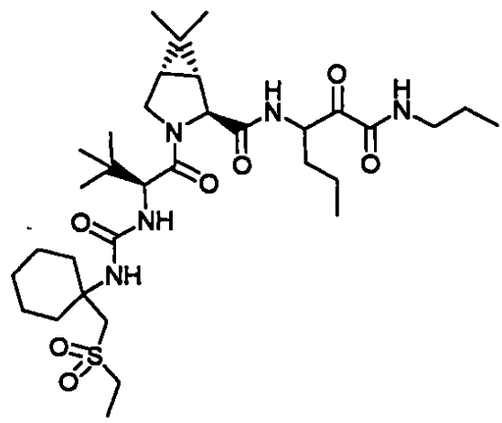


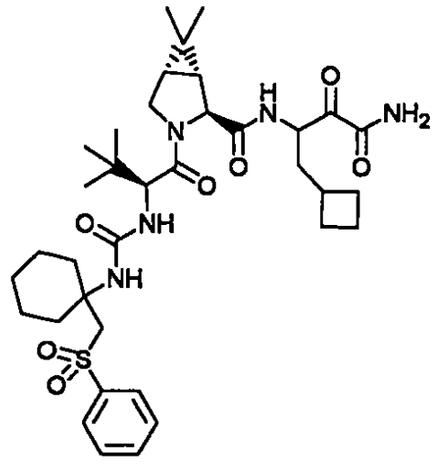


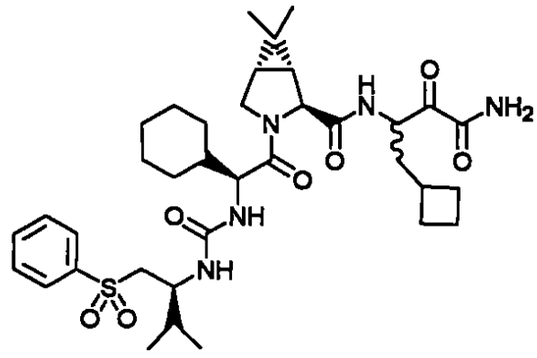


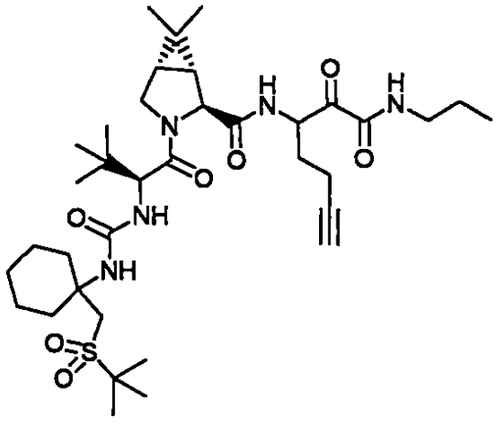
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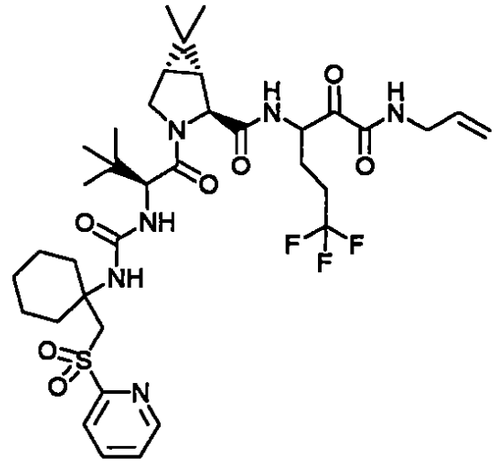




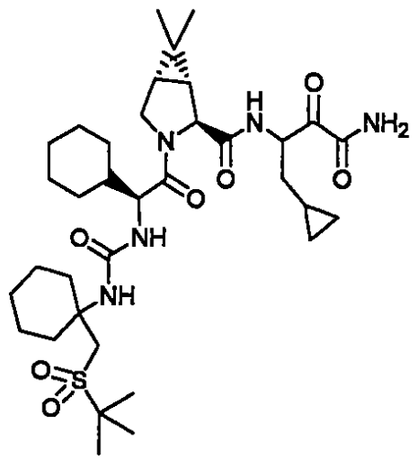


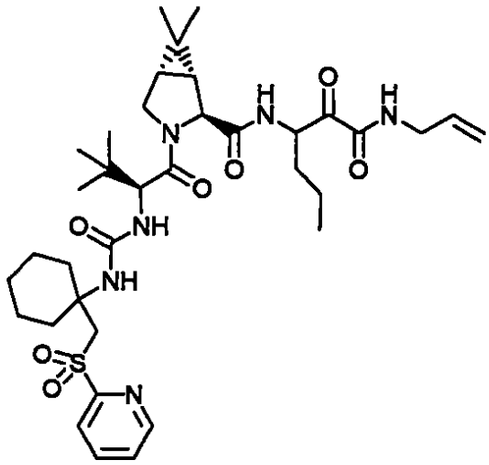


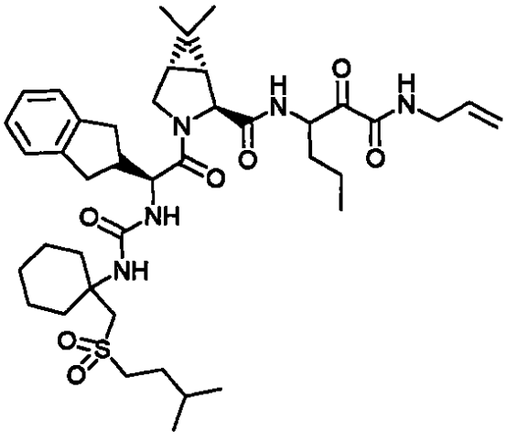


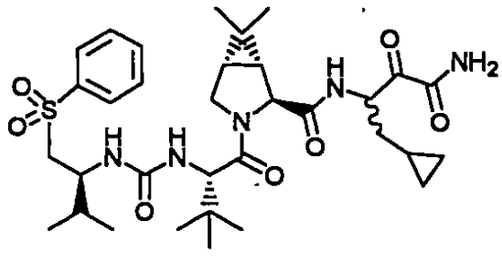


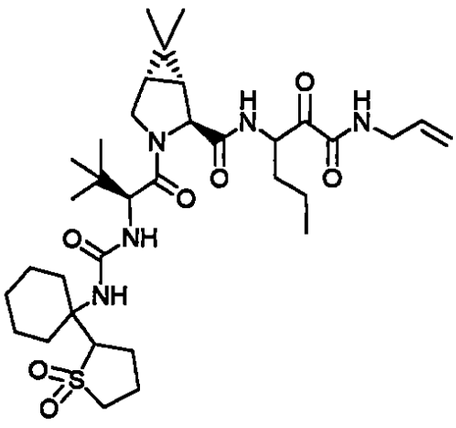
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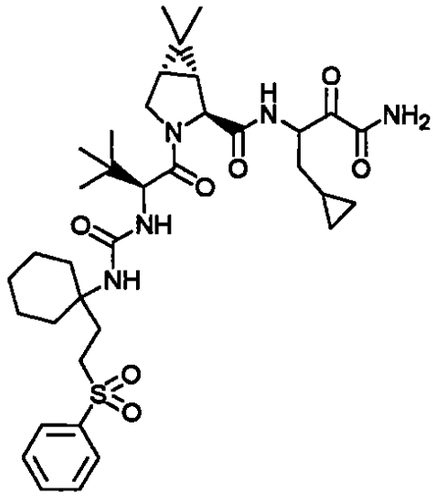




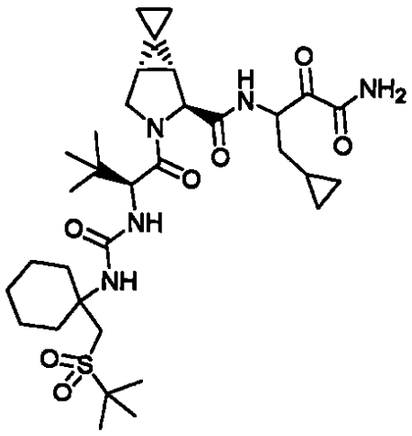


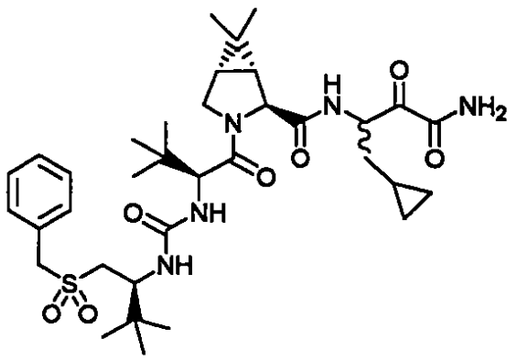


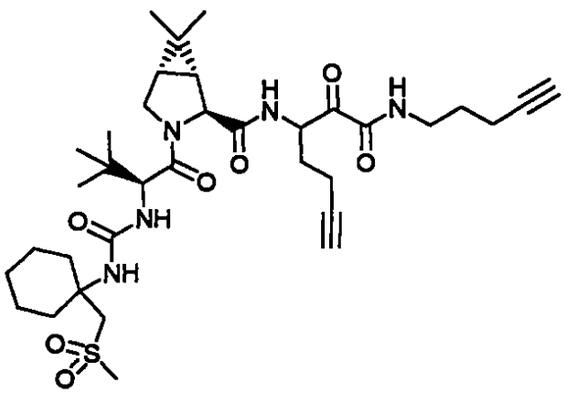


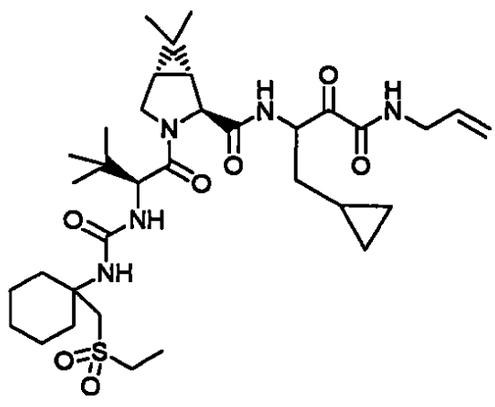


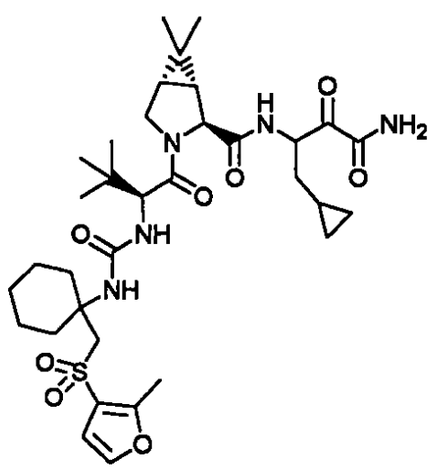
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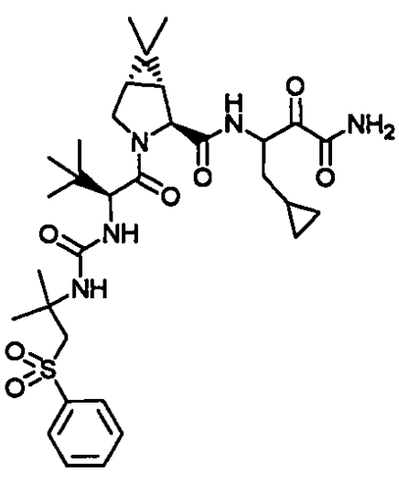




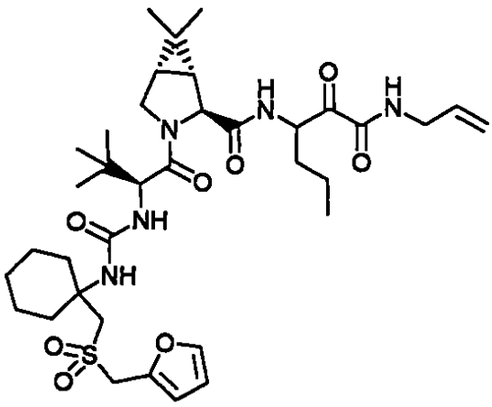


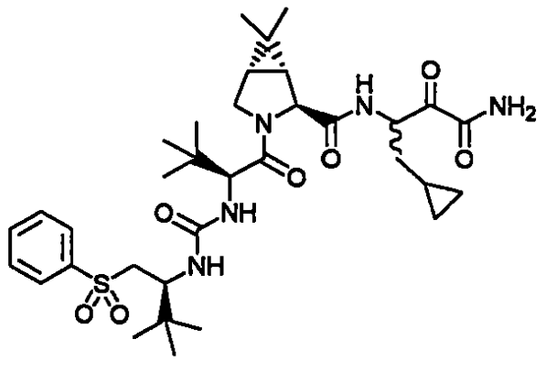


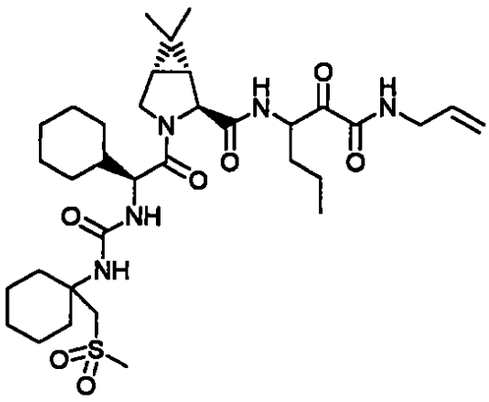


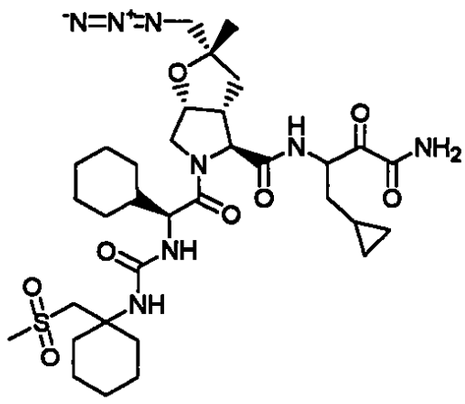


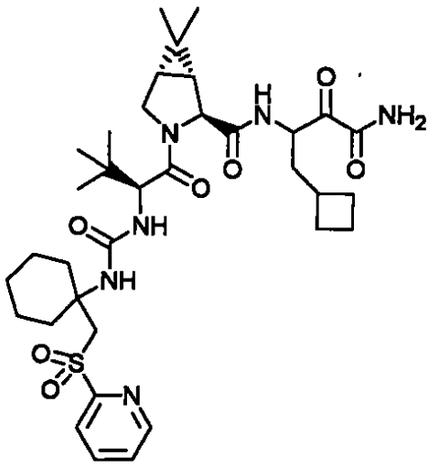
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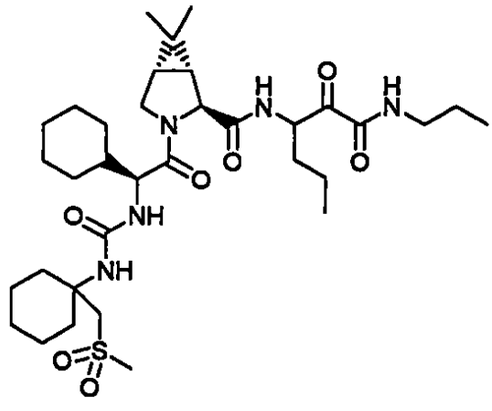




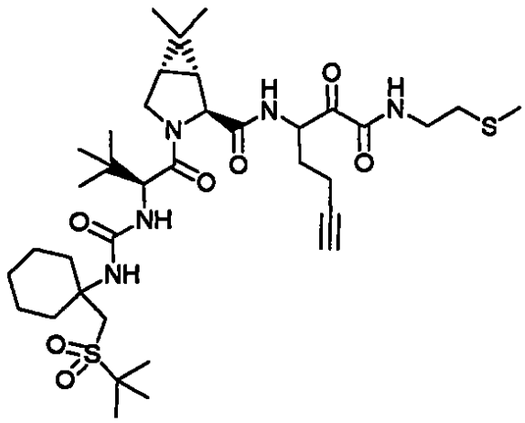


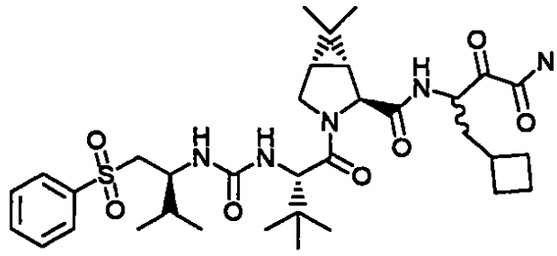


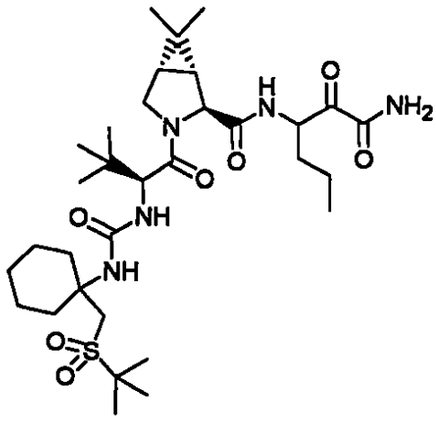


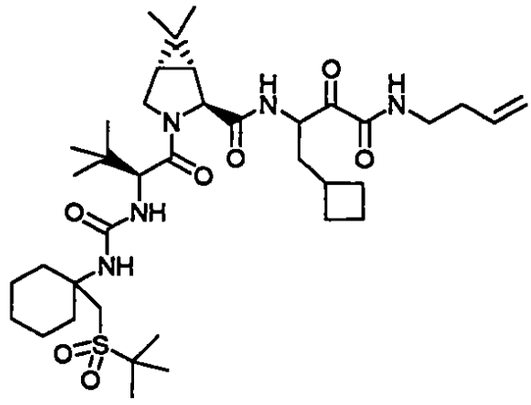


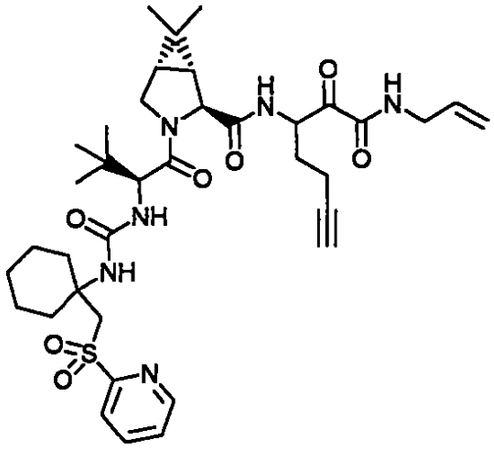
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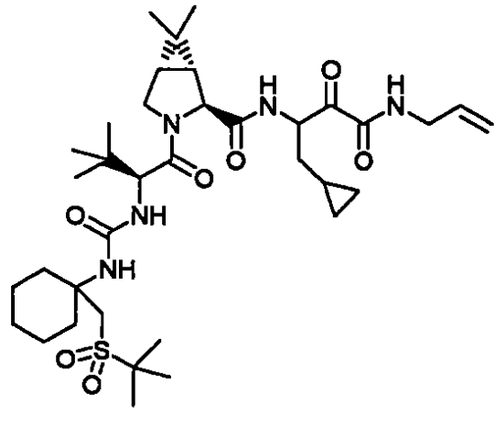


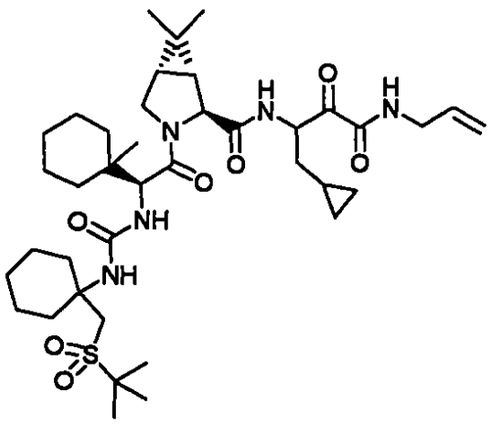


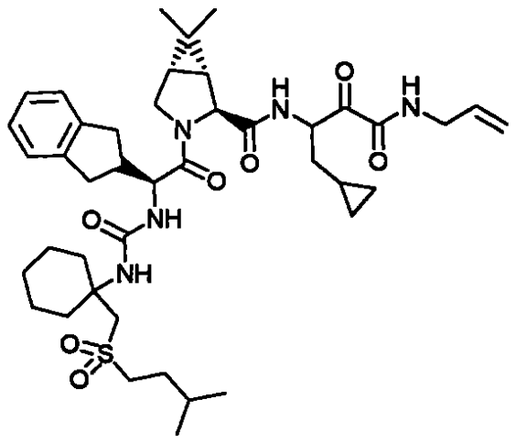


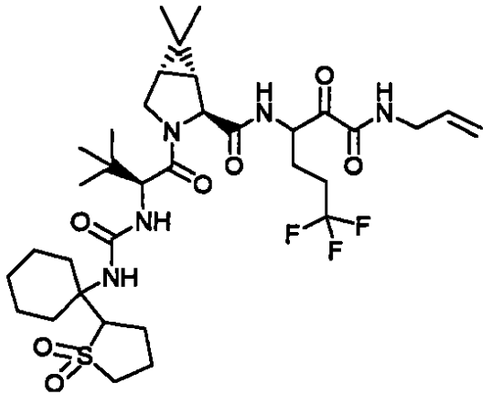


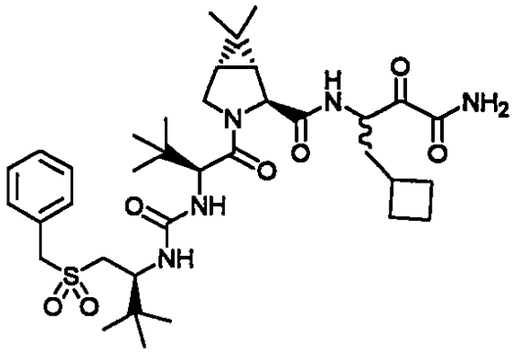


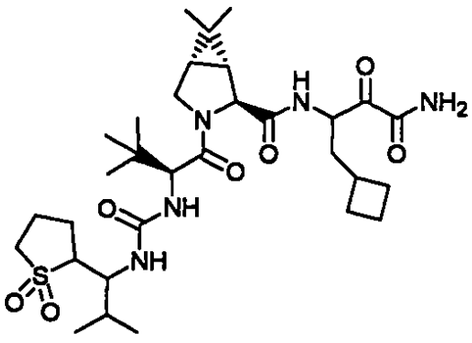


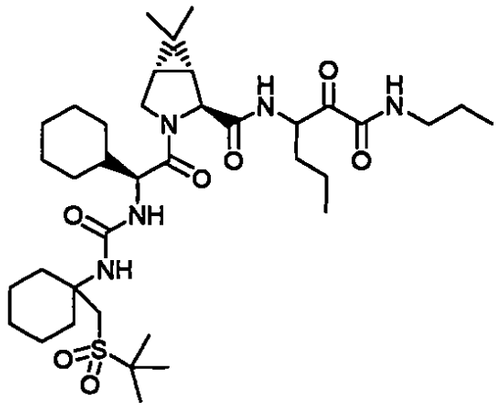




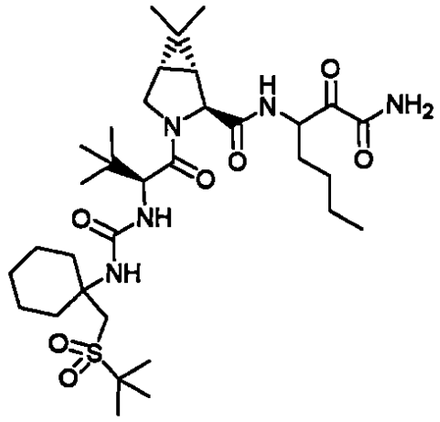


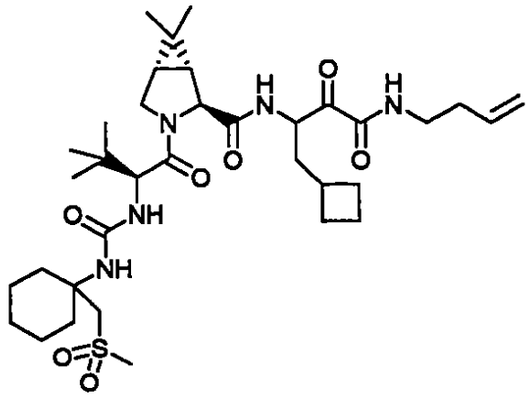


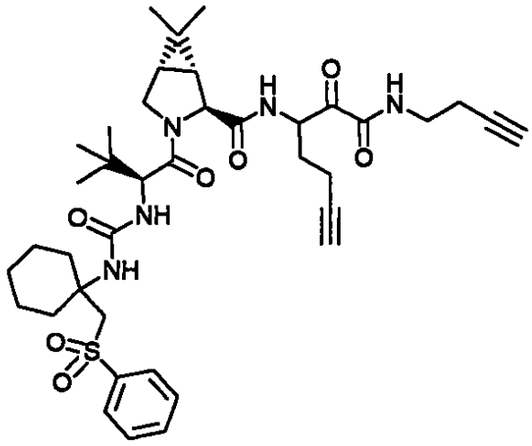


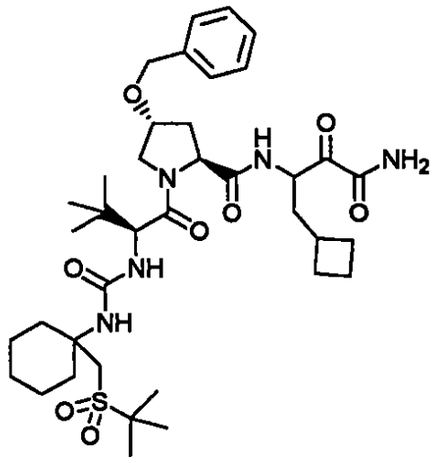


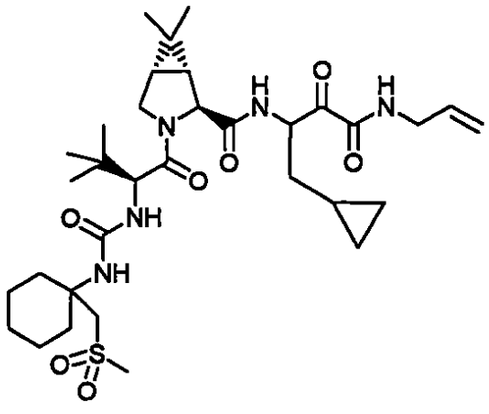
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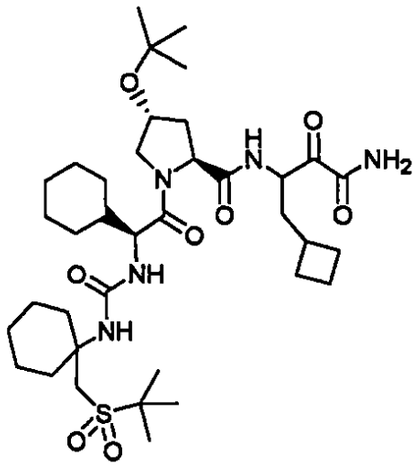




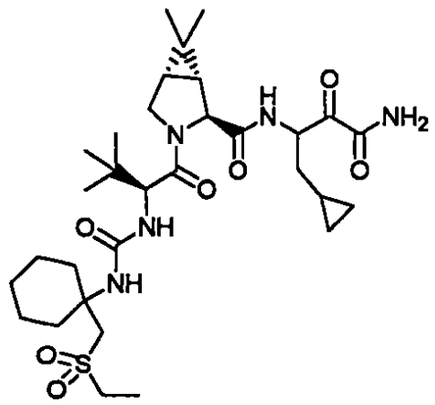


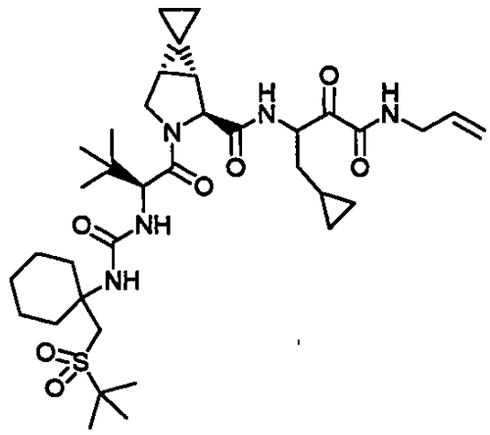


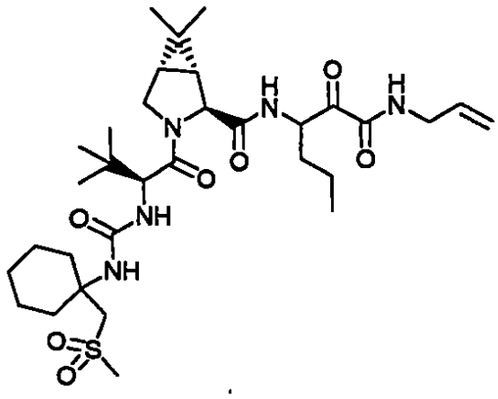


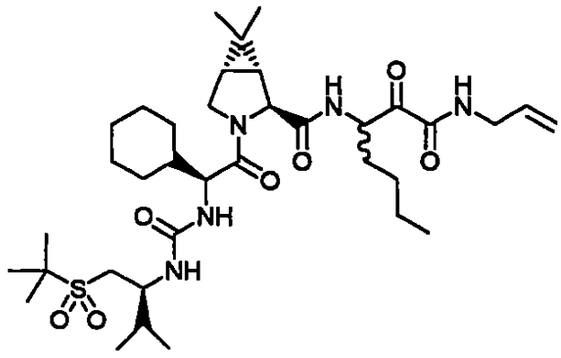


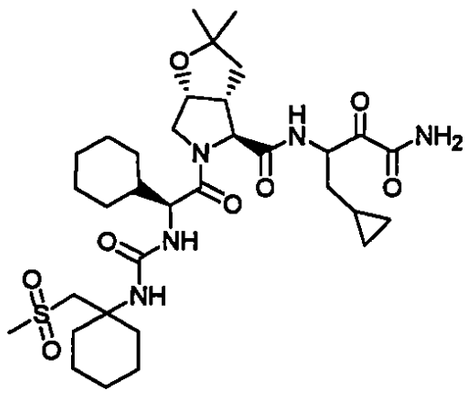
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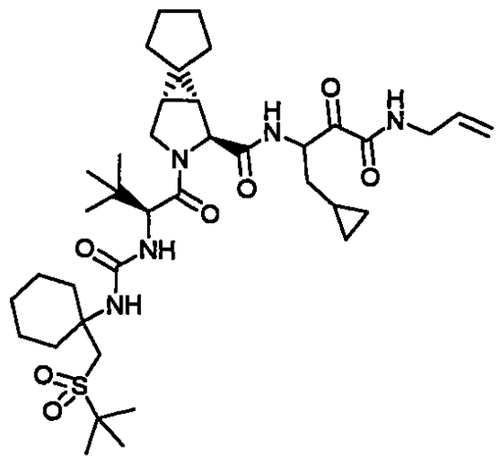




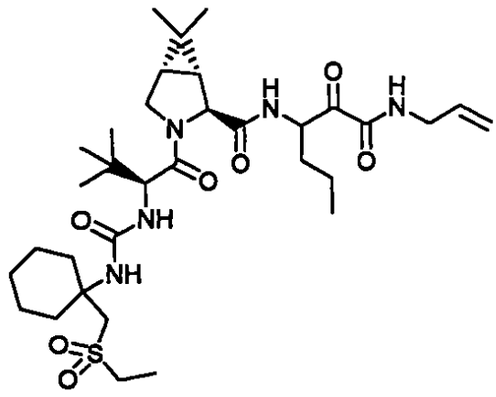


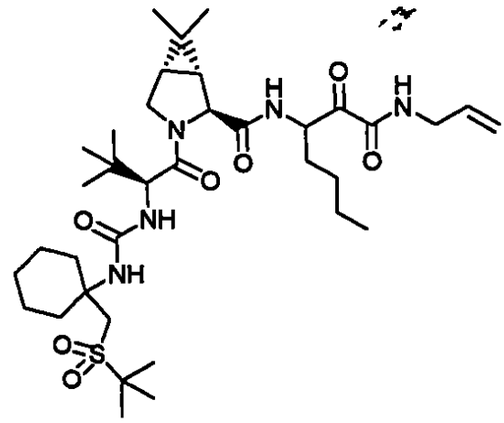






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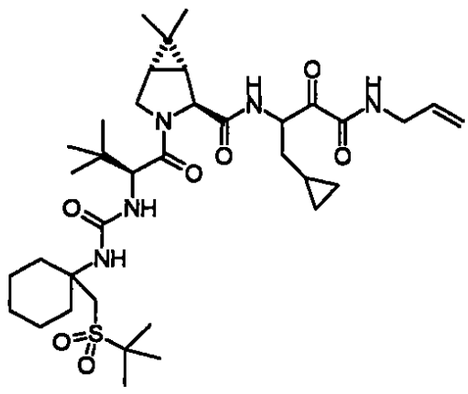


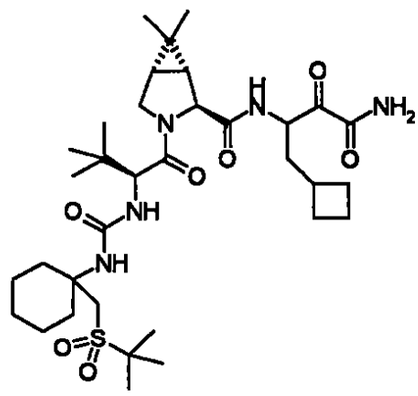


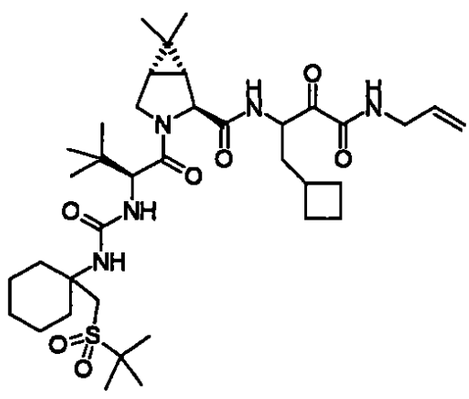
En una realización adicional, esta invención revela los siguientes compuestos de la **Tabla 2**.

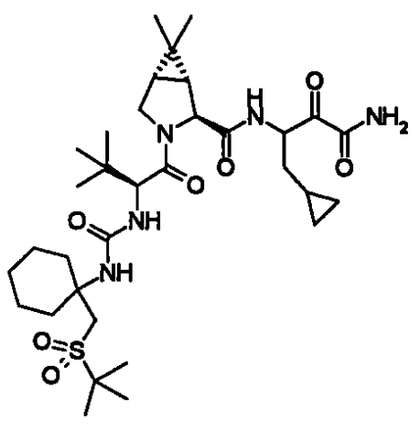
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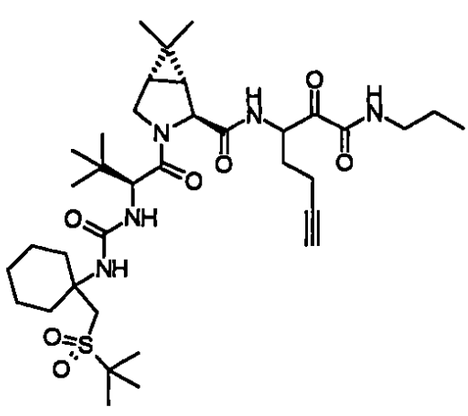
Tabla 2

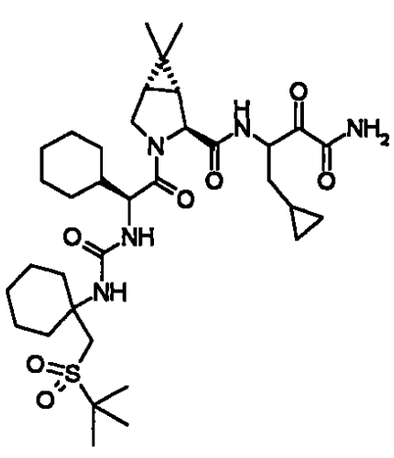




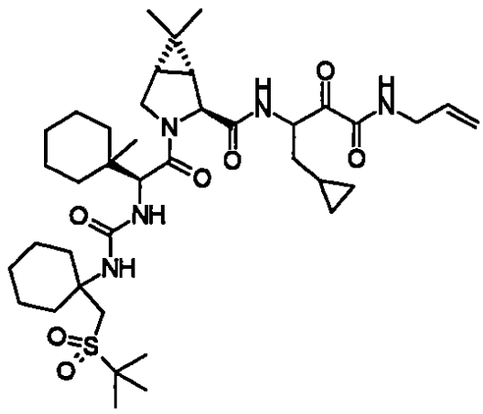


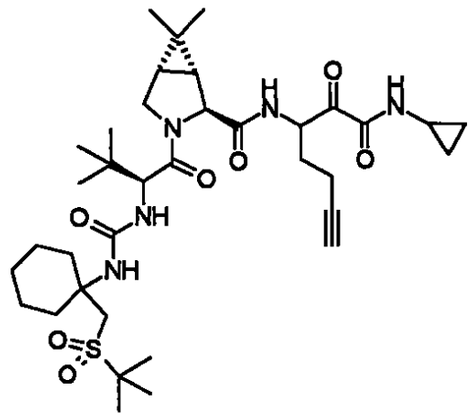


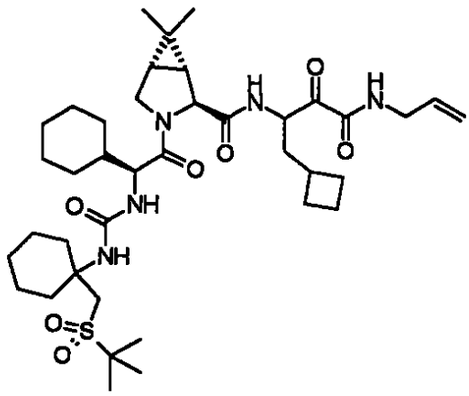


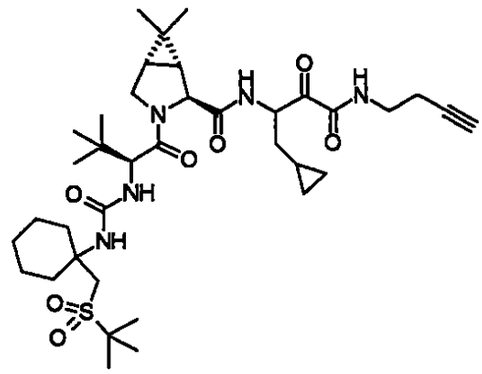


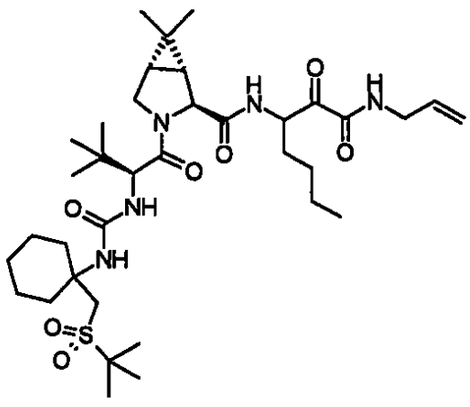
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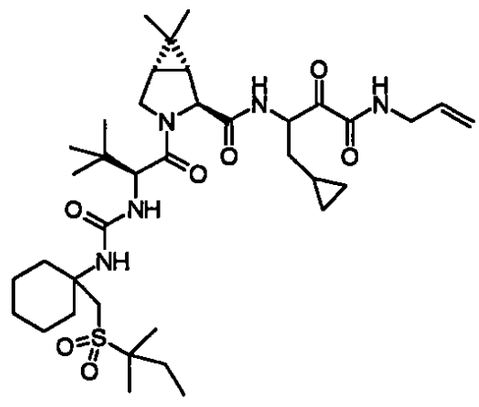




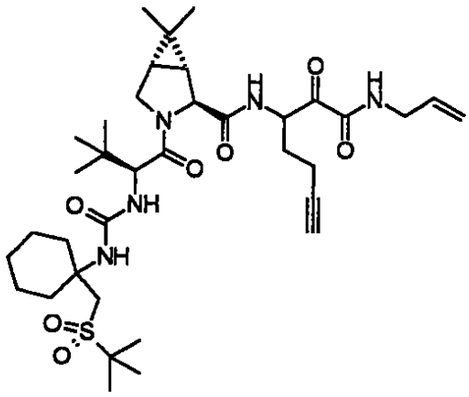


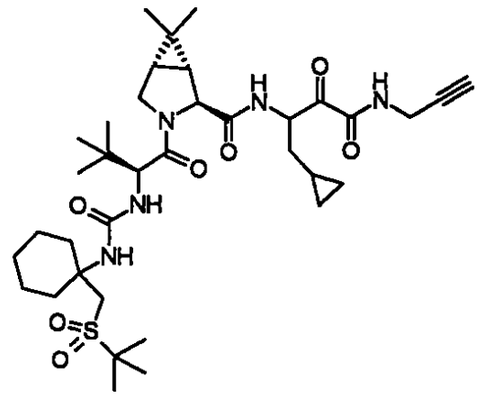


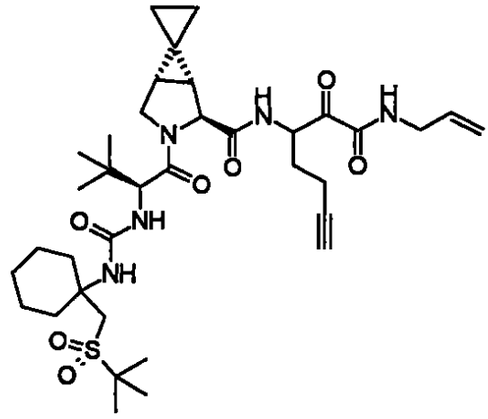




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Como se usaron con anterioridad, y en todo el texto de esta memoria descriptiva, se entenderá que los siguientes términos, salvo que se indique de otro modo, tienen los siguientes significados:

"Paciente" incluye tanto humanos como animales

"Mamífero" se refiere a humanos y otros animales mamífero.

"Alquilo" se refiere a 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 inferior tales como metilo, etilo o propilo, están unidos a

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una cadena alquilo lineal. "Alquilo inferior" se refiere a un grupo que tiene aproximadamente 1 hasta aproximadamente 6 átomos de carbono en la cadena que puede ser recto o ramificado. El término "alquilo sustituido" se refiere a que el grupo alquilo puede estar sustituido por uno o más substituents que pueden ser iguales o diferentes, cada sustituyente se selecciona en forma independiente del grupo formado por halo, alquilo, arilo, cicloalquilo, ciano, hidroxi, alcoxi, alquiltio, amino, -NH(alquil), -NH(cicloalquil), -N(alquil)$_2$, -N(alquil)$_2$, carboxi y –C(O)O-alquilo. Ejemplos no limitativos de grupos alquilo apropiados incluyen metilo, etilo, n-propilo, isopropilo y t-butilo.

"Alquenilo" se refiere a un grupo hidrocarburo alifático que contiene por lo menos un enlace doble carbono-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 con mayor preferencia aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior tales como metilo, etilo o propilo, están unidos a una cadena de alquenilo lineal. "Alquenilo inferior" se refiere a aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena que puede ser recto o ramificado. El término "alquenilo sustituido" significa que el grupo alquenilo puede estar sustituido por uno o más sustituyentes que pueden ser iguales o diferentes, cada sustituyente se selecciona en forma independiente del grupo formado por halo, alquilo. arilo, cicloalquilo, ciano, alcoxi y –S(alquilo). Ejemplos no limitativos de suitable alquenilo groups incluyen etenilo, propenilo, n-butenilo, 3-metilbut-2-enilo, n-pentenilo, octenilo y decenilo.

"Alquinilo" se refiere a un grupo hidrocarburo alifático que contiene por lo menos un enlace triple carbono-carbono y que puede ser recto o ramificado y que comprende aproximadamente 2 hasta aproximadamente 15 átomos de carbono

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en la cadena Los grupos alquinilo preferidos tienen aproximadamente 2 hasta aproximadamente 12 átomos de carbono en la cadena, y con mayor preferencia aproximadamente 2 hasta aproximadamente 4 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior tales como metilo, etilo o propilo, están unidos a una cadena alquinilo lineal. "Alquinilo inferior" se refiere a aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena que puede ser recto o ramificado. Ejemplos no limitativos de grupos alquinilo apropiados incluyen etinilo, propinilo, 2-butinilo y 3-metilbutinilo. El término "alquinilo sustituido" significa que el grupo alquinilo puede estar sustituido por uno o más sustituyentes que pueden ser iguales o diferentes, cada sustituyente se selecciona en forma independiente del grupo formado por alquilo, arilo y cicloalquilo

"Arilo" se refiere a un sistema anular aromático monocíclico o multicíclico que comprende aproximadamente 6 hasta aproximadamente 14 átomos de carbono, con preferencia aproximadamente 6 hasta aproximadamente 10 átomos de carbono. El grupo arilo puede estar sustituido en forma opcional con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son como se los definió aquí. Ejemplos no limitativos de grupos arilo apropiados incluyen fenilo y naftilo.

"Heteroarilo" se refiere a un sistema anular aromático monocíclico o multicíclico que comprende aproximadamente 5 hasta aproximadamente 14 átomos en el anillo, con preferencia aproximadamente 5 hasta aproximadamente 10 átomos en el anillo, en el cual uno o más de los átomos en el anillo es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o combinado Los heteroarilos preferidos contienen aproximadamente 5 hasta aproximadamente 6 átomos en el anillo. El "heteroarilo" puede estar sustituido en forma opcional por uno o más "sustituyentes del sistema anular" que pueden ser

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iguales o diferentes, y son como se los definió aquí. El prefijo aza, oxa o tia antes del nombre de raíz del heteroarilo significa 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 oxidarse de manera opcional 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, benzimidazolilo, benzotienilo, quinolinilo, imidazolilo, tienopiridilo, quinazolinilo, tienopirimidilo, pirrolopiridilo, imidazopiridilo, isoquinolinilo, benzoazaindolilo, 1,2,4-triazinilo, benzotiazolilo y similares. El término "heteroarilo" se refiere además a restos heteroarílicos parcialmente saturados tales como, por ejemplo, tetrahidroisoquinolilo, tetrahidroquinolilo y similares

"Aralquilo" o "arilalquilo" se refiere a un grupo aril-alquilo- en los cuales el arilo y alquilo son como se los definió con anterioridad. Los aralquilos preferidos comprenden un grupo alquilo inferior. Ejemplos no limitativos de grupos aralquilo apropiado incluyen bencilo, 2-fenetilo y naftalenilmetilo El enlace con el resto de origen es a través del alquilo.

"Alquilarilo" se refiere a un grupo alquil-arilo- en el cual el alquilo y el arilo son como se los definió con anterioridad. Los alquilarilos preferidos comprenden un grupo alquilo inferior Un ejemplo no limitativo de un grupo alquilarilo apropiado es el tolilo El enlace con el resto de origen es a través del arilo

"Cicloalquilo" se refiere a un sistema anular no aromático, mono- o multicíclico que comprende aproximadamente 3 hasta aproximadamente 10 átomos de carbono, con preferencia aproximadamente 5 hasta aproximadamente

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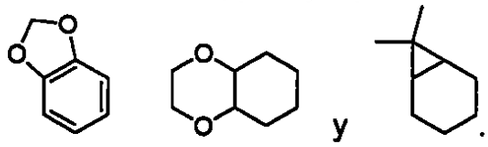
10 átomos de carbono. Los anillos cicloalquilo preferidos contienen aproximadamente 5 hasta aproximadamente 7 átomos en el anillo. El cicloalquilo puede estar sustituido en forma opcional con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son como se los definió con anterioridad. Ejemplos no limitativos de cicloalquilos monocíclicos apropiados incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo y similares. Ejemplos no limitativos de cicloalquilos multicíclicos incluyen 1-decalinilo, norbornilo, adamantilo y similares, como también especies parcialmente saturadas tales como, por ejemplo, indanilo, tetrahidronaftilo y similares.

"Halógeno" o "halo" se refiere a flúor, cloro, bromo, o yodo. Se prefieren el flúor, cloro y bromo

"Sustituyente del sistema anular" se refiere a un sustituyente unido a un sistema anular aromático o no aromático que, por ejemplo, reemplaza un hidrógeno disponible en el sistema anular. Los sustituyentes del sistema anular pueden ser iguales o diferentes, cada uno seleccionado en forma independiente del grupo formado por alquilo, alquenilo, alquinilo, arilo, heteroarilo, aralquilo, alquilarilo, heteroaralquilo, heteroariloalquenilo, heteroariloalquinilo, alquilheteroarilo, hidroxi, hidroxialquilo, alcoxi, ariloxi, aralcoxi, acilo, aroilo, 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-alquilo-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- y -$SO_2NY_1Y_2$, en los cuales Y_1 e Y_2 pueden ser iguales o diferentes y se seleccionan en forma independiente del grupo formado por hidrógeno, alquilo, arilo, cicloalquilo, y aralquilo "Sustituyente del sistema anular" puede significar, además, un resto único que reemplaza en forma simultánea dos hidrógenos disponibles en dos átomos de carbono adyacentes (un H en cada carbono) en un

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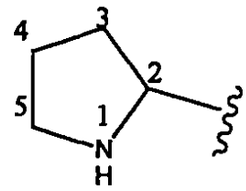
sistema anular. Ejemplos de dicho resto son metilendioxi, etilendioxi, $-C(CH_3)_2-$ y similares que forman restos tales como, por ejemplo

 y .

"Heterociclilo" se refiere a un sistema anular aromático saturado multicíclico o monocíclico que comprende aproximadamente 3 hasta aproximadamente 10 átomos en el anillo, con preferencia aproximadamente 5 hasta aproximadamente 10 átomos en el anillo, en el cual uno o más de los átomos en el sistema anular es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o combinado. No hay átomos de oxígeno y/o azufre adyacentes presentes en el sistema anular. Los heterociclilos preferidos contienen aproximadamente 5 hasta aproximadamente 6 átomos en el anillo. El prefijo aza, oxa o tia antes del nombre de raíz heterociclilo significa que por lo menos un átomo de nitrógeno, oxígeno o azufre respectivamente está presente como átomo del anillo. Cualquier –NH en un anillo heterociclilo puede existir protegido tal como, por ejemplo, como un grupo -N(Boc), -N(CBz), -N(Tos) y similares; dichas protecciones se consideran también parte de esta invención. El heterociclilo puede estar sustituido en forma opcional por uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son como se los definió aquí. El átomo de nitrógeno o azufre del heterociclilo puede oxidarse de manera opcional al correspondiente N-óxido, S-óxido o S,S-dióxido. Ejemplos no limitativos de anillos heterociclilo monocíclicos apropiados incluyen piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,4-dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, lactama, lactona, y similares.

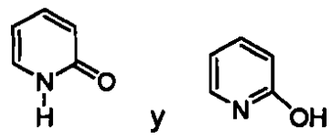
Se debe observar que en los sistemas anulares que contienen heteroátomos de esta invención, no hay grupos hidroxilo sobre los átomos de

carbono adyacentes a un N, O o S, como tampoco hay grupos N o S sobre el carbono adyacente a otro heteroátomo. De este modo, por ejemplo, en el anillo



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

Se debe observar, además, que formas tautoméricas tales como, por ejemplo, los restos:



se consideran equivalentes en ciertas realizaciones de esta invención

"Alquinilalquilo" se refiere a un grupo alquinil-alquil- en el cual el alquinilo y alquilo son como se los definió con anterioridad. Los alquinilalquilos preferidos contienen un alquinilo inferior y un grupo alquilo inferior. El enlace con el resto de origen es a través del alquilo Ejemplos no limitativos de grupos alquinilalquilo apropiados incluyen propargilmetilo.

"Heteroaralquilo" se refiere a un grupo heteroaril-alquilo- en el cual el heteroarilo y el alquilo son como se los definió con anterioridad. Los heteroaralquilos apropiados contienen un grupo alquilo inferior. Ejemplos no limitativos de grupos aralquilo apropiados incluyen piridilmetilo, y quinolin-3-ilmetilo. El enlace con el resto de origen es a través del alquilo.

"Hidroxialquilo" se refiere a un grupo HO-alquilo- en el cual el alquilo es como se lo definió con anterioridad. Los hidroxialquilos preferidos contienen alquilo inferior Ejemplos no limitativos de grupos hidroxialquilo apropiados incluyen hidroximetilo y 2-hidroxietilo.

"Acilo" se refiere a un grupo H-C(O)-, alquil-C(O)- o cicloalquil-C(O)- en el cual los varios grupos son como se los definió con anterioridad. El enlace con el

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resto de origen es a través del carbonilo. Los acilos preferidos contienen un alquilo inferior Ejemplos no limitativos de grupos acilo apropiados incluyen formilo, acetilo y propanoilo.

"Aroílo" se refiere a un grupo aril-C(O)- en el cual el grupo arilo es como se describió con anterioridad El enlace con el resto de origen es a través del carbonilo. Ejemplos no limitativos de suitable groups incluyen benzoílo y 1-naftoílo.

"Alcoxi" se refiere a un grupo alquil-O- en el cual el grupo alquilo es como se describió con anterioridad. Ejemplos no limitativos de grupos alcoxi apropiados incluyen metoxi, etoxi, n-propoxi, isopropoxi y n-butoxi. El enlace con el resto de origen es a través del oxígeno del éter.

"Ariloxi" se refiere a an aril-O- group en el cual el grupo arilo es como se describió con anterioridad Ejemplos no limitativos de suitable ariloxi groups incluyen phenoxi y naphthoxi. El enlace con el resto de origen es a través del oxígeno del éter.

"Aralquiloxi" se refiere a un grupo aralquil-O- en el cual el grupo aralquilo es como se describió con anterioridad Ejemplos no limitativos de grupos aralquiloxi apropiados incluyen benciloxi y 1- o 2-naftalenemetoxi. El enlace con el resto de origen es a través del oxígeno del éter.

"Alquiltio" se refiere a un grupo alquil-S- en el cual el grupo alquilo es como se describió con anterioridad Ejemplos no limitativos de grupos alquiltio apropiados incluyen metiltio y etiltio El enlace con el resto de origen es a través del azufre.

"Ariltio" se refiere a un grupo aril-S- en el cual el grupo arilo es como se describió con anterioridad Ejemplos no limitativos de grupos ariltio apropiados incluyen fenilotio y naftiltio. El enlace con el resto de origen es a través del azufre.

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"Aralquiltio" se refiere a un grupo aralquil-S- en el cual el grupo aralquilo es como se describió con anterioridad Un ejemplo no limitativo de un grupo aralquiltio apropiado ess benciltio. El enlace con el resto de origen es a través del azufre

"Alcoxicarbonilo" se refiere a un grupo alquil-O-CO-. Ejemplos no limitativos de grupos alcoxicarbonilo apropiados incluyen metoxicarbonilo y etoxicarbonilo. El enlace con el resto de origen es a través del carbonilo

"Ariloxicarbonilo" se refiere a un grupo aril-O-C(O)- Ejemplos no limitativos de grupos ariloxicarbonilo apropiados incluyen fenoxicarbonilo y naftoxicarbonilo. El enlace con el resto de origen es a través del carbonilo.

"Aralcoxicarbonilo" se refiere a un grupo aralquil-O-C(O)-. Un ejemplo no limitativo de un grupo aralcoxicarbonilo apropiado es benciloxicarbonilo El enlace con el resto de origen es a través del carbonilo.

"Alquilosulfonilo" se refiere a un grupo alquil-$S(O_2)$-. Los grupos preferidos son aquellos en los cuales el grupo alquilo es alquilo inferior. El enlace con el resto de origen es a través del sulfonilo.

"Arilsulfonilo" se refiere a un grupo aril-$S(O_2)$-. El enlace con el resto de origen es a través del sulfonilo

El término "sustituido" se refiere a que uno o más hidrógenos sobre el átomo designado está reemplazado con una selección del grupo indicado, siempre que la valencia normal del átomo designado bajo las circustancias existentes no se exceda, y que la sustitución produzca un compuesto estable. Se permiten combinaciones de sustituyentes y/o variables sólo si dichas combinaciones producen compuestos estables. Por "compuesto estable" o "estructura estable" se entiende un compuesto que es lo suficientemente robusto para sobrevivir al aislamiento hasta un grado útil de pureza a partir de una mezcla de reacción, y su formulación en un agente terapéutico eficiente.

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El término "uno o más" o "por lo menos uno", cuando indica el número sustituyentes, compuestos, agentes de combinación y similares, se refiere a por lo menos uno, y hasta el número máximo de compuestos, agentes de combinación y similares permitibles química y físicamente que están presentes o agregados, dependiendo del contexto. Dichas técnicas y conocimiento son conocidos para la experiencia de personas involucradas.

El término "sustituido de manera opcional" se refiere a sustitución opconal con los grupos especificados, radicales o restos.

El término "aislado" o "en forma aislada" para un compuesto se refiere a el estado físico de dicho compuesto luego de ser aislado a partir de un proceso sintético o su origen natural o combinación El término "purificado" o "en forma purificada" para un compuesto se refiere al estado físico de dicho compuesto luego de obtenerse a partir de un proceso o los procesos de purificación descritos aquí o conocidos por los expertos en el arte, en pureza suficiente para ser caracterizable por técnicas de análisis estándares descritas aquí o conocidas para aquellos expertos en el arte

Se debe observar, además, que supuestamente cualquier heteroátomo con valencias no satisfechas en el texto, los esquemas, los ejemplos y las Tablas de esta invención tienen el(los) átomo(s) de hidrógeno para satisfacer dichas valencias.

Cuando un grupo funcional en un compuesto se denomina "protegido", esto significa que el grupo se encuentra en forma modificada para evitar las reacciones colaterales indeseables en el sitio protegido cuando el compuesto se somete a una reacción Los grupos protectores apropiados serán reconocidos por aquellos con experiencia en el arte, como también por referencia a los libros de texto estándares 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 ej , arilo, heterociclo, R^2, etc.) ocurre más de una vez en cualquier constituyente o en la Fórmula I, su definición en cada caso es independiente de su definición en cualquier otra ocurrencia.

Como se usa aquí, el término "composición" pretende abarcar un producto que comprende los ingredientes específicos en las cantidades específicas, como también cualquier producto generado, directa o indirectamente, de la combinación de los ingredientes específicos en las cantidades específicas.

Además, se contemplan aquí los profármacos y solvatos de los compuestos de la invención. El término "profármaco", como se emplea aquí, denota un compuesto que es un precursor farmacológico que, luego de la administración a un sujeto, sufre conversión química por procesos metabólicos o químicos para producir un compuesto de Fórmula I o una de sus sales y/o solvatos Una discusión sobre profármacos se provee en T. Higuchi and V Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 de la A C.S. Symposium Series, y en *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, ambos incorporados aquí a modo de referencia

"Solvato" se refiere a una asociación física de un compuesto de esta invención con una o más moléculas de solvente. Esta asociación física incluye grados variables de enlaces iónicos y covalentes, incluyendo uniones con hidrógeno En ciertos casos, el solvato será capaz de aislamiento, por ejemplo cuando una o más moléculas de solvente se incorporan en el retículo de cristal del sólido cristalino "Solvato" abarca ambos solvatos, de fase en solución y no 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 efectiva" o "cantidad terapéuticamente efectiva" pretende describir una cantidad de compuesto o una composición de la presente invención efectiva para inhibir la CDK(s) y de este modo producir el efecto terapéutico, atenuante, inhibidor o preventivo deseado.

Los compuestos de Fórmula I pueden formar sales que también se encuentran dentro del alcance de esta invención. La referencia a un compuesto de Fórmula I aquí se entiende como inclusivo de la referencia sus sales, salvo que se indique de otro modo. El término "sal(es)", como se emplea aquí, denota sales ácidas formadas con ácidos inorgánicos y/u orgánicos, como también sales alcalinas formadas con bases inorgánicas y/u orgánicas. Además, cuando un compuesto de Fórmula I contiene tanto un resto alcalino, tal como, sin carácter limitativo, una piridina o imidazol, y un resto ácido, tal como, sin carácter limitativo un ácido carboxílico, pueden formarse zwitteriones ("sales internas") y se incluyen dentro del término "sal(es)" como se usa aquí. Las sales aceptables desde el punto de vista farmacéutico (es decir, no tóxicas, fisiológicamente aceptables) son las preferidas, aunque también son útiles otras sales. Las sales de los compuestos de fórmula I pueden formarse, por ejemplo, haciendo reaccionar 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 la sal se precipita o en un medio acuoso seguido de liofilización.

Las sales de adición con ácido ejemplificativas incluyen acetatos, ascorbatos, benzoatos, bencensulfonatos, bisulfatos, boratos, butiratos, citratos, alcanforatos, alcanforsulfonatos, fumaratos, clorhidratos, bromhidratos, yodhidratos, lactatos, maleatos, metansulfonatos, naftalensulfonatos, nitratos, oxalatos, fosfatos, propionatos, salicilatos, succinatos, sulfatos, tartaratos, tiocianatos, toluensulfonatos (conocidos también como tosilatos,) y similares En forma adicional, los ácidos que generalmente se consideran apropiados para la

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formación de sales útiles desde el punto de vista farmacéutico de compuestos farmacéuticos se describen, por ejemplo, en el texto escrito 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; y en *The Orange Book* (Food & Drug Administration, Washington, D.C en su sitio en Internet). Estas revelaciones se incorporan aquí a modo de referencia.

Las sales con bases ejemplificativas incluyen sales de amonio, sales de metales alcalinos tales como sales de sodio, litio, y potasio, sales de metales alcalino-térreos tales como sales de calcio y magnesio, sales con bases orgánicas (por ejemplo, aminas orgánicas) tales como diciclohexilaminas, t-butil aminas, y sales con aminoácidos tales como arginina, lisina y similares Los grupos básicos que contienen nitrógeno pueden cuaternizarse con tales como haluros de alquilo inferior (por ej cloruros, bromuros y yoduros de metilo, etilo y butilo), dialquil sulfatos (por ej. dimetil, dietil, y dibutil sulfatos), haluros de cadena larga (por ej cloruros, bromuros y yoduros de decilo, laurilo y estearilo), haluros de aralquilo (por ej. bromuros de bencilo y fenetilo), y otros.

Todas dichas sales de ácidos y sales de bases pretenden ser sales aceptables desde el punto de vista farmacéutico dentro del alcance de la invención y todas las sales de ácidos y bases se consideran equivalentes a la forma libre de los correspondientes compuestos para los fines de la invención.

Los ésteres aceptables desde el punto de vista farmacéutico de los presentes compuestos incluyen los siguientes grupos: (1) ésteres de ácido carboxílico obtenidos por esterificación de los grupos hidroxi, en los cuales el resto no carbonilo de la porción de ácido carboxílico de la agrupación éster se

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selecciona de alquilo recto o ramificado (por ejemplo, acetilo, n-propilo, t-butilo, o n-butil), alcoxialquilo (por ejemplo, metoximetilo), aralquilo (por ejemplo, bencilo), ariloxialquilo (por ejemplo, fenoximetilo), arilo (por ejemplo, fenilo sustituido de manera opcional con, por ejemplo, halógeno, alquilo C_{1-4}, o alcoxi C_{1-4} o amino); (2) ésteres de sulfonato, tales como alquil- o aralquilsulfonilo (por ejemplo, metansulfonilo), (3) ésteres de aminoácidos (por ejemplo, L-valilo o L-isoleucilo); (4) ésteres de fosfonato y (5) ésteres de mono-, di- o trifosfato. Los ésteres de fosfato pueden esterificarse en forma adicional mediante, por ejemplo, un alcohol C_{1-20} o su derivado reactivo, o por un a 2,3-di (C_{6-24})acil glicerol.

Los compuestos de Fórmula I, y sus sales, solvatos, ésteres y profármacos, pueden existir en sus formas tautoméricas (por ejemplo, como éter de amida o imino). Todas dichas formas tautoméricas se contemplan aquí como parte de la presente invención.

Todos los estereoisómeros (por ejemplo, isómeros geométricos, isómeros ópticos y similares) de los presentes compuestos (incluyendo aquellos de las sales, los solvatos, ésteres y profármacos de los compuestos como también las sales y los solvatos de los profármacos), tales como aquellos que pueden existir debido a los carbonos asimétricos sobre varios sustituyentes, incluyendo la forma enantiomérica (que pueden existir aun en ausencia de carbonos asimétricos), forma rotamérica, atropoisómeros y forma diastereomérica, se consideran dentro del alcance de esta invención, como son los isómeros de posición (tales como, por ejemplo, 4-piridilo y 3-piridilo). Los estereoisómeros individuales de los compuestos de la invención pueden, por ejemplo, ser sustancialmente libres de otros isómeros, o pueden mezclarse, por ejemplo, como racematos o con todos los demás estereoisómeros, o los seleccionados. Los centros quirales de la presente invención pueden tener la configuración S o R como se define en las *IUPAC* 1974 Recommendations El uso de los términos "sal", "solvato"

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"profármaco" y similares, pretende aplicarse igualmente a la sal, el solvato y el profármaco de enantiómeros, stereoisómeros, rotámero, tautómeros, isómeros de posición, racematos o profármacos de los compuestos de la invención

Las formas polimórficas de los compuestos de Fórmula I, y de las sales, los solvatos, ésteres y profármacos de los compuestos de Fórmula I, pretenden incluirse en la presente invención

Se debe entender que la utilidad de los compuestos de Fórmula I para las aplicaciones terapéuticas discutidas aquí se aplica a cada compuesto en sí mismo o a la combinación o las combinaciones de uno o más compuestos de Fórmula I como se ilustra, por ejemplo, en el párrafo inmediato siguiente. La misma regla se aplica además a composiciones farmacéuticas que comprenden dicho compuesto o compuestos y método(s) de tratamiento que incluyen compuesto o compuestos

Los compuestos de acuerdo con la invención pueden tener propiedades farmacológicas; en particular, los compuestos de Fórmula I pueden ser inhibidores de la proteasa del VHC, cada compuesto solo o uno o más compuestos de Fórmula I pueden combinarse con uno o más compuestos seleccionados de dentro de la Fórmula I. El(los) compuesto(s) pueden ser útiles para tratar enfermedades tales como, por ejemplo, VHC, VIH, (SIDA, Síndrome de Inmuno Deficiencia Adquirida), y trastornos relacionados, como también para modular la actividad de la proteasa del virus de la hepatitis C (VHC), prevenir el VHC, o atenuar uno o más síntomas de la hepatitis C

Los compuestos de Fórmula I pueden usarse para la fabricación de un medicamento para tratar trastornos asociados con la proteasa del VHC, por ejemplo, el método comprende hacer estrecho contacto de un compuesto de Fórmula I con un vehículo aceptable desde el punto de vista farmacéutico

En otra realización, esta invención provee composiciones farmacéuticas que comprenden el compuesto o los compuestos de la invención como

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componente activo. Las composiciones farmacéuticas comprenden, generalmente, en forma adicional por lo menos un diluyente vehículo, excipiente o vehículo aceptables desde el punto de vista farmacéutico (denominados aquí de manera colectiva materiales vehículo). Debido a su actividad inhibidora del VHC, dichas composiciones farmacéuticas poseen utilidad en el tratamiento de la hepatitis C y trastornos relacionados.

Incluso en otra realización, la presente invención revela métodos para preparar composiciones farmacéuticas que comprenden los compuestos de la invención como componente activo. En las composiciones farmacéuticas y métodos para la presente invención, los componentes activos normalmente se administrarán mezclados con materiales vehículo apropiados seleccionados con respecto a la forma de administración pretendida, es decir comprimidos orales, cápsulas (ya sea con relleno sólido, con relleno semisólido o con relleno líquido), polvos para constitución, geles orales, elixires, gránulos dispersables, jarabes, suspensiónes y similares, y consistentes con las prácticas farmacéuticas convencionales. Por ejemplo, para administración oral en forma de comprimidos o cápsulas, el componente farmacológico activo puede combinarse con un vehículo inerte no tóxico aceptable desde el punto de vista farmacéutico, tal como lactosa, almidón, sacarosa, celulosa, estearato de magnesio, fosfato de dicalcio, sulfato de calcio, talco, manitol, alcohol etílico (forma líquida) y similares. Más aún, cuando se desee o se necesite, pueden incorporarse también a la mezcla aglutinantes, lubricantes, agantes desintegrantes, y agentes colorantes apropiados. los polvos y los comprimidos pueden incluirse desde aproximadamente 5 hasta aproximadamente 95 por ciento de la composición de la invención

Los aglutinantes apropiados incluyen almidón, gelatina, azúcares naturales, edulcorantes a base de maíz, gomas naturales o sintéticas tales como acacia, alginato de sodio, carboximetilcelulosa, polietilenglicol y ceras Entre los

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lubricantes pueden mencionarse para usar en esta forma de dosificación, ácido bórico, benzoato de sodio, acetato de sodio, cloruro de sodio. Los desintegrantes incluyen almidón, metilcelulosa, goma guar y similares.

También pueden incluirse agentes edulcorantes y saborizantes y los conservantes cuando sea apropiado. Algunos de los términos observados anteriormente, es decir, desintegrantes, diluyentes, lubricantes, aglutinantes y similares, se discuten a continuación en mayor detalle

En forma adicional, las composiciones de la presente invención pueden formularse en forma de liberación prolongada para proporcionar la tasa de liberación controlada de cualquiera de los componentes o componentes activos para optimizar los efectos terapéuticos, es decir actividad inhibidora de VHC y similares Las formas de dosificación apropiadas para la liberación prolongada incluyen comprimidos estratificados, que contienen capas de velocidades variables de desintegración o matrices poliméricas de liberación controlada impregnadas con los componentes activos y con fomrma de comprimido o cápsula que contienen dichas matrices poliméricas porosas impregnadas o encapsuladas

Las preparaciones de forma líquida incluyen soluciones, suspensiónes y emulsiones. Como ejemplo pueden mencionarse soluciones en agua o agua-propilenglicol para inyecciones parenterales o el agregado de edulcorantes o opacantes para soluciones, suspensiónes y emulsiones orales Las preparaciones de forma líquida pueden incluir, además, soluciones para administración intranasal.

Las preparaciones en aerosol apropiadas para inhalación pueden incluir soluciones y sólidos en forma de polvo, que pueden encontrarse en combinación con un vehículo aceptable desde el punto de vista farmacéutico tal como gas comprimido inerte, por ej nitrógeno

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

Además se incluyen preparaciones de forma sólida que pretenden convertirse, inmediatamente antes de usar, en preparaciones de forma líquida, ya sea para administración oral o parenteral. Dichas formas líquidas incluyen soluciones, suspensiónes y emulsiones

Los compuestos de la invención pueden administrarse también por vía transdérmica. Las composiciones transdérmicas pueden tomar la forma de cremas, lociones, aerosoles y/o emulsiones y pueden incluirse en un parche transdérmico del tipo de matriz o reservorio como los que son convencionales en el arte para este fin

Los compuestos de la invención pueden administrarse además por vía oral, endovenosa, intranasal, o subcutánea.

Los compuestos de la invención pueden comprender, además, preparaciones que se encuentran en forma de dosificación unitaria. En dicha forma, la preparación se subdivide en dosis unitarias de igual tamaño que contienen las cantidades apropiadas de componentes activos, por ej , una cantidad efectiva para lograr la finalidad deseada

La cantidad de composición activa de la invención en una dosis unitaria de preparación puede variarse o ajustarse en general 1,0 miligramo hasta aproximadamente 1,000 miligramos, con preferencia desde aproximadamente 1,0 hasta aproximadamente 950 miligramos, con mayor preferencia desde aproximadamente 1,0 hasta aproximadamente 500 miligramos, y normalmente desde aproximadamente 1 hasta aproximadamente 250 miligramos, de acuerdo

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con la aplicación particular. La dosificación real empleada variará dependiendo de la edad, el sexo, el peso del paciente y la graveda de la afección tratada Dichas técnicas son conocidas para aquellos expertos en el arte.

En general, la forma de dosificación oral en humanos que contiene los componentes activos puede administrarse 1 o 2 vecer por día. La cantidad y la frecuencia de administración se regulará de acuerdo con el criterio del médico a cargo. Un régimen de dosificación diaria recomendada en general para administración oral puede variar desde aproximadamente 1,0 miligramo hasta aproximadamente 1,000 miligramos por día, en una dosis o en dosis divididas,.

Algunos términos útiles son como se los describe a continuación:

Cápsula - se refiere a un contenedor o recipiente especial realizado con metil celulosa, alcoholes polivinílicos, o gelatinas desnaturalizadas o almidón para contener o que contienen composiciones que comprenden los componentes activos. Las cápsulas de recubrimiento duro normalmente están hechas de mezclas de gelatinas de piel de cerdo y hueso de resistencia de gel relativamente alta. La cápsula misma contiene pequeñas cantidades de colorantes, agentes opacantes, plastificantes y conservantes.

Comprimido - se refiere a una forma de dosificación sólida moldeada o comprimida que contiene los componentes activos con diluyentes apropiados. El comprimido puede prepararse por compresión de mezclas o granulaciones obtenidas por granulación húmeda, granulación seca o por compactación.

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

Polvo para constitución se refiere a mezclas de polvo que contienen los componentes activos y diluyentes apropiados que pueden suspenderse en agua o jugos.

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Diluyente - se refiere a sustancias que normalmente conforman la porción principal de la composición o la forma de dosificación. Los diluyentes apropiados incluyen azúcares tales como lactosa, sacarosa, manitol y sorbitol; almidones derivados del trigo, maíz, arroz y papa; y celulosas tales como celulosa microcristalina. La cantidad de diluyente en la composición puede variar desde aproximadamente 10 hasta aproximadamente 90% en peso de la composición total, con preferencia desde aproximadamente 25 hasta aproximadamente 75%, con mayor preferencia desde aproximadamente 30 hasta aproximadamente 60% en peso, incluso con mayor preferencia desde aproximadamente 12 hasta aproximadamente 60%

Desintegrante - se refiere a materiales agregados a la composición para ayudarla a romperse (desintegrarse) y liberar los medicamentos. Los desintegrantes apropiados incluyen almidones, almidones modificados "solubles en agua fría" tales como carboximetil almidón sódico; gomas naturales y sintéticas tales como de acacia, karaya, guar, tragacanto y agar, derivados de la celulosa tales como metilcelulosa y carboximetilcelulosa sódica; celulosas microcristalina y celulosas microcristalinas entrecruzadas tales como croscarmelosa sódica; alginatos tales como ácido algínico y alginato de sodio, arcillas tales como bentonitas; y mezclas efervescentes. La cantidad de desintegrante en la composición puede variar desde aproximadamente 2 hasta aproximadamente 15% en peso de la composición, con mayor preferencia desde aproximadamente 4 hasta aproximadamente 10% en peso

Aglutinante - se refiere a sustancias que unen o "pegan" los polvos y los hacen cohesivos mediante formación de gránulos, sirviendo de este modo como el "adhesivo" de la formulación. Los aglutinantes agregan fuerza cohesiva ya disponible en el diluyente o agente a granel Los aglutinantes apropiados incluyen azúcares tales como sacarosa; almidones derivados del trigo, del maíz, del arroz

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y de la papa, gomas naturales tales como acacia, gelatina y tragacanto; derivados de semillas ales como ácido algínico, alginato de sodio y alginato cálcico de amonio; materiales a base de celulosa tales como metilcelulosa y carboximetilcelulosa de sodio e hidroxipropilmetilcelulosa; polivinilpirrolidona; e inorgánicos tales como silicato de magnesio y aluminio. La cantidad de aglutinante en la composición puede variar desde aproximadamente 2 hasta aproximadamente 20% en peso de la composición, con mayor preferencia desde aproximadamente 3 hasta aproximadamente 10% en peso, incluso con mayor preferencia desde aproximadamente 3 hasta aproximadamente 6% en peso.

Lubricante - se refiere a una sustancia agregada a la forma de dosificación para permitir que el comprimido, los gránulos, etc luego de comprimirse, se liberen del molde o matriz por 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, polietilenglicoles y d'l-leucina. Los lubricantes usualmente se agregan en el último paso antes de la compresión, ya que deben estar presentes en las superficies de los gránulos y entre ellos y las partes de la prensa para comprimidos La cantidad de lubricante en la composición puede variar desde aproximadamente 0,2 hasta aproximadamente 5% en peso de la composición, con preferencia desde aproximadamente 0,5 hasta aproximadamente 2%, con mayor preferencia desde aproximadamente 0,3 hasta aproximadamente 1,5% en peso.

Deslizante - material que previene la aglomeración y mejora las características de fluidez de las granulaciones, de manera de permitir que la fluidez sea suave y uniforme Los deslizantes apropiados incluyen dióxido de silicio y talco La cantidad de deslizante en la composición puede variar desde

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aproximadamente 0,1% hasta aproximadamente 5% en peso de la composición total, con preferencia desde aproximadamente 0,5 hasta aproximadamente 2% en peso.

Agentes colorantes - excipientes que proporcionan coloración a la composición o a la forma de dosificación. Tales excipientes pueden incluir colorantes de calidad alimenticia y colorantes de calidad alimenticia adsorbidos sobre un adsorbente adecuado, tales como arcilla u óxido de aluminio. La cantidad de agente colorante puede variar desde aproximadamente 0,1 hasta aproximadamente 5% en peso de la composición, con preferencia desde aproximadamente 0,1 hasta aproximadamente 1%.

Biodisponibilidad - se refiere a la velocidad y la medida en el cual el componente farmacológico activo o resto terapéutico se absorbe en la circulación sistémica a partir de una forma de dosificación administrada, comparado con un estándar o control.

Los métodos convencionales para preparar comprimidos son conocidos. Dichos métodos incluyen métodos en seco, tales como compresión directa y compresión de la granulación producida por compactación, o métodos en húmedo u otros procedimientos especiales. Los métodos convencionales para realizar otra forma de administración tal como, por ejemplo, cápsulas, supositorios y similares también son muy conocidos

Otra realización de la invención revela el uso de los compuestos de la invención o composiciones farmacéuticas descritos con anterioridad para el tratamiento de enfermedades tales como, por ejemplo, hepatitis C y similares. El método comprende administrar una cantidad terapéuticamente efectiva del compuesto de la invención o composición farmacéutica a un paciente que tiene dicha enfermedad o dichas enfermedades y que necesita de dicho tratamiento.

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Incluso en otra realización, los compuestos de la invención pueden usarse para el tratamiento de VHC en humanos en modo de monoterapia o como terapia de combinación (por ej., combinación dual, combinación triple etc.) 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), Maxamina™ (Maxim Pharmaceuticals, San Diego, California), micofenolato mofetil (de Hoffman-LaRoche, Nutley, New Jersey), interferón (tales como, por ejemplo, interferón-alpha, PEG-interferón alpha conjugates) y similares. "conjugados PEG-interferón alfa" son moléculas de interferón alfa unidas a una molécula de PEG. Los conjugados de PEG-interferón alfa ilustrativos incluyen interferón alfa-2a (Roferon™, de Hoffman La-Roche, Nutley, New Jersey) en forma de interferón alfa-2a pegilado (por ej., el comercializado con el nombre comercial Pegasys™), interferón alfa-2b (Intron™, from Schering-Plough Corporation) en forma de interferón alfa-2b pegilado (por ej., comercializado con el nombre comercial PEG-Intron™), interferón alfa-2c (Berofor Alfa™, de Boehringer Ingelheim, Ingelheim, Germany) o interferón de consenso definido por determinación de una secuencia de consenso de interferones alfa naturales (Infergen™, de Amgen, Thousand Oaks, California).

Como se indicó con anterioridad, la invención incluye tautómeros, rotámeros, enantiómeros y otros estereoisómeros de los compuestos de la invención también. De este modo, como aprecia una persona con experiencia en

el arte, algunos de los compuestos de la invención pueden existir en formas isoméricas apropiadas. Se considera que dichas variaciones se encuentran dentro del alcance de la invención.

Otra realización de la invención revela un método de producir los compuestos revelados aquí. Los compuestos pueden prepararse por varias técnicas conocidas en el arte. Los procesos ilustrativos se definen en los siguientes esquemas de reacción Las ilustraciones no deben considerarse limitantes del alcance de la invención que se define en las reivindicaciones anexas Las vías mecanísticas alternativas y estructuras análogas resultarán obvias para aquellos expertos en el arte

Se debe entender que aunque los siguientes esquemas ilustrativos describen la preparación de algunos compuestos representativos de la invención, la sustitución apropiada de cualquiera de los aminoácidos tanto naturales como no naturales producirá la formación de los compuestos deseados en base a dicha sustitución Tales variaciones se consideran dentro del alcance de la invención.

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

THF: Tetrahidrofurano

DMF: N,N-Dimetilformamida

EtOAc: Acetato de etilo

AcOH: Ácido acético

HOOBt 3-Hidroxi-1,2,3-benzotriazin-4(3H)-ona

EDCI clorhidrato de 1-(3-dimetiloaminopropil)-3-etilcarbodiimida

NMM N-Metilmorfolina

ADDP: 1,1'-(Azodicarbonil)dipiperidina

DEAD: Dietilazodicarboxilato

MeOH: Metanol

EtOH: Etanol

Et2O: Dietil éter

DMSO: Dimetilsulfóxido

HOBt· N-Hidroxibenzotriazol

PyBrOP: Hexafluorofosfato de bromo-tris-pirrolidinfosfonio

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

DMF-DMA: N,N-Dimetilformamida-dimetilacetal

iBoc: isobutoxicarbonilo

iPr: isopropilo

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

Boc: ter-Butiloxicarbonilo

Cbz: Benciloxicarbonilo

Cp: Ciclopentildienilo

Ts: p-toluensulfonilo

Me· Metilo

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

DMAP: 4-N,N-Dimetilaminopiridina

BOP : Benzotriazol-1-il-oxi-tris(dimetilamino)hexafluorofosfato

PCC: Clorocromato de piridinio

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KHMDS: Hexametildisilazida de potasio o bis(trimetilsililamida) de potasio

NaHMDS: Hexametildisilazida de Sodio o Bis(trimetilsililamida) de sodio

LiHMDS: Hexametildisilazida de Litio o bis(trimetilsililamida) de litio

Pd/C al 10%. Paladio sobre carbón al 10% (en peso).

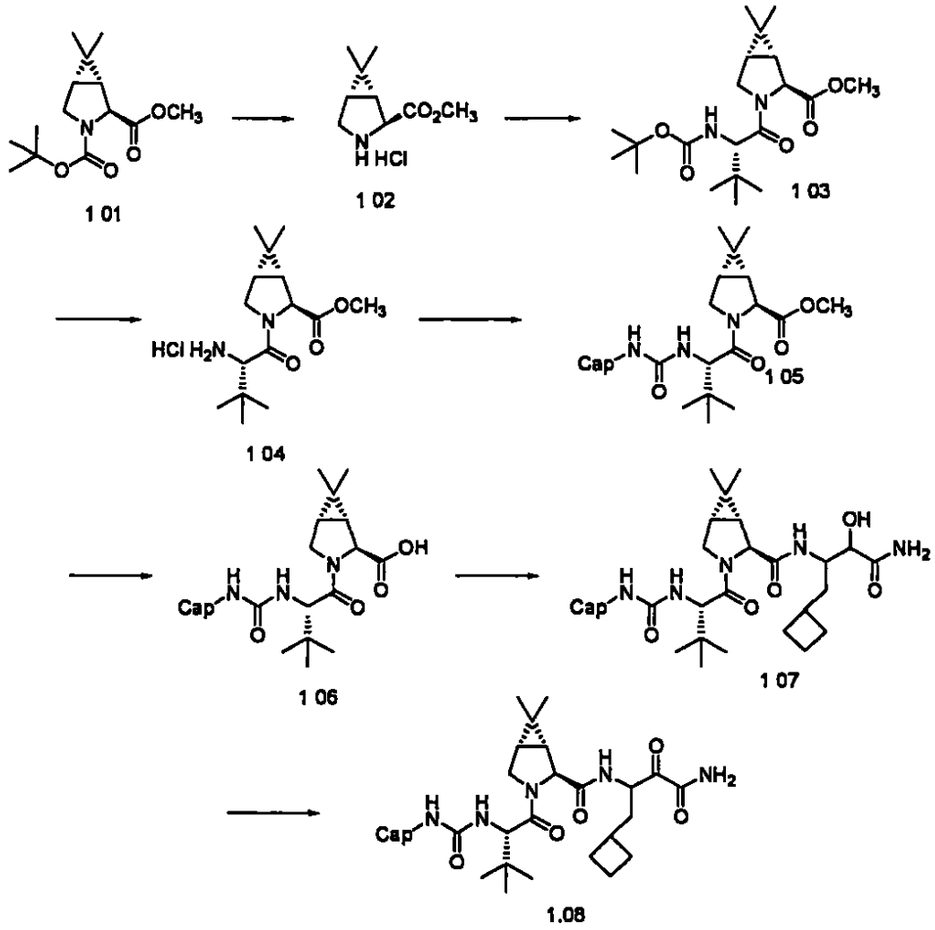
TG. Tioglicerol

Esquemas Generales para Preparación de Compuestos Buscados

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

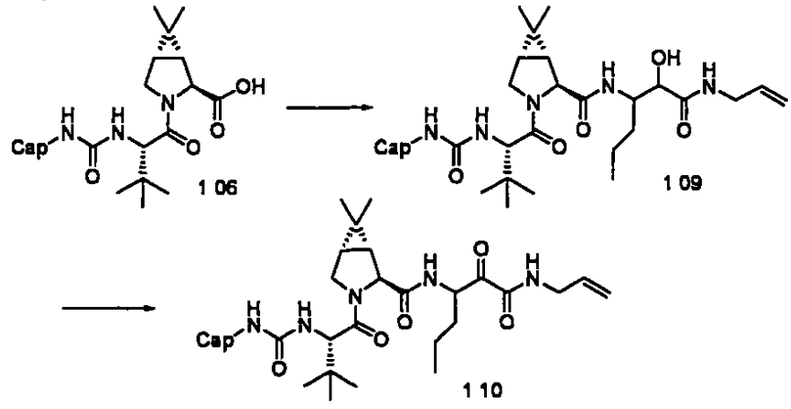
Método A

La desprotección del grupo funcional N-Boc de 1.01 en condiciones ácidas proveyó el clorhidrato 1.02 que posteriormente se acopló con N-Boc-ter-leucina con metodología de acoplamiento de péptidos para obtener 1.03. La desprotección con N-Boc seguido de tratamiento con el isocianato apropiado dio la urea 1.05 La hidrólisis del metil éster proveyó el ácido 1.06. El acoplamiento peptídico del ácido 1.06 con el resto amida primaria apropiado P_1-P' produjo la hidroxil amida 1.07. La oxidación (oxidación de Moffatt o proceso relacionado – *ver*, T. T. Tidwell, *Synthesis*, 1990, 857), o Periodinano de Dess-Martin – *J. Org. Chem.*, (1983) 48, 4155) produjo el compuesto buscado 1.08.



Método B

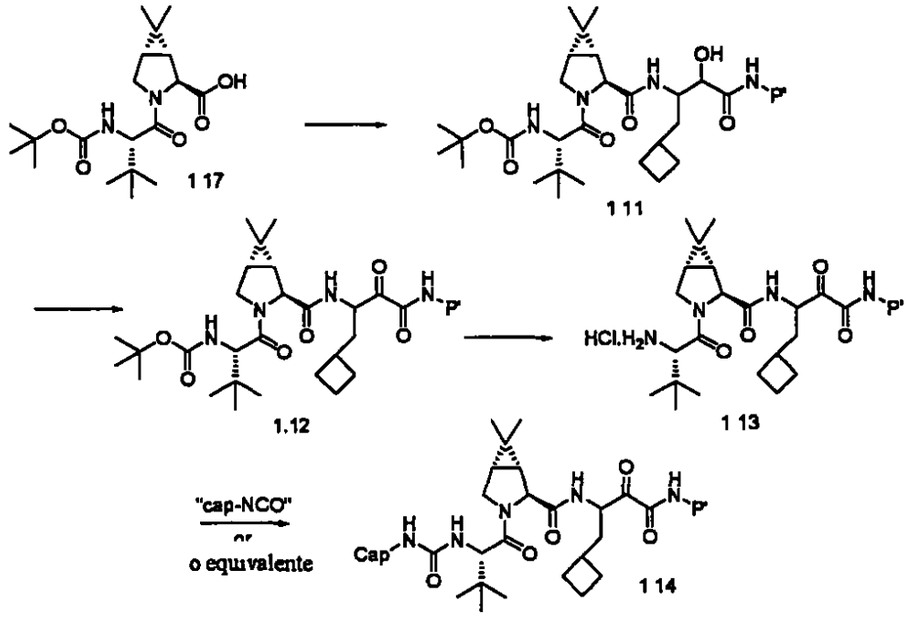
El acoplamiento peptídico del ácido 1.06 con el resto amida secundaria P_1-P' apropiado produjo la hidroxil amida 1.09. La oxidación (Moffatt o Dess-Martin) produjo el compuesto buscado 1.10.



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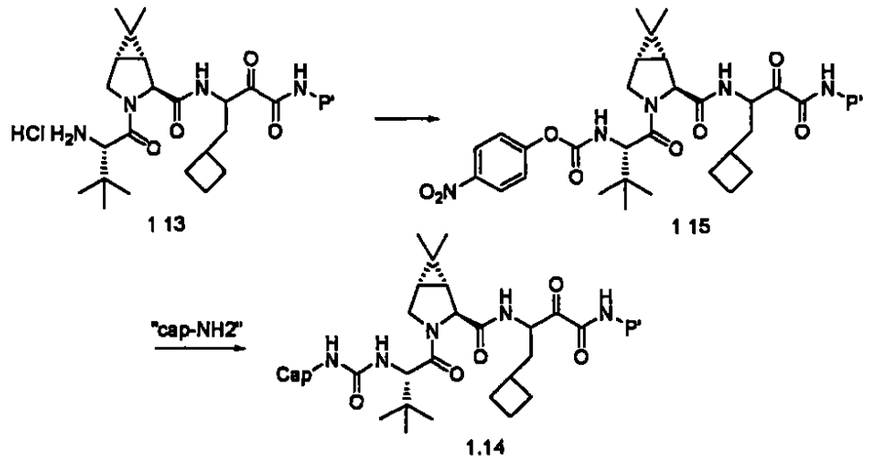
Método C

En otra variación, el acoplamiento peptídico del ácido N-Boc-P2-P_3- 1.17 con el resto amida P_1-P' apropiado produjo la hidroxil amida 1.11. La oxidación (Moffatt o Periodinano de Dess-Martin) produjo la ceto amida 1.12 La desprotección del grupo funcional N-Boc dio el clorhidrato 1 13. El tratamiento con un isocianato apropiado (o equivalente de isocianato) produjo el compuesto buscado 1 14



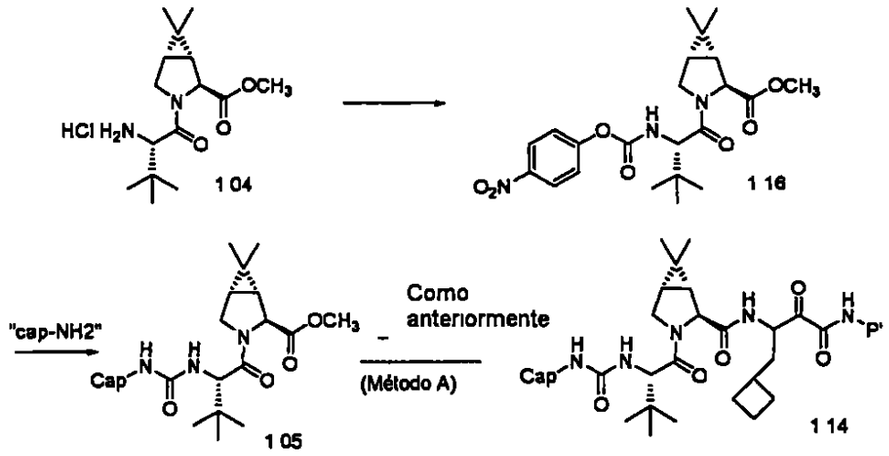
Método D

Incluso en otra variación, el clorhidrato 1.13 se convirtió en el carbamato de 4-nitrofenilo 1.15 por reacción con cloroformiato de 4-nitrofenilo. El tratamiento posterior con una amina (o clorhidrato de amina) de elección proveyó el compuesto buscado 1.14.



Método E

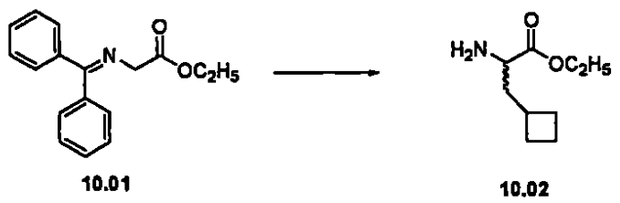
Incluso en otra variación, el clorhidrato del dipéptido 1.03 se convirtió en el carbamato de 4-nitrofenilo como se describió con anterioridad. El tratamiento con una amina (o clorhidrato de amina) de elección proveyó la urea derivada 1.05. La hidrólisis y elaboración adicional como se describió en los Métodos A/B dio los compuestos buscados 1.14.



Preparación de los restos P1-P'

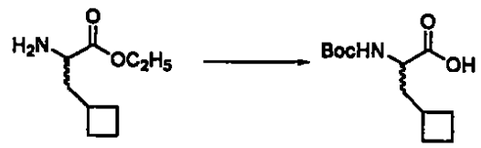
Preparación de los intermediarios **10.11 y 10.12**

Paso 1.



Una solución agitada de la cetimina **10,01** (50 g, 187,1 mmol) bajo N_2 en THF anhidro (400 ml) se enfrió hasta –78°C y se trató con solución 1 M de K-^{t}BuO (220 ml, 1,15 equiv.) en THF. La mezcla de reacción se entibió hasta 0°C y se agitó durante 1 h y se trató con bromometil ciclobutano (28 ml, 249 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 48 h y se concentró *al vacío*. El residuo se disolvió en Et_2O (300 ml) y se trató con HCl acuoso (2 M, 300 ml) La solución resultante se agitó a temperatura ambiente durante 5 h y se extrajo con Et_2O (1 l). La fase acuosa se alcalinizó hasta un pH ~12-14 con NaOH (50% ac.) y se extrajo con CH_2Cl_2 (3x300 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron para dar la amina pura (**10.02**, 18 g) como un aceite incoloro.

Paso 2.

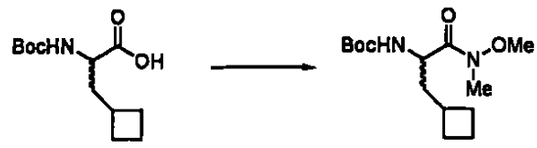


10.02 **10.03**

Una solución de la amina **10.02** (18g, 105,2 mmol) a 0°C en CH_2Cl_2 (350 ml) se trató con di-*ter*-butildicarbonato (23 g, 105,4 mmol) y se agitó a temperatura ambiente durante 12 h. Luego de 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 mmol) y se agitó a temperatura ambiente durante 3 h La mezcla de reacción se concentró y la fase acuosa alcalina se extrajo con Et_2O La fase acuosa se acidificó con HCl conc. hasta un pH~1-2 y se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron *al vacío* para producir **10.03** como aceite viscoso incoloro que se usó para el siguiente paso sin ninguna purificación adicional.

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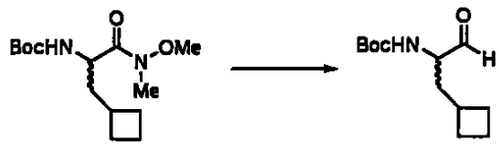
Paso 3.



10 03 10.04

Una solución del ácido **10.03** (15,0 g, 62 mmol) en CH_2Cl_2 (250 ml) se trató con reactivo BOP (41,1 g, 93 mmol), N-metil morfolina (27 ml), clorhidrato de N,O-dimetil hidroxilamina (9,07 g, 93 mmol) y se agitó hasta la mañana siguiente a temperatura ambiente. La mezcla de reacción se diluyó con HCl acuoso 1 N (250 ml), y se separaron las fases y la fase acuosa se extrajo con CH_2Cl_2 (3x300 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron *al vacío* y se purificaron por cromatografía (SiO_2, EtOAc/Hex 2:3) para producir la amida **10.04** (15,0 g) como un sólido incoloro

Paso 4.



10.04 10.05

Una solución de la amida **10.04** (15 g, 52,1 mmol) en THF anhidro (200 ml) se trató gota a gota con una solución de $LiAlH_4$ (1M, 93 ml, 93 mmol) a 0°C. La mezcla de reacción se agitó a temperatura ambiente durante 1 h y se desactivó cuidadosamente a 0°C con una solución de $KHSO_4$ (10% ac.) y se agitó durante 0,5 h. La mezcla de reacción se diluyó con HCl acuoso (1 M, 150 ml) y se extrajo con CH_2Cl_2 (3x200 ml), Las fases orgánicas combinadas se lavaron con HCl acuoso (1 M), $NaHCO_3$ saturado, salmuera, y se secaron ($MgSO_4$). Se filtró la mezcla y se concentró *al vacío* para producir **10.05** como un aceite viscoso incoloro (14 g).

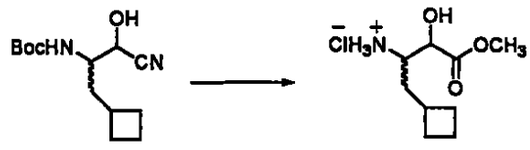
Paso 5:



10.05 10.06

Una solución del aldehído **10.05** (14 g, 61,6 mmol) en CH_2Cl_2 (50 ml), se trató con Et_3N (10,73 ml, 74,4 mmol), y cianhidrdina de la acetona (10,86 g, 127,57 mmol) y se agitó a temperatura ambiente durante 24 hrs. La mezcla de reacción se concentró *al vacío* y se diluyó con HCl acuoso (1 M, 200 ml) y se extrajo en CH_2Cl_2 (3x200 ml). Se lavó la fase orgánica combinada 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 producir **10.06** (10,3 g) como un líquido incoloro

Paso 6



10.06 10.07

Se trató metanol saturado con HCl*, preparado burbujeando HCl gaseoso a través de CH_3OH (700 ml) a 0°C, con la cianhidrina **10.06** y se calentó a reflujo durante 24 h. La reacción se concentró *al vacío* para producir **10.07**, que se usó en el paso siguiente sin purificación

* Alternativamente también puede usarse HCl 6M preparado mediante el agregado de AcCl a metanol anhidro

Paso 7.

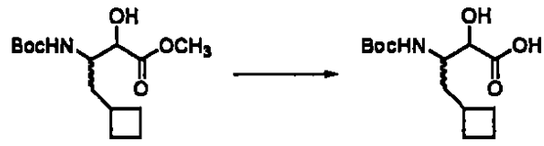


10.07 10.08

858

Una solución del clorhidrato de amina **10.07** en CH_2Cl_2 (200 ml) se trató con Et_3N (45,0 ml, 315 mmol) y Boc_2O (45,7g, 209 mmol) a –78°C. La mezcla de reacción se agitó luego a temperatura ambiente hasta la mañana siguiente y se diluyó con HCl (2 M, 200 ml) y se extrajo en CH_2Cl_2 Las fases orgánicas combinadas se secaron ($MgSO_4$) se filtró, se concentraron *al vacío* y se purificaron por cromatografía (EtOAc/Hex 1:4) para producir el hidroxi éster **10.08**.

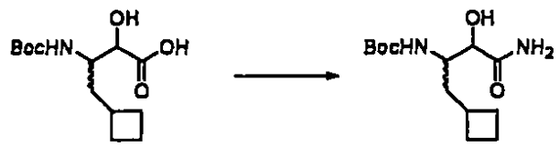
Paso 8.



10.08 **10.09**

Una solución del metil éster **10.08** (3g, 10,5 mmol) en THF/H_2O (1:1) se trató con LiOH•H_2O (645 mg, 15,75 mmol) y se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se acidificó con HCl ac (1 M, 15 ml) y se concentró *al vacío*. El residuo se secó al vacío para obtener **10.09** con rendimiento cuantitativo.

Paso 9



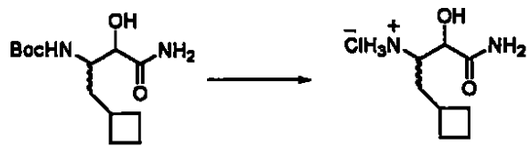
10.09 **10.10**

Una solución del ácido **10.09** (del paso anterior) en CH_2Cl_2 (50 ml) y DMF (25 ml) se trató con NH_4Cl (2,94 g, 55,5 mmol), EDCI (3,15 g, 16,5 mmol), HOOBt (2,69 g, 16,5 mmol), y NMM (4,4 g, 44 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 d Se eliminaron los solventes al *vacío* y el residuo se diluyó con HCl acuoso (250 ml) y se extrajo con CH_2Cl_2 Las fases orgánicas combinadas se lavaron con $NaHCO_3$ acuoso saturado, se secaron ($MgSO_4$) se filtraron y se concentraron al vacío para obtener **10.10**, que se usó tal cual en los pasos siguientes. (Alternativamente **10.10** también puede obtenerse

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directamente mediante la reacción de **10.06** (4,5 g, 17,7 mmol) con H_2O_2 ac. (10 ml), $LiOH•H_2O$ (820 mg, 20,8 mmol) a 0°C en 50 ml de CH_3OH durante 0,5 h)

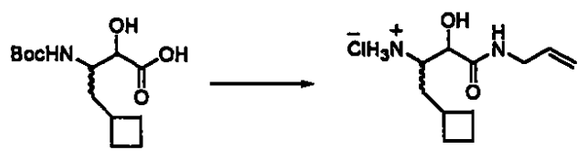
Paso 10.



10.10 **10.11**

Una solución de **10.10** obtenida en el paso anterior se disolvió en HCl 4 N en dioxano y se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró al vacío para dar el intermediario **10.11** como un sólido, que se usó sin purificación adicional.

Paso 11.

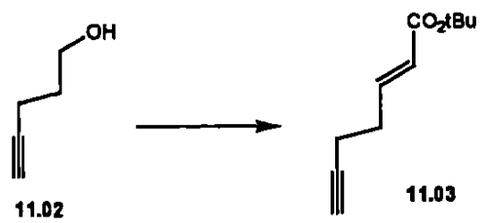


10.09 **10.12**

El intermediario requerido **10.12** se obtuvo a partir del compuesto **10.09** usando en esencia los procedimientos descritos con anterioridad en los Pasos 9, 10 con los reactivos apropiados.

Preparación del Intermediario **11.01**

Paso 1



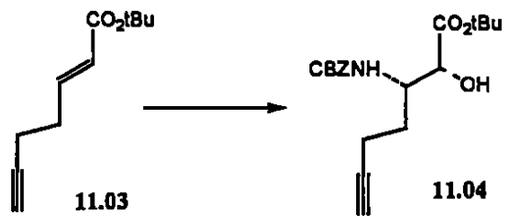
11.02 **11.03**

A una solución de 4-pentin-1-ol, **11.02** (4,15 g; Aldrich), se agregó Periodinano de Dess-Martin (30,25 g, Aldrich) y la mezcla resultante se agitó durante 45 min antes del agregado de (ter-Butoxicarbonilometilen)trifenilfosforano (26,75 g, Aldrich). La reacción oscura resultante se agitó hasta la mañana

860

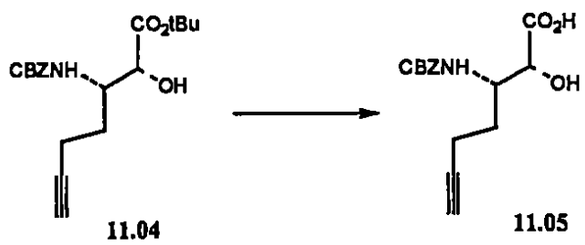
siguiente, se diluyó con EtOAc), se lavó con sulfito de sodio ac., NaHCO3 ac. sat., agua, salmuera y se secó Los volátiles se eliminaron a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice usando EtOAc al 1% en hexanos como eluyente para dar el compuesto deseado, **11.03** (3,92g). Se obtuvieron, además, algunas fracciones impuras pero se dejaron de lado en este momento.

Paso 2



El uso del alqueno **11.03** (1,9 g) en n-propanol (20 ml; Aldrich)), carbamato de bencilo (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 (0,423 g; Aldrich)) en n-propanol (37,5 ml), y osmiato de potasio.dihidrato (0,1544g, Aldrich) y el procedimiento establecido en *Angew. Chem. Int. Ed. Engl* (1998), 35, (23/24), pp. 2813-7, dio un producto en bruto que se purificó por cromatografía en columna de gel de sílice usando EtOAc.Hexanos (1:5) para dar el amino alcohol deseado **11.04** (1,37g, 37%) como un sólido blanco.

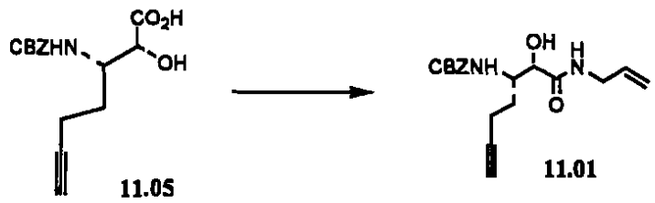
Paso 3



Al éster **11.04** (0,700 g) se agregó HCl 4M en dioxano (20 ml, Aldrich) y la mezcla resultante se dejó reposar a temperatura ambiente hasta la mañana siguiente. Los volátiles se eliminaron a presión reducida para dar el ácido **11.05** (0,621g) como un sólido blanco.

861

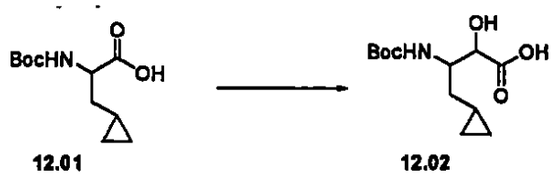
Paso 4



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

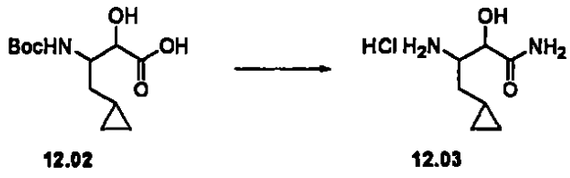
Preparación de los intermediarios **12.03** y **12.04**

Paso 1



El Compuesto **12.01** se convirtió en el material requerido **12.02** usando en esencia los procedimientos descritos para el intermediario **10.11**, Pasos 3-8.

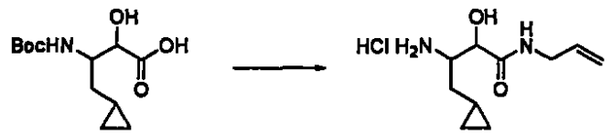
Paso 2



El Compuesto **12.02** se convirtió en el intermediario requerido **12.03** usando en esencia los procedimientos descritos para el intermediario **10.11**, Pasos 9, 10

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Paso 3



12.02 12.04

El Compuesto **12.02** se convirtió en el intermediario requerido **12.03** usando en esencia los procedimientos descritos para el intermediario **10.12**, Paso 11

Preparación del Intermediario **13.01**

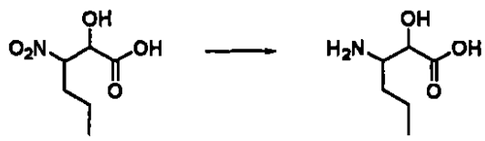
Paso 1



13.02 13.03

A una solución agitada de 1-nitrobutano, **13.02** (16,5 g, 0,16 mol), y ácido glicoxílico en H_2O (28,1 g, 0,305 mol) y MeOH (122 ml) a 0°C-5°C, se agregó gota a gota trietilamina (93 ml, 0,667 mol) durante 2 hrs. La solución se entibió hasta la temperatura ambiente, se agitó hasta la mañana siguiente y se concentró hasta sequedad para dar un aceite. Luego se disolvió el aceite en H_2O y se acidificó hasta pH =1 con HCl 10%, 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 dar el producto **13.03** (28,1 g, 99% de rendimiento)

Paso 2



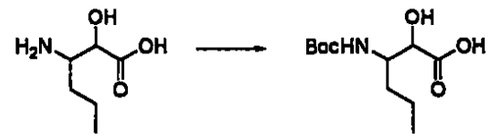
13.03 13.04

A una solución agitada del compuesto **13.03** (240 g, 1,35 mol) en ácido acético (1,25 l) se agregó Pd/C al 10% (37 g). La solución resultante se hidrogenó

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a 4,07 x 10^5 Pa (59 psi) durante 3 hrs y luego a 4,14 x 10^5 Pa (60 psi) hasta la mañana siguiente. Se evaporó luego el ácido acético y se destiló azeotrópicamente 3 veces con tolueno, luego se trituró con MeOH y éter. La solución luego se filtró y se destiló azeotrópicamente dos veces con tolueno para obtener **13.04** como un sólido blancuzco (131 g, 0,891 mol, 66%).

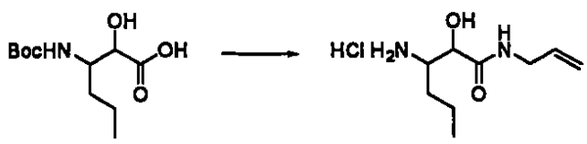
Paso 3



13.04 **13.05**

A una solución agitada del aminoácido **13.04** (2,0 g, 13,6 mmol) en dioxano (10 ml) y H_2O (5 ml) a 0°C, se agregó solución 1N de NaOH (4,3 ml, 14,0 mmol). La solución resultante se agitó durante 10 minutos, seguido del agregado de di-*t*-butildicarbonato (0,110 g, 14,0 mmol) y se agitó a 0°C durante 15 minutos. La solución se entibió luego hasta la temperatura ambiente, se agitó durante 45 minutos y se mantuvo en la heladera hasta la mañana siguiente y se concentró hasta sequedad para dar un material en bruto. A la solución de este material en bruto en EtOAc (100 ml) y hielo, se agregó $KHSO_4$ (3,36 g) y H_2O (32 ml) y se agitó durante 4-6 minutos. Luego se separó la fase orgánica y la fase acuosa se extrajo dos veces con EtOAc y la fase orgánica combinada se lavó con agua, salmuera, se secó sobre Na_2SO_4, se filtró y se concentró hasta sequedad para dar el producto **13.05** como una goma clara (3,0 g, 89% de rendimiento).

Paso 4

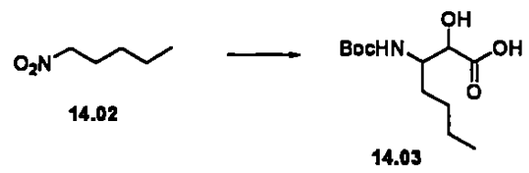


13.05 **13.01**

El Compuesto **13.05** se convirtió en el intermediario requerido **13.01** usando en esencia los procedimientos descritos para el intermediario **10.12**, Paso 11.

Preparación del Intermediario **14.01**

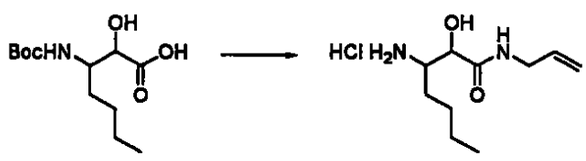
Paso 1



14.02 **14.03**

El Compuesto **14.02** se convirtió en el material requerido **14.03** usando en esencia los procedimientos descritos para el intermediario **13.01**, Pasos 1-3.

Paso 2



14.03 **14.01**

El Compuesto **14.03** se convirtió en el intermediario requerido **14.01** usando en esencia los procedimientos descritos para el intermediario **10.12**, Paso 11.

Preparación del Intermediario **15.01**

Paso 1



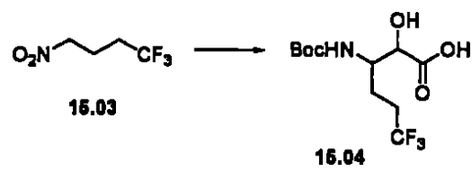
15.02 **15.03**

A una suspensión de nitrito de plata (9 g, 58,5 mmol) en dietil éter (25 ml) a 0°C se agregó una solución de 4-iodo-1,1,1-trifluorobutano, **15.02** (10 g, 42,0 mmol) en dietil éter (25 ml) lentamente a través de un embudo de incorporación (aprox. 15 min). La mezcla resultante se agitó vigorosamente a 0°C y se entibió hasta la temperatura ambiente. Luego de 50 h, se eliminó el material sólido por filtración a través de un taco de celite La solución de éter dietílico resultante se

865

concentró *al vacío* para dar **15.03** como aceite incoloro, que se usó sin purificación adicional

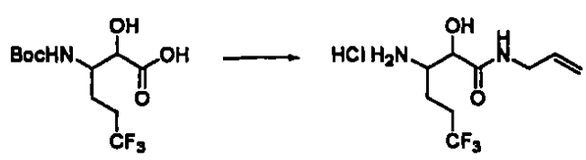
Paso 2



15.03 **15.04**

El Compuesto **15.03** se convirtió en el material requerido **15.04** usando en esencia los procedimientos descritos para el intermediario **13.01**, Pasos 1-3.

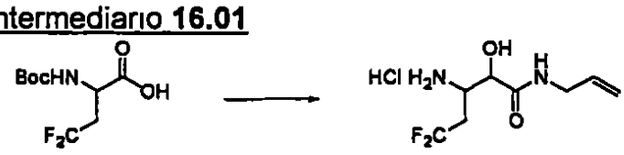
Paso 3



15.04 **15.01**

El Compuesto **15.04** se convirtió en el intermediario requerido **15.01** usando en esencia los procedimientos descritos para el intermediario **10.12**, Paso 11

Preparación del Intermediario **16.01**

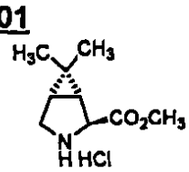


16.02 **16.01**

El ácido **16.02** (Winkler, D.; Burger, K., *Synthesis*, **1996**, 1419) se procesa como se describió con anterioridad (preparación del Intermediario **10.12**) para dar el intermediario esperado **16.01**

PREPARACIÓN DE LOS RESTOS P2 / P3-P2

Preparación del Intermediario **20.01**



20.01

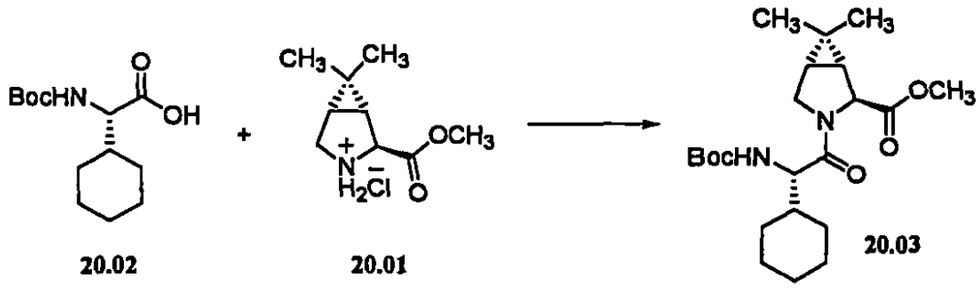
866

El amino éster **20.01** se preparó siguiendo el método de R. Zhang y J S. Madalengoitia (*J. Org. Chem.* **1999**, *64*, 330), con la excepción de que el grupo Boc se escindió mediante la reacción de los aminoácidos Boc-protegidos con HCl metanólico.

(Nota En una variante de la síntesis informada, el iluro de sulfonio se reemplazó con el correspondiente iluro de fosfonio).

Preparación del Intermediario **20.04**

Paso 1

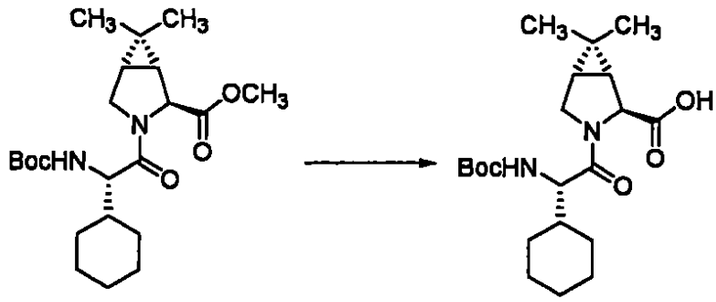


20.02 **20.01** **20.03**

Una solución del aminoácido comercial Boc-Chg-OH, **20.02** (Senn chemicals, 6,64 g, 24,1 mmol), y el clorhidrato de amina **20.01** (4,5 g, 22 mmol) en CH_2Cl_2 (100 ml) a 0°C se trató con reactivo BOP y se agitó a temperatura ambiente durante 15 h La mezcla de reacción se concentró *al vacío*, luego se diluyó con HCl ac. 1 M y se extrajo en EtOAc (3x200 ml). Las fases 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) como un sólido incoloro.

Paso 2

867

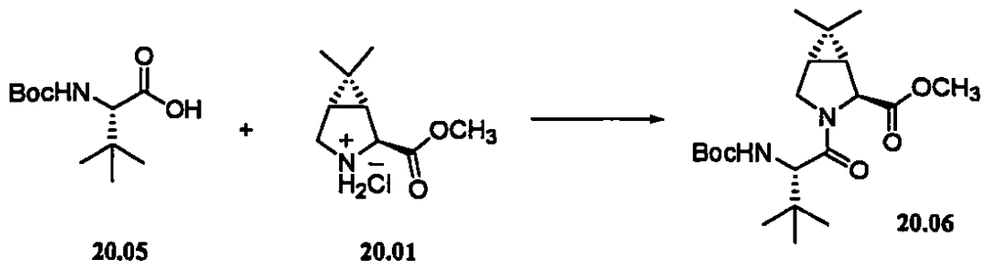


20.03 **20.04**

Una solución del metil éster **20.03** (4,0 g, 9,79 mmol) en THF/H_2O (1.1) se trató con LiOH•H_2O (401 mg, 9,79 mmol) y se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se acidificó con HCl acuoso y se concentró al vacío para obtener el intermediario requerido, el ácido libre **20.04**.

Preparación del Intermediario **20.07**

Paso 1

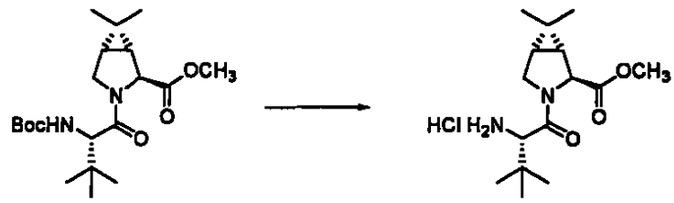


20.05 **20.01** **20.06**

Una solución de Boc-ter-Leu **20.05** (Fluka, 5,0 g 21,6 mmol) en CH_2Cl_2 anhidro/DMF (50 ml, 1:1) se enfrió hasta 0°C y se trató con la sal de amina **20.01** (5,3 g, 25,7 mmol). NMM (6,5 g, 64,8 mmol) y reactivo BOP (11,6 g, 25,7 mmol). La reacción se agitó a temperatura ambiente durante 24 h, se diluyó con HCl acuoso (1 M) y se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se lavaron con HCl (ac, 1 M), $NaHCO_3$ saturado, salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron *al vacío* y se purificaron por cromatografía (SiO2, Acetona/Hexano 1 5) para dar **20.06** como un sólido incoloro.

Paso 2

868

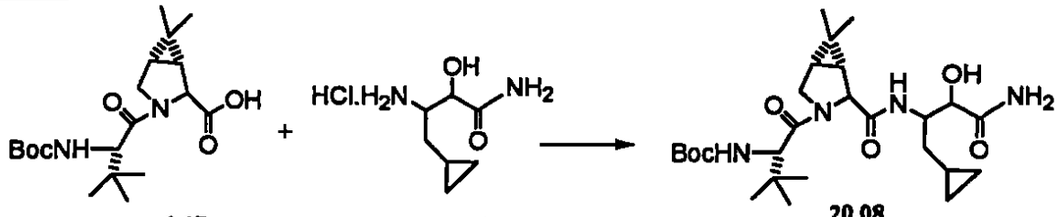


20.06 20.07

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

Preparación del Intermediario **20.10**

Paso 1

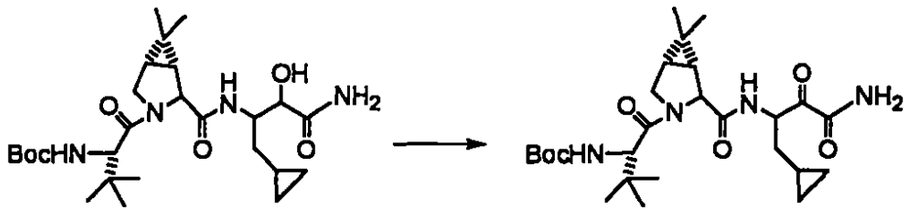


1.17 12.03 20.08

A una solución a -20°C de **1.17** (10,4 g, 28 mmol) en DCM (300 ml) se agregó HATU (1,05 equiv, 29,4 mmol, 11,2g), sal de amina, Intermediario **12.03** (1,0 equiv, 28 mmol, 5,48 g). Luego de 10 min a -20°C, se agregó DIPEA (3,6 equiv, 100 mmol, 17,4 ml). La reacción se agitó a esta temperatura durante 16 hr. Luego de 16 hr, la reacción se diluyó con EtOAc y se lavó sucesivamente con $NaHCO_3$, ácido cítrico (10% p/p) y salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* para producir 14 g del intermediario requerido **20.08**

Paso 2

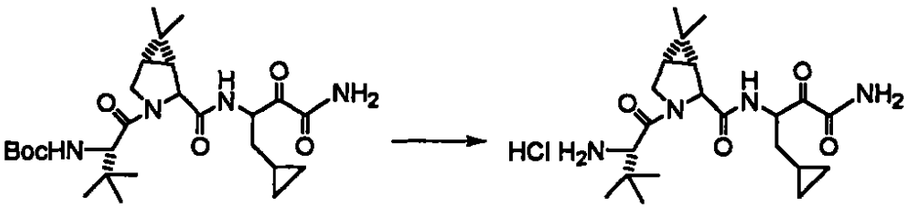
869



20.08 20.09

La hidroxiamida **20.08** se oxidó a la cetoamida requerida **20.09** del modo descrito para el Ejemplo **198 (Paso 8)** CL-EM = 507 $(M+H)^+$.

Paso 3

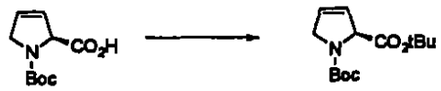


20.09 20.10

La desprotección del grupo funcional t-Boc de **20.09** para dar el material requerido **20.10** se llevó a cabo como se describió para la transformación de **20.06** a **20.07**.

Preparación del Intermediario **21.01:**

Paso 1.



21.02 21.03

A una solución agitada de *N*-Boc-3,4-dehidroprolina **21.02** (5,0 g, 23,5 mmol), di-*ter*-butil dicarbonato (7,5 g, 34,4 mmol), y 4-*N,N*-dimetilaminopiridina (0,40 g, 3,33 mmol) en acetonitrilo (100 ml) a temperatura ambiente se agregó trietilamina (5,0 ml, 35,6 mmol). La solución resultante se agitó a esta temperatura durante 18 h antes de concentrarse *al vacío* El residuo marrón oscuro se purificó por cromatografía flash eluyendo con 10-25% EtOAc/Hexano para dar el producto **21.03** como un aceite amarillo pálido (5,29 g, 84%).

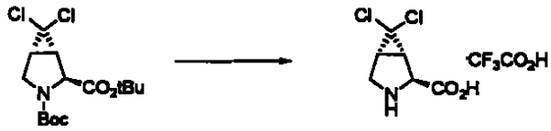
Paso 2:



21.03 21.04

A una solución agitada del derivado de dehidroprolina **21.03** (10,1 g, 37,4 mmol), cloruro de benciltrietilamonio (1,60 g, 7,02 mmol) en cloroformo (120 ml) a temperatura ambiente, se agregó hidróxido de sodio acuoso al 50% (120 g). Luego de agitar vigorosamente a esta temperatura durante 24 h, la mezcla oscura se diluyó con CH_2Cl_2 (200 ml) y dietil éter (600 ml). Luego de separadas las fases, la solución acuosa se extrajo con CH_2Cl_2/Et_2O (1:2, 3x600 ml). La solución orgánica se secó ($MgSO_4$) y se concentró. El residuo se purificó por cromatografía flash usando EtOAc/Hexano 5-20% para obtener 9,34 g (71%) de **21.04** como un sólido blancuzco

Paso 3:



21.04 21.05

La solución de **21.04** (9,34 g, 26,5 mmol) en CH_2Cl_2 (25 ml) y CF_3CO_2H (50 ml) se agitó a temperatura ambiente durante 4,5 h antes de concentrarse *al vacío* para dar un residuo marrón, **21.05,** que se usó en el Paso 4 sin purificación adicional.

Paso 4



21 05 21.01

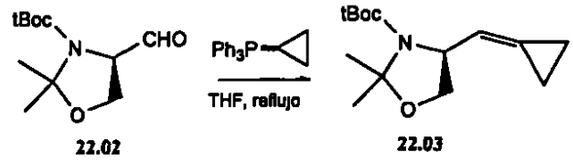
Se agregó ácido clorhídrico concentrado (4,5 ml) a una solución del residuo **21.05** del Paso 3 en metanol (70 ml) y la mezcla resultante se entibió hasta 65°C

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en un baño de aceite. Luego de 18 h, la mezcla se concentró *al vacío* para dar un aceite marrón **21.01**, que se usó sin purificación adicional.

Preparación del Intermediario **22.01**

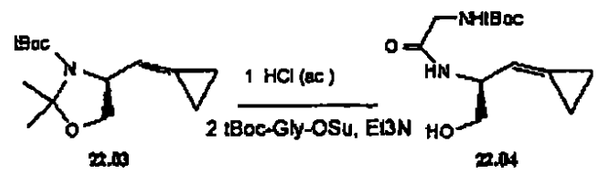
Paso 1



22.02 **22.03**

Se agregó bis(trimetilsilil)amida de potasio (158 ml de una solución 0,5M en tolueno; 79mmol) a una suspensión agitada de bromuro de ciclopropiltrifenilfosfonio (33,12 g; 86,4 mmol) en tetrahidrofurano anhidro (130 ml) y la mezcla naranja resultante se agitó bajo una atmósfera de nitrógeno a temperatura ambiente durante un período de 1h., antes del agregado del aldehído **22.02** (9,68 g; 42,2 mmol) en THF (8ml). Luego se reflujó la reacción bajo una atmósfera de nitrógeno durante un período de 2h. Luego de enfriar, se agregaron metanol, dietil éter y sal de Rochelle. Se separó la fase orgánica, se lavó con salmuera, se secó y se concentró a presión reducida. El producto de la reacción en bruto se purificó por cromatografía en columna de gel de sílice usando EtOAc-Hexano (1:99) to EtOAc-Hexano (5:95) para dar el alqueno **22.03** (8,47g) como un aceite amarillo.

Paso 2



22.03 **22.04**

Una solución de HCl 1M en MeOH/MeOAc se preparó agregando 14,2 ml de cloruro de acetilo gota a gota en metanol frío y diluyendo la solución resultante hasta 200 ml a temperatura ambiente.

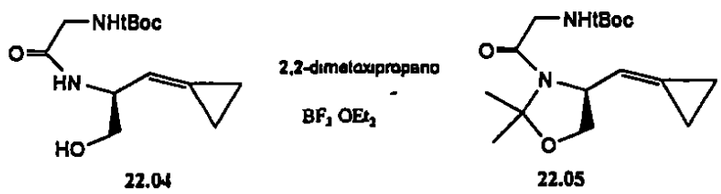
El carbamato **22.03** (9,49 g; 37,5 mmol) se disolvió en metanol (12 ml) y se agregó a HCl 1M en MeOH/MeOAc (150 ml) mientras se enfriaba en un baño de

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El carbamato **22.03** (9,49 g, 37,5 mmol) se disolvió en metanol (12 ml) y se agregó a HCl 1M en MeOH/MeOAc (150 ml) mientras se enfriaba en un baño de hielo. La mezcla resultante se mantuvo a esta temperatura durante 1h., luego se retiró el baño de hielo y se continuó la agitación hasta la mañana siguiente a temperatura ambiente. Los volátiles se eliminaron a presión reducida para producir un aceite amarillo que se usó en el paso siguiente sin purificación.

El aceite amarillo se disolvió en una mezcla de THF (30 ml) y MeOH (20 ml) y se trató con trietilamina (15 ml; 108 mmol) hasta que la solución tuvo un pH=9-10. Luego de colocar en un baño de hielo, la mezcla se trató con N-Boc-Gly-OSu (11,22g; 41mmol). Se retiró el baño de hielo y la reacción se agitó a temperatura ambiente durante 1h. Los volátiles se eliminaron a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice usando metanol (1-3%) en diclorometano, dando la amida deseada **22.04** (9,09 g)

Paso 3

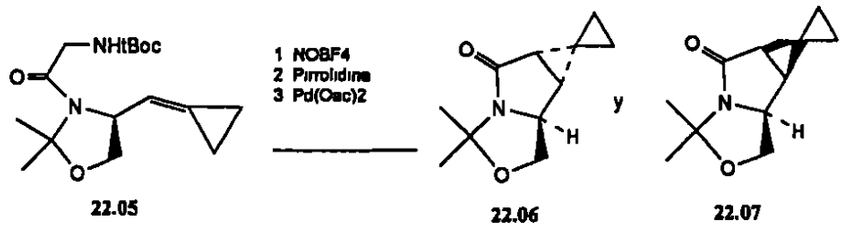


22.04 22.05

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

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Paso 4

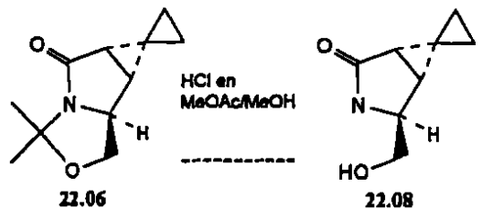


22.05 22.06 22.07

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

El aceite amarillo se disolvió en benceno anhidro (220 ml) y se agregó acetato de paladio (0,317 g, 1,41 mmol) antes de calentar la mezcla resultante a reflujo, bajo una atmósfera de nitrógeno durante un período de 1,5 h. Luego de enfriar, los volátiles se eliminaron a presión reducida y el residuo oscuro se purificó por cromatografía en columna de gel de sílice usando EtOAc-Hexano (1:4) para dar i) la trans-pirrolidinona **22.06** (1,94g) seguida de ii) la cis-pirrolidinona **22.07** (1,97g).

Paso 5



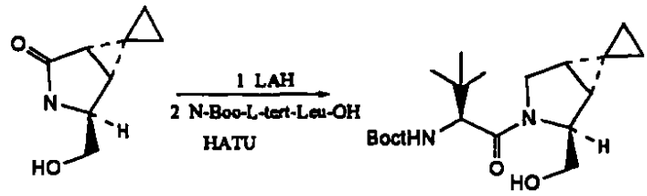
22.06 22.08

Se agregó HCl 1M recién preparado en MeOAc/MeOH (10 ml, como se describió con anterioridad) al N,O-acetal **22.06 y se agitó** a temperatura ambiente

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durante 1h. El solvente se eliminó a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice usando MeOH 0-4% en diclorometano como eluyente para dar el alcohol deseado **22.08** (1,42g), un aceite amarillo

Paso 6

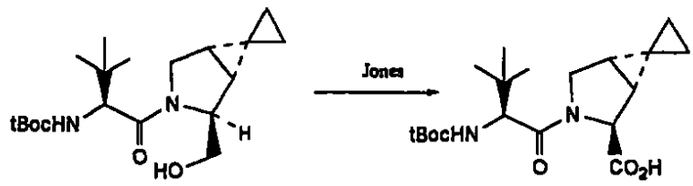


22.08 **22.09**

A una solución de la lactama **22.08** (1,29 g, 8,44 mmol) en tetrahidrofurano anhidro (55 ml) se agregó hidruro doble de litio y aluminio (2,40g; 63,2 mmol) y la mezcla resultante se refluió durante 8h. Luego de enfriar, se agregó agua seguida de NaOH ac. al 15% y la mezcla resultante se filtró a través de celite y el sólido se lavó minuciosamente con THF y MeOH El solvente se eliminó a presión reducida y el residuo se re-disolvió en diclorometano, se secó y se concentró a presión reducida para proveer la pirrolidina, usada sin purificación.

Se agregó base de Hunigs (4,5 ml, 25,8 mmol) a una mezcla de N-Boc-L-ter-Leu-OH (1,76g; 7,6 mmol), la pirrolidina en bruto y HATU (2,89 g; 7,6 mmol) en diclorometano anhidro (50 ml) a –60°C, bajo una atmósfera de nitrógeno. La reacción resultante se dejó llegar hasta la temperatura ambiente lentamente, hasta la mañana siguiente. Se agregó EtOAc y la solución amarilla se lavó con HCl acuoso, bicarbonato de sodio ac sat., agua, salmuera La fase orgánica se secó y se concentró a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice usando EtOAc·Hexanos (1·3) para dar la amida deseada **22.09** (2,00 g).

Paso 7

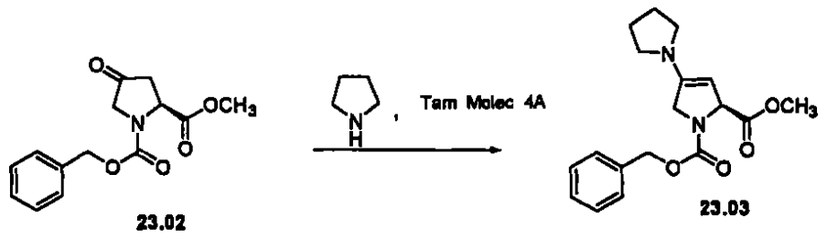


22.09 22.01

El alcohol **22.09** (2,00 g; 5,67 mmol) se disolvió en acetona (116 ml) y se enfrió en un baño de hielo durante 10 min. Esta solución se agregó luego a un ractivo de Jones enfriado (14,2 ml; aprox. 2 mmol/ml) y la mezcla resultante se agitó a 5°C durante 0,5h y se retiró el baño refrigerante La reacción se agitó durante un adicional de 2 h. a temp. ambiente, antes de agregar a sulfato de sodio (28,54g), celite (15 g) en EtOAc (100 ml) Se agregó isopropanol (15 ml) luego de 1 min y luego se agitó durante un adicional de 10 min. y se filtró. El filtrado se concentró a presión reducida, proveyendo un aceite marrón que se disolvió en EtOAc. Esta solución se lavó con agua, ácido cítrico ac al 3%, salmuera, se secó y se concentró para proveer el ácido carboxílico deseado **22.01** (1,64 g) como un sólido blanco.

Preparación del Intermediario **23.01**

Paso 1:

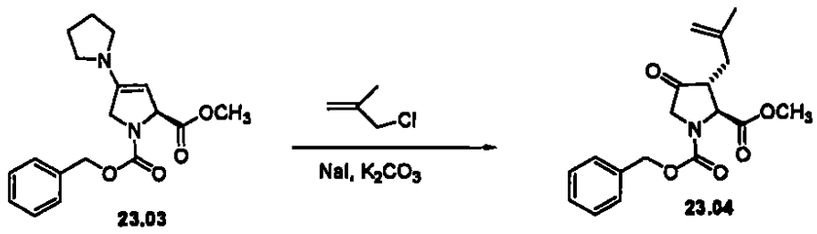


23.02 23.03

A la mezcla del éster **23.02** (6,0 g) y tamices moleculares (5,2 g) en cloruro de metileno anhidro (35 ml) se agregó pirrolidina (5,7 ml, 66,36 mmol). La suspensión marrón resultante se agitó a temperatura ambiente bajo N_2 durante 24 h, se filtró y se lavó con CH_3CN anhidro. El filtrado concentrado se concentró para producir el producto deseado, **23.03**.

Paso 2:

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23.03 23.04

A una solución del producto **23.03** del paso anterior en CH_3CN (35 ml) se agregó K_2CO_3 anhidro, cloruro de metalilo (2,77g, 30,5 mmol), NaI (1.07g, 6,7 mmol). La suspensión resultante se agitó a temperatura ambiente bajo N_2 durante 24 h Se agregaron 50 ml de agua enfriada con hielo seguida de solución de $KHSO_4$ 2N hasta que el pH fue 1. Se agregó EtOAc (100 ml) y la mezcla se agitó durante 0,75h. Se recolectó la fase orgánica combinada y se lavó con salmuera, se secó sobre $MgSO_4$, y se evaporó para obtener el producto deseado, **23.04**.

Paso 3



23.04 23.05

El producto **23.04** del paso anterior (2,7 g, 8,16 mmol) se disolvió en dioxano (20 ml) y se trató con LiOH 1N recién preparado (9 ml). La mezcla de reacción se agitó a temperatura ambiente bajo N_2 durante 20 h. La mezcla de reacción se absorbió en EtOAc y se lavó con H_2O. La fase orgánica combinada se enfrió hasta 0^0C y se acidificó hasta un pH 1,65 usando HCl 1N. La mezcla turbia se extrajo con EtOAc (2 x 100 ml). La fase orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$, y se concentró para dar el ácido deseado, **23.05** (3,40 g).

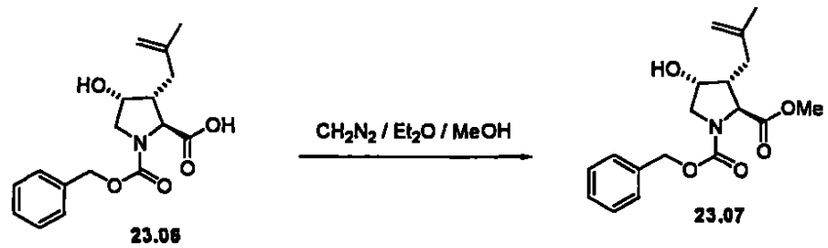
Paso 4:

877



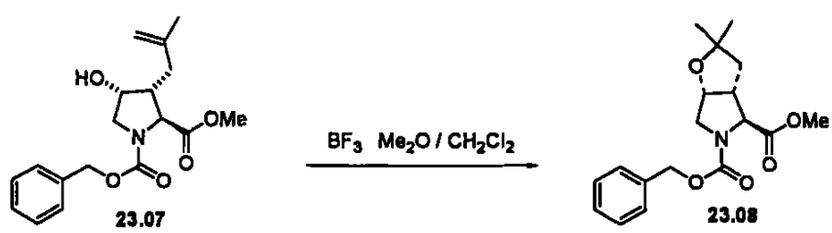
A una suspensión de $NaBH(OAc)_3$ (3,93g, 18,5 mmol) en CH_2Cl_2 (55 ml) se agregó una solución de producto **23.05** del paso anterior en CH_2Cl_2 anhidro (20 ml) y ácido acético (2 ml). La suspensión se agitó a temperatura ambiente durante 20 h Se agregó agua enfriada con hielo (100 ml) a la suspensión y se agitó durante 1/2 hr La fase orgánica se separó, se filtró y se secó y se evaporó para dar el producto deseado, **23.06**.

Paso 5:



Una solución del producto **23.06** del paso anterior (1,9 g) en MeOH (40 ml) se trató con exceso de solución de CH_2N_2/Et_2O y se agitó hasta hasta la mañana siguiente. La mezcla de reacción se concentró hasta sequedad para producir un residuo en bruto El residuo se cromatografió sobre gel de sílice, eluyendo con un gradiente de EtOAc/Hexano para obtener 1,07 g del producto puro deseado, **23.07**.

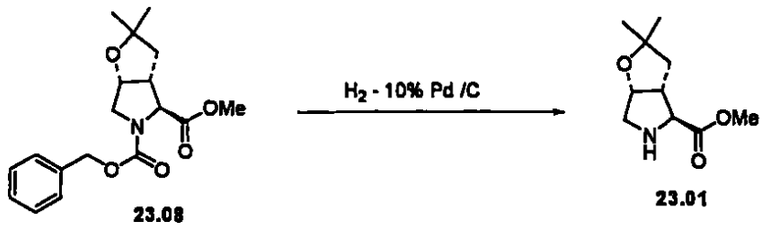
Paso 6:



878

Una solución de producto **23.07** del paso anterior (1,36 g) en CH_2Cl_2 anhidro (40 ml) se trató con $BF_3.Me_2O$ (0,7 ml). La mezcla de reacción se agitó a temperatura ambiente durante 20 h y se desactivó con $NaHCO_3$ sat. (30 ml) y se agitó durante 1/2 hr. Se separó la fase orgánica y la fase orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$, se concentró para dar el residuo en bruto. El residuo se cromatografió sobre gel de sílice eluyendo con un gradiente de EtOAc/Hexano para obtener 0,88 g del compuesto deseado, **23.08**.

Paso 7:



23.08 **23.01**

A una solución del producto **23.08** (0,92 g) del paso anterior en MeOH (30 ml) se agregó Pd/C al 10% (0,16 g) a temperatura ambiente y se hidrogenó a temperatura ambiente a una presión de 101300 Pa (1 atm). La mezcla de reacción se agitó durante 4 h y se concentró hasta sequedad para producir el compuesto deseado, **23.01**.

PREPARACIÓN DE RESTOS P3

Preparación del Intermediario **50.01**

Paso 1

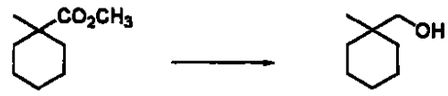


50.02 **50.03**

A una solución de **50.02** (15 g) en MeOH (150 ml) se agregó HCl conc (3-4 ml) y la mezcla se reflujó durante 16 h. La mezcla de reacción se enfrió hasta la temperatura ambiente y se concentró El residuo se absorbió en dietil éter (250 ml) y se lavó con solución fría saturada de bicarbonato de sodio, y salmuera. La

fase orgánica se secó (Na_2SO_4) y se concentró para obtener el metil éster **50.03** (12,98 g) que se llevó al paso siguiente sin purificación adicional

Paso 2



50.03 **50.04**

El metil éster **50.03** del paso anterior se disolvió en cloruro de metileno (100 ml) y se enfrió hasta -78°C, bajo atmósfera de nitrógeno. Se agregó gota a gota DIBAL (solución 1,0 M en cloruro de metileno, 200 ml) durante un período de 2 h La mezcla de reacción se entibió hasta la temperatura ambiente durante 16 h. La mezcla de reacción se enfrió hasta 0°C y se agregó MeOH (5-8 ml) gota a gota. Una solución de tartrato de sodio y potasio acuoso al 10% (200 ml) se agregó lentamente con agitación. Se diluyó con cloruro de metileno (100 ml) y se separó la fase orgánica (junto con algo de precipitado blanco) La fase orgánica se lavó con HCl 1 N (250 ml), salmuera (200 ml), se secó (Na_2SO_4) y se concentró para dar el alcohol **50.04** (11,00 g) como un aceite claro.

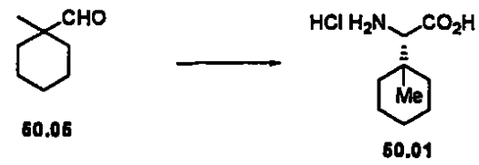
Paso 3



50.04 **50.05**

El alcohol **50.04** del paso anterior se disolvió en cloruro de metileno (400 ml) y se enfrió hasta 0°C bajo atmósfera de nitrógeno. Se agregó PCC (22,2 g) en porciones y la mezcla de reacción se entibió lentamente hasta la temperatura ambiente durante 16 h. La mezcla de reacción se diluyó con dietil éter (500 ml) y se filtró a través de un taco de celite El filtrado se concentró y el residuo se absorbió en dietil éter (500 ml) Éste se pasó a través de un taco de gel de sílice y el filtrado se concentró para dar el aldehído **50.05** que se llevó al paso siguiente sin purificación adicional.

Paso 4

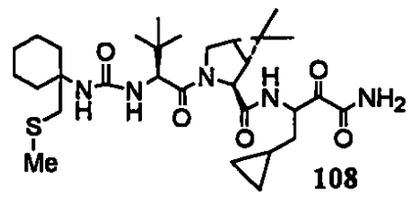


50.05 **50.01**

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

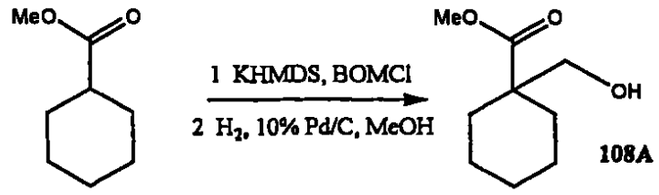
PREPARACIÓN DE EJEMPLOS ESPECÍFICOS

Ejemplo 108·



108

Pasos 1 y 2:



108A

Paso1:

Se agregó KHMDS (200ml de una solución 0,5M en tolueno), gota a gota a una solución agitada de ciclohexancarboxilato de metilo (11,1g; 78 mmol) en THF anhidro (200 ml), a -78°C bajo una atmósfera de nitrógeno. Cuando el agregado estuvo completo la reacción se mantuvo a esta temperatura durante un adicional de 0,5 h. antes del agregado de bencil clorometil éter (18,6ml; 134 mmol) La reacción se dejó entibiar hasta la temperatura ambiente hasta la mañana siguiente y se agregó agua (100 ml) El procesamiento acuoso proveyó un residuo que se purificó por cromatografía en columna de gel de sílice usando

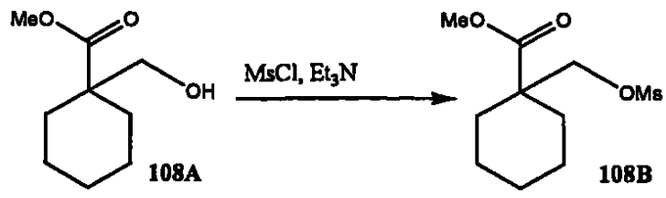
881

EtOAc·Hexanos (1.10) como eluyente para dar el éter intermediario deseado, impuro (14,98g) como un aceite incoloro.

Paso2:

Una suspensión negra de Pd/C al 10% (0,5 g) y el éter en bruto mencionado anteriormente (4,1 g) en MeOH (80 ml) se expuso a una atmósfera de nitrógeno (globo) a temp. ambiente, hasta la mañana siguiente. La reacción se filtró a través de un taco de celite y el sólido se lavó minuciosamente con metanol. El filtrado concentrado se concentró a presión reducida y el producto en bruto se purificó por cromatografía en columna de gel de sílice usando EtOAc Hexanos (1:5) para dar el alcohol primario (**108A**; 0,62g), un aceite incoloro.

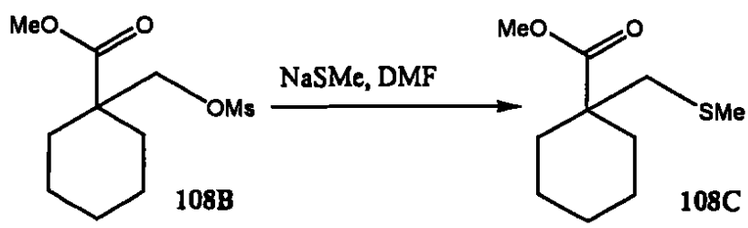
Paso 3:



108A **108B**

Se agregó cloruro de metansulfonilo (0,31ml) seguido de trietilamina (0,75 ml) a una solución agitada del alcohol primario (**108A**; 0,62g) a 0°C, bajo una atmósfera de nitrógeno. La mezcla resultante se agitó a esta temperatura durante 0,5 h. La mezcla de reacción se extrajo en EtOAc y se lavó con HCl 1M acuoso, NaHCO3 ac. sat., agua, se secó (MgSO4) y se concentró. El residuo (mesilato **108B**; 0,74g), se obtuvo como un aceite amarillo, que se usó en pasos posteriores sin purificación.

Paso 4.

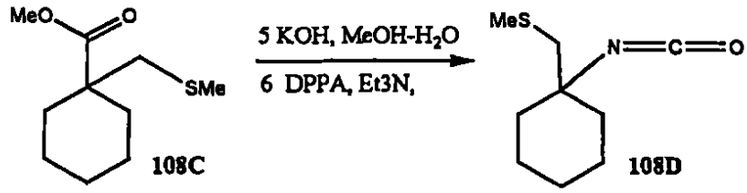


108B **108C**

882

Se agregó metantiolato de sodio (0,236g; 2eq.) a una solución en DMF (2 ml) del mesilato (**108B**; 0,42g) y la mezcla se calentó hasta 100°C durante 1h. El procesamiento acuoso y purificación del producto de la reacción en bruto por cromatografía en columna de gel de sílice usando EtOAc:Hexanos (1:20) dio el sulfuro (**108C**; 0,089 g).

Pasos 5 y 6:



108C **108D**

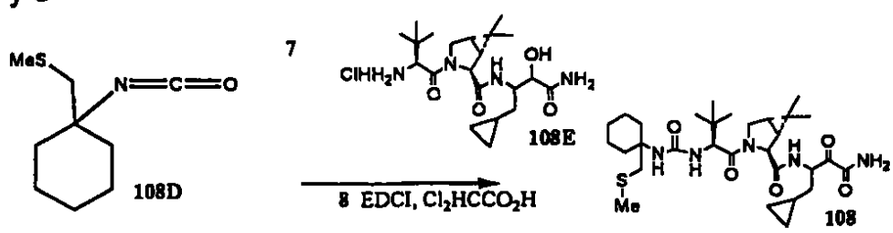
Paso 5:

Se disolvió hidróxido de potasio (0,25 g) en una mezcla de agua (1ml) y etanol (5 ml) y se agregó al metil éster (**108C**, 0,089 g) y la mezcla resultante se calentó a reflujo, bajo una atmósfera de nitrógeno durante el fin de semana (aprox. 72h.). Luego de enfriar, la reacción se repartió entre EtOAc y HCl acuoso diluido. Se separó la fase orgánica, se lavó con salmuera, se secó y se concentró para producir el ácido carboxílico intermediario, usado sin purificación.

Paso 6.

Se agregaron trietilamina (61ul) seguido de DPPA (95ul) a una solución en tolueno del ácido carboxílico del paso anterior y la reacción se calentó hasta 100°C hasta la mañana siguiente. Luego de enfriar, la mezcla de reacción se repartió entre EtOAc y bicarbonato de sodio ac. sat . Se separó la fase orgánica, dried y se concentró para producir el isocianato (**108D**; 50 mgs), usado sin purificación.

Pasos 7 y 8



108D **108E** **108**

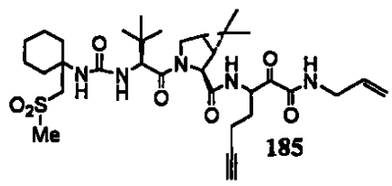
Paso 7:

El isocianato (**108D**; 50 mg) en diclorometano (1ml) se agregó a una mezcla del clorhidrato (**108E**; preparada a partir de 20.08 de un modo descrito para la transformación de 20.06 a 20.07; 100mg) y trietilamina (111ul) en diclorometano (2 ml) y la mezcla resultante se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se repartió entre EtOAc y HCl acuoso al 10%. Se separó la fase orgánica, se lavó con bicarbonato de sodio ac. sat., agua, se secó (sulfato de magnesio) y se concentró para producir un residuo que se usó en el Paso 8 sin purificación.

Paso 8:

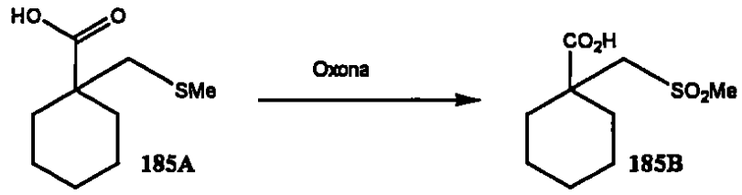
El residuo del paso antes mencionado se disolvió en una mezcla de tolueno (3 ml) y se agregaron dimetilsulfóxido (3 ml) y EDCI (647 mg) seguido de ácido dicloroacético (140 ul) y la mezcla de reacción resultante se agitó a temperatura ambiente durante un período de 4h. La mezcla de reacción se repartió entre EtOAc y sulfito de sodio ac. al 5%. Se separó la fase orgánica, se lavó con HCl acuoso al 10%, bicarbonato de sodio ac. sat., agua, se secó (sulfato de magnesio) y se concentró para producir un residuo que se purificó por cromatografía en columna de gel de sílice usando acetona.hexanos (40.60) como eluyente para proveer la ceto-amida deseada (**108**; 11,5mgs). EM: MH+, 592,1.

Ejemplo 185:



185

Paso 1

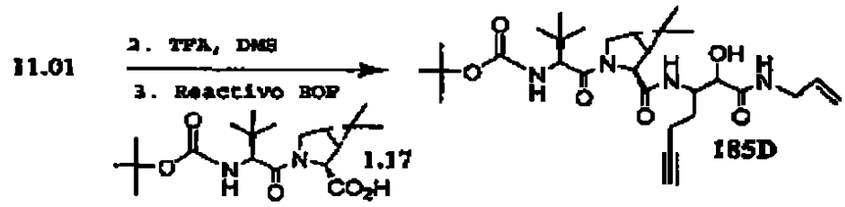


185A **185B**

884

Se disolvió oxona (5,68g) en agua (5 ml) y se agregó al ácido carboxílico **185A** (1,25 g) en metanol (5 ml) mientras se enfriaba en un baño de hielo. La mezcla de reacción se dejó entibiar hasta la temperatura ambiente, hasta la mañana siguiente. Los volátiles se eliminaron a presión reducida y el residuo se repartió entre cloruro de metileno y agua. Se separó la fase acuosa y se extrajo con cloruro de metileno (X2). Las fases orgánicas combinadas se secaron y se concentraron para producir la sulfona (**185B**; 1,10 g) como un sólido blanco, usado en procedimientos posteriores sin purificación.

Pasos 2 y 3:



Paso 2:

El carbamato de bencilo (**11.01**; 0,16 g) se disolvió en TFA (7 ml) y se agregó sulfuro de dimetilo (1,78 ml) y la mezcla resultante se dejó reposar a temperatura ambiente durante un período de 3h., antes de eliminar los volátiles a presión reducida Esto dio un residuo que se usó en el Paso 3 siguiente.

Paso3:

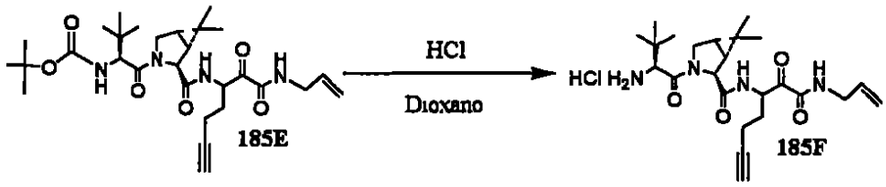
Se agregó trietilamina (111ul) a una mezcla del residuo del paso 2, el ácido carboxílico (**1.17**; 0,180 g) y reactivo BOP (0,236g) en diclorometano (5 ml) y la mezcla de reacción se agitó a temperatura ambiente hasta la mañana siguiente. La reacción se repartió entre acetato de etilo y HCl ac. al 10%. Se separó la fase orgánica, se lavó con bicarbonato de sodio ac. sat., agua, se secó (sulfato de magnesio) y los volátiles se eliminaron a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice usando EtOAc: Hexanos (70:30) como eluyente para dar la hidroxi-amida deseada (**185D**; 0,165 g) como un sólido blanco.

Paso 4.



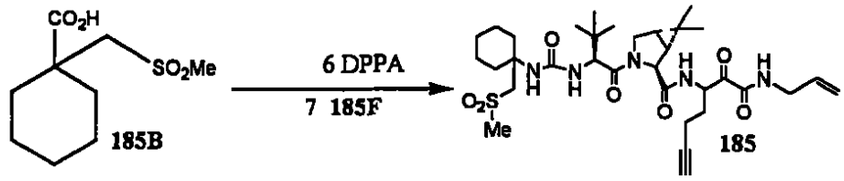
Se agregó periodinano (0,236g) a una solución agitada del alcohol (**185D**, 0,152g) en diclorometano (5 ml) y la suspensión blanca resultante se agitó durante un período de 2h. antes de agregarse a una mezcla de EtOAc y sulfito de sodio ac. al 5% Se separó la fase orgánica se lavó con bicarbonato de sodio ac. sat., agua, se secó y los volátiles se eliminaron a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice usando EtOAc: Hexanos (40:60) como eluyente para dar la ceto-amida deseada (**185E**; 0,147g) como un sólido blanco EM: MH+, 545,5.

Paso 5·



Una solución de HCl en dioxano (4M; 5 ml; Aldrich) se agregó al carbamato (**185E**; 0,14g) y se dejó reposar a temperatura ambiente durante un período de 3h. Los volátiles se eliminaron a presión reducida para proveer el clorhidrato (**185F**; 0,126 g· contiene una pequeña cantidad de dioxano).

Pasos 6 y 7·



Paso 6:

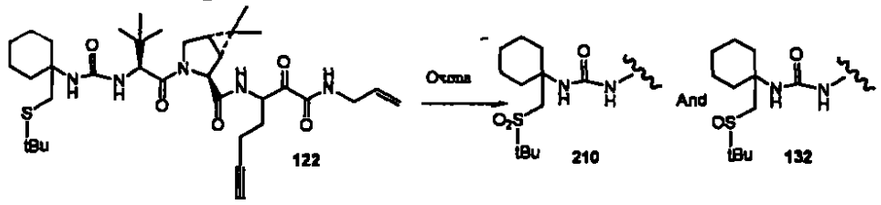
Se agregó DPPA (19ul) a una mezcla del ácido carboxílico (**185B**; 20 mg) y trietilamina (13ul) en tolueno (1ml) y la mezcla de reacción resultante se calentó a

reflujo durante un período de 1h. Luego de enfriar, la reacción se repartió entre EtOAc y bicarbonato de sodio ac. sat.. Se separó la fase orgánica, se secó y los volátiles se eliminaron a presión reducida Se obtuvo el isocianato intermediario en bruto que se usó en el Paso 7 a continuación sin purificación.

Paso 7:

El producto del paso 6 se disolvió en diclorometano (1ml) y se agregó a una mezcla del clorhidrato (**185F**; 20 mgs) y trietilamina (60ul) en diclorometano (1ml) y la mezcla resultante se agitó a temperatura ambiente durante un período de 1h. La reacción se repartió entre EtOAc y HCl acuoso al 10%. Se separó la fase orgánica, se lavó con bicarbonato de sodio ac. sat., agua, se secó y los volátiles se eliminaron a presión reducida El residuo resultante se purificó por cromatografía en placa de gel de sílice usando EtOAc: Hexanos (1:1) como eluyente para proveer la cetoamida (**185**; 16,3mgs) como un sólido blanco. EM: MH+, 662,5

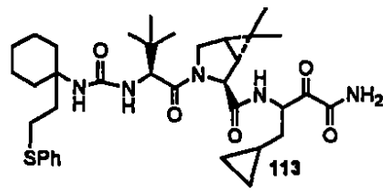
Preparación de los Compuestos de Fórmulas **132** y **210** Directamente a Partir de un Compuesto de Fórmula **I22**



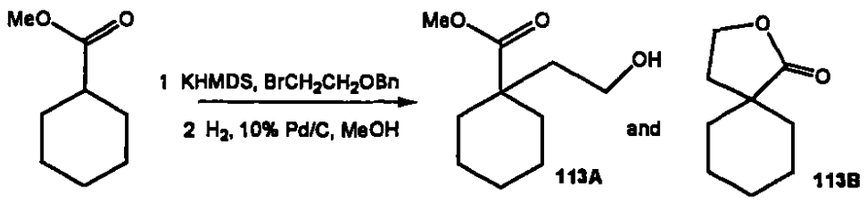
Usando el sulfuro **122** (preparado de un modo similar al de 108 usando el metil éster 210A en lugar de 108C; 20 mg), oxona (27mg; 1,5eq.), agua (1ml), metanol (1ml) y el procedimiento establecido anteriormente (**185A** a **185B**), se obtuvo un producto de reacción en bruto que se purificó por cromatografía en placa de gel de sílice usando EtOAc como eluyente. Se obtuvo la sulfona (**210**; MH+= 704,4; 5,6mg) como un sólido blanco seguido de una mezcla de sulfóxidos (**132**, MH+ = 688,5, 6,3mg), también un sólido blanco.

Preparación del Compuesto **113**

887



Pasos 1 y 2



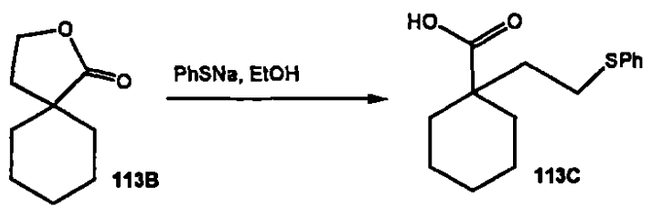
Paso 1:

Usando ciclohexancarboxilato de metilo (5,55 g), KHMDS (100ml de una solución 0,5M en tolueno), THF anhidro (100 ml) y bencil 2-bromoetil éter (10.09 g) y el procedimiento establecido con anterioridad (Ejemplo **108**, Paso 1), se obtuvo el bencil éter intermediario deseado (6,83g) luego de la cromatografía en columna de gel de sílice (EtOAc:Hexanos:15:85).

Paso 2:

Usando el bencil éter antes mencionado (5,00 g), Pd/C al 10% (1,00 g), metanol (20 ml) y el procedimiento establecido anteriormente (Ejemplo **108**; Paso 2) se obtuvieron la lactona (**113B**, 0,87g), seguida del alcohol (113A; 2,01g) después de la cromatografía en columna sobre gel de sílice (EtOAc:Hexanos 1.10).

Paso 3:



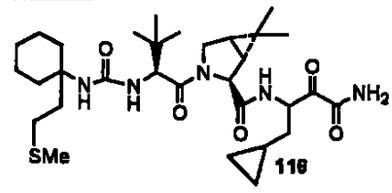
Paso 3:

888

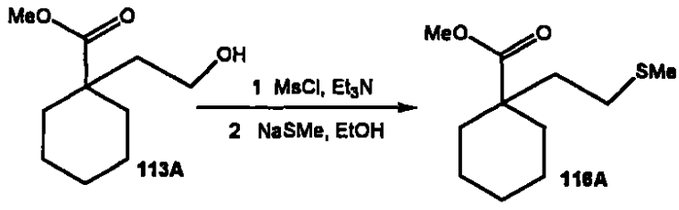
Se agregó tiofenóxido de sodio (0,68g) a una solución de la lactona (**113B**; 0,84g) en etanol (15 ml) y la mezcla resultante se calentó a reflujo, bajo una atmósfera de nitrógeno hasta la mañana siguiente Luego de enfriar, el procesamiento acuoso y la purificación del producto de la reacción en bruto por cromatografía en columna de gel de sílice (EtOAc:Hexanos 30:70) dio el ácido carboxílico (**113C**; 0,32g) como un sólido amarillo.

Usando la química descrita anteriormente para la conversión de **108C** en **108, 113C** se convirtió en **113** de un modo similar. EM, MH+, 668,3.

Preparación del Compuesto **116:**



Pasos 1 y 2



Paso 1:

Usando el alcohol (**113A**, 1,00 g), cloruro de metansulfonilo (1.12g), trietilamina (0,82g), cloruro de metileno (10 ml) y el procedimiento establecido anteriormente (**108A** a **108B**), se obtuvo el mesilato intermediario deseado y se usó en el paso siguiente, sin purificación

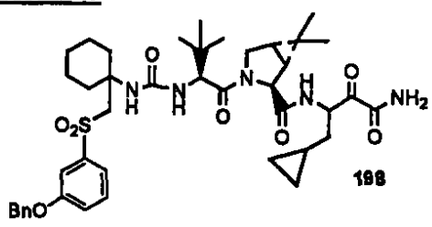
Paso 2:

Usando el mesilato antes mencionado, metantiolato de sodio (0,75 g), etanol (10 ml) y el procedimiento establecido anteriormente (**108B** to **108C**) a temperatura ambiente, se obtuvo el sulfuro deseado (**116A**; 0,78g) luego de la cromatografía en columna de gel de sílice (EtOAc-Hexanos, 1:10). Usando los

989 986

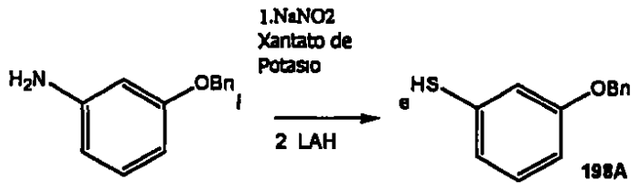
procedimientos establecidos con anterioridad (**108C** a **108D**) y (**108D** a **108**), el intermediario **116A** se transformó en **116**. MS; MH+, 606,1.

Preparación del Compuesto **198**



198

Pasos 1 y 2"



198A

Pasos 1 y 2:

Paso 1.

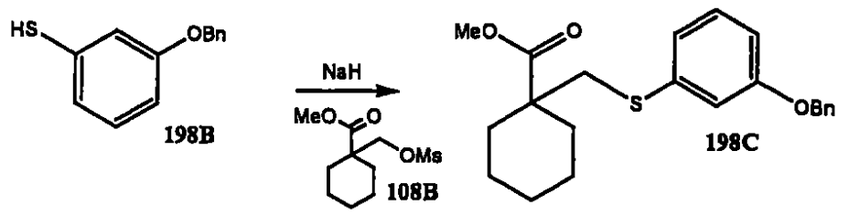
Se disolvió 3-benciloxianilina (5,00 g; Aldrich) en una mezcla de HCl conc. (10 ml) y se agregó hielo (10.00 g). Se agregó nitrito de sodio (1,85 g) en agua (10 ml) mientras se enfriaba en un baño de hielo. Cuando el agregado estuvo completo, se agregó O-etilxantato de potasio y se agitó a esta temperatura hasta que cesó la evolución de nitrógeno gaseoso, luego se calentó a 40-45°C durante un período de 1,5h. Luego de enfriar, se realizó el procesamiento acuoso y purificación por cromatografía en columna de gel de sílice (EtOAc 2-5% en hexanos) para dar el xantato intermediario (3,60 g).

Paso 2·

Se agregó gota a gota hidruro doble de litio y aluminio (6,4 ml de una solución 1M en THF) a una solución agitada del xantato mencionado anteriormente (1,49 g) en THF (10 ml) y se agitó a T.A. durante un período de 0,5 h. La reacción se desactivó con acetona en exceso y se repartió entre EtOAc y HCl ac. 1M Se separó la fase orgánica, se secó y se concentró El producto de la

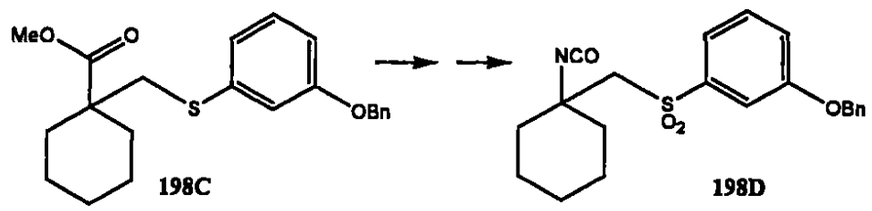
reacción en bruto se purificó por cromatografía en columna de gel de sílice (EtOAc 1-2% en hexanos) para dar el tiofenol (**198A**; 0,84g), un sólido blanco.

Paso 3:



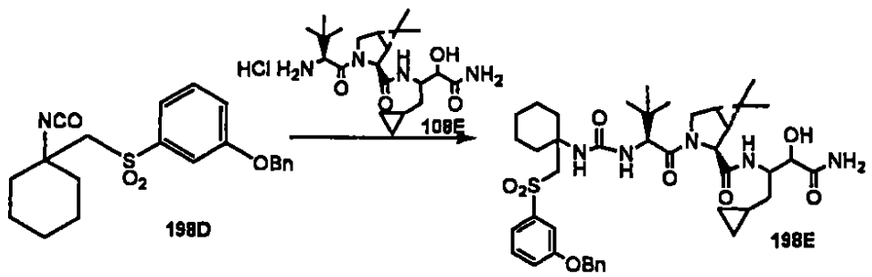
El mercaptano (**198B**; 0,72g) se agregó a una suspensión de NaH (0,08g de una dispersión 60% en aceite mineral) en DMF anhidra, mientras que se enfriaba en un baño de hielo bajo una atmósfera de nitrógeno. La mezcla resultante se agitó durante 1h. y se agregó el mesilato (**108B**; 0,417g) y la reacción se dejó entibiar hasta T A , hasta la mañana siguiente. El procesamiento acuoso y purificación del producto de la reacción en bruto por cromatografía en columna de gel de sílice (3% EtOAc en hexanos) dio el sulfuro (**198C**; 0,313g).

Pasos 4-6:



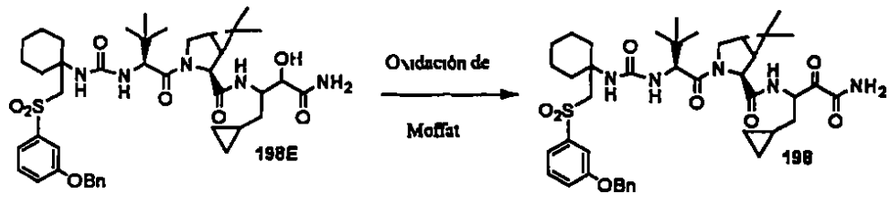
Usando el sulfuro (**198C**) generado en paso previo, el isocianato (**198D**) se produce usando procedimientos descriptos en (**108C** a **108D**) y **185A** a **185D**). El isocianato (**198D**) se utiliza en procedimientos posteriores sin purificación.

Paso 7:



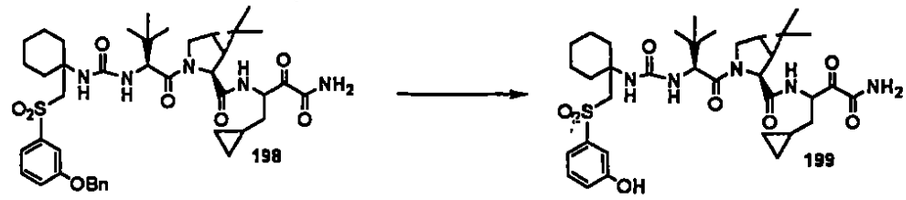
El isocianato (**198D**, 0,139 g) en una cantidad mínima de diclorometano (aprox. 1ml) se agregó a una mezcla del clorhidrato (**108E**; 0,080 g) y trietilamina (0,126 ml) y la mezcla resultante se agitó a temperatura ambiente durante un período de 4 horas. La mezcla de reacción se repartió entre EtOAc y HCl acuoso al 10%. Se separó la fase orgánica, se lavó con bicarbonato de sodio ac. sat., agua, se secó y se concentró. El producto de la reacción en bruto (**198E**) se usó bruto en el paso siguiente.

Paso 8:



El producto en bruto del paso anterior (**198E**) se disolvió en DMSO (3ml) y tolueno (3ml) y se agregó EDCI (0,346g) seguido de ácido dicloroacético (0,074 ml) y la mezcla resultante se agitó a temperatura ambiente durante un período de 4 horas. La reacción se repartió entre EtOAc y sulfito de sodio ac. 5%. Se separó la fase orgánica, se lavó con bicarbonato de sodio ac. sat., agua, se secó y se concentró El producto de la reacción en bruto se purificó por cromatografía en columna de gel de sílice usando acetona·hexano (30.70) como eluyente para dar la cetoamida (**198**; MH+ = 792,2; 55 mg)

Preparación del Fenol **199** a partir del Bencil Éter **198:**

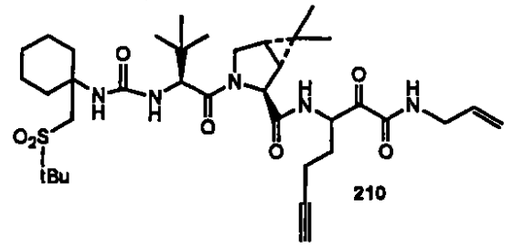


Se agregó Pd-C 10% (25mg) seguido de ácido fórmico (0,125 ml) a una solución del bencil éter (**198**; 50mg) en etanol (4 ml) y la suspensión negra resultante se reflujó durante un período de 1 hora Luego de enfriar, la reacción se filtró a través de un taco de celite y el sólido se lavó con metanol. El filtrado

892

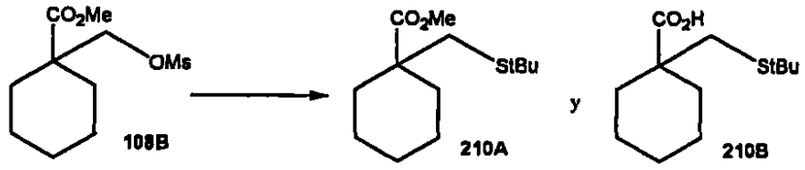
concentrado se concentró a presión reducida para dar el fenol deseado (**199**; MH+= 702,2; 23mg).

Preparación Alternativa del Compuesto de Fórmula **210:**



210

Paso1:

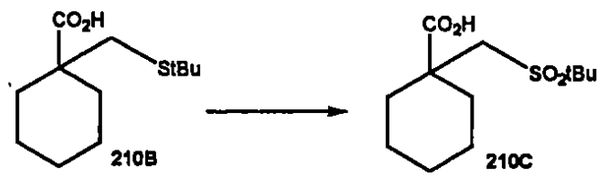


108B **210A** **210B**

Se agregó dimetilformamida (20 ml; anhidra, Aldrich) a hidruro de sodio (0,56g; Aldrich) y se agregó ter-butil mercaptano a la suspensión mientras se enfriaba en un baño de hielo bajo una atmósfera de nitrógeno. Una vez que el agregado se completó, se agregó el mesilato (**108B**; preparado como anteriormente a partir de 2,00g de alcohol; **108A**) y la mezcla resultante se agitó hasta la mañana siguiente a temperatura ambiente. La reacción se repartió entre EtOAc y agua y se separó la fase orgánica, se secó ($MgSO_4$). La cromatografía en columna sobre gel de sílice gel usando EtOAc-Hexanos (2:98) proveyó el metil éster-sulfuro (**210A**; 1,75 g)

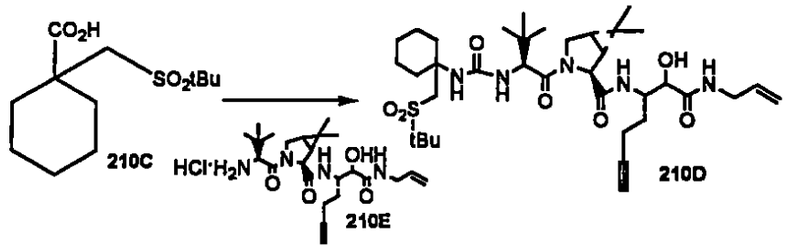
Se agregó EtOAc a la fase acuosa y se agregó HCl acuoso al 10% hasta lograr que la capa acuosa tuviera un pH=1. La fase orgánica se separó, se lavó con agua, se secó y se concentró a presión reducida para dar el sulfuro-ácido carboxílico (**210B**; 0,747g) como un sólido blanco

Paso 2·



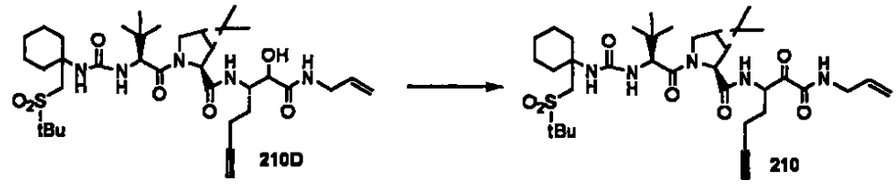
Al sulfuro (**210B**; 2,287g) en metanol (75 ml) se agregó una solución de oxona (18,00 g; Aldrich) y la suspensión blanca resultante se agitó hasta la mañana siguiente a temperatura ambiente. Los volátiles se eliminaron a presión reducida y el sólido blanco se repartió entre EtOAc y agua. Se separó la fase orgánica, se secó y se concentró para dar la sulfona (**210C**; 2,52g; contiene algo de solvente).

Paso 3:



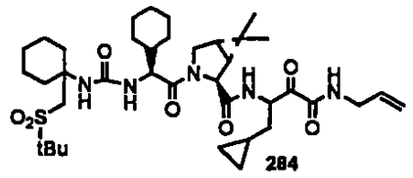
Se agregó trietilamina (0,173ml) seguida de DPPA (0,268ml) a una solución del ácido carboxílico (**210E**, 0,325 g) en tolueno (3ml) y la mezcla resultante se calentó hasta 110°C (baño de aceite) durante un período de 1 hora. Luego de enfriar, la mezcla de reacción se repartió entre EtOAc y bicarbonato de sodio ac. sat.. Se separó la fase orgánica, se secó y se concentró. El residuo se disolvió en diclorometano (1ml) y se agregó a una mezcla del clorhidrato (**185F**, 0,300 g) y trietilamina (0,044 ml) en diclorometano (3ml) y la mezcla de reacción resultante se agitó a temperatura ambiente hasta la mañana siguiente. La reacción se repartió entre EtOAc y HCl acuoso al 10%, Se separó la fase orgánica, se lavó con bicarbonato de sodio saturado ac., agua, se secó y se concentró para producir un producto en bruto que se usó en el paso siguiente sin purificación

Paso 4.

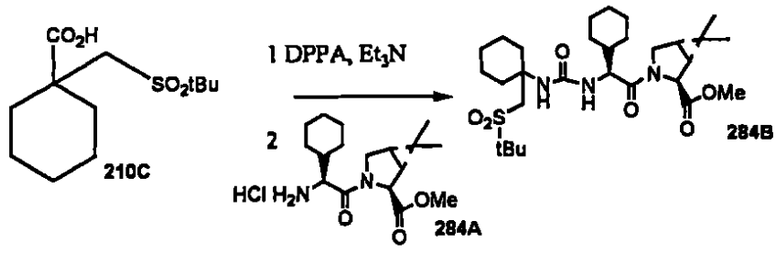


El residuo del paso anterior (**210D**) se disolvió en diclorometano (5 ml) y se agregó Periodinano de Dess-Martin (0,527g) y la mezcla de reacción se agitó a temperatura ambiente durante 3 horas La reacción se repartió entre EtOAc y sulfito de sodio ac. 5% Se separó la fase orgánica, se lavó con bicarbonato de sodio ac. sat., agua, se secó y los volátiles se eliminaron a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice usando EtOAc:Hexanos (70:30) como eluyente para dar la ceto-amida deseada (**210**; 0,310 g).

Preparación de Compuesto de Fórmula **284:**



Pasos 1 y 2:



Paso1·

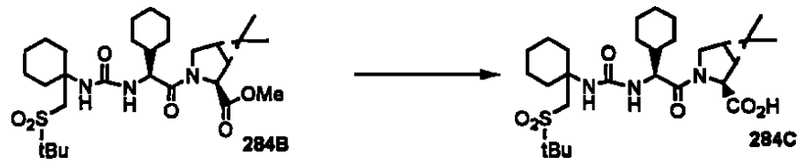
Usando el ácido carboxílico (**210C**, 2,52g), DPPA (2,07 ml), trietilamina (1,34 ml) en tolueno (10 ml) y el procedimiento expuesto anteriormente, se obtuvo el isocianato bruto.

Paso 2:

El isocianato intermediario se disolvió en diclorometano (2 ml) y se agregó a una mezcla del clorhidrato **284A** (preparado a partir de 20.04 usando la

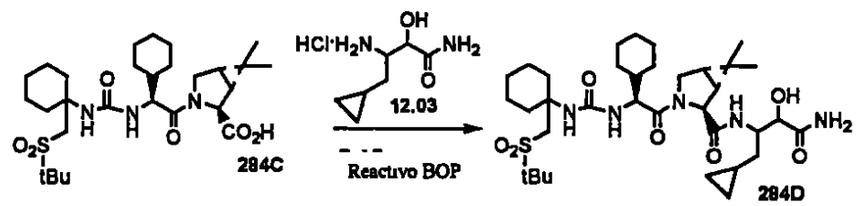
transformación descripta para 20.06 a 20 07; 1,66g) y trietilamina (3,4 ml) y la mezcla se agitó a temperatura ambiente hasta la mañana siguiente. El procesamiento acuoso y la purificación del residuo sobre gel de sílice usando EtOAc Hexanos (3·97) dio la urea deseada (**284B**) .

Paso 3·



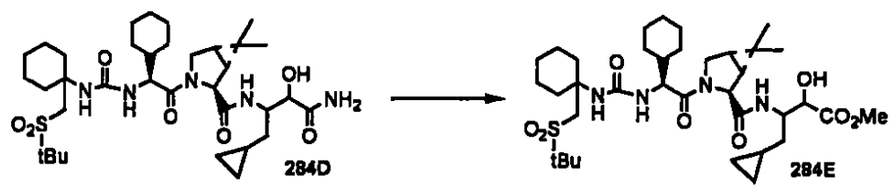
El metil éster (**284B**) se disolvió en una mezcla de dioxano (90 ml) y agua (30 ml) y se agregó hidróxido de litio monohidrato (0,402g; 2eq) y la reacción se dejó agitar a temperatura ambiente durante 3 horas La mezcla de reacción se repartió entre EtOAc y HCl acuoso al 10%. Se separó la fase orgánica, se secó y se concentró para producir el ácido carboxílico (**284C**; 2,65 g).

Paso 4·



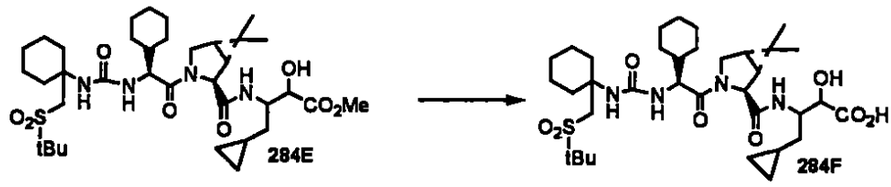
Se agregó reactivo BOP (2,54g) seguido de trietilamina (2,4 ml) a una solución del ácido carboxílico (**284C**; 2,65 g) y el clorhidrato (**12.03**; 0,933g) en diclorometano (20 ml) y se agitó a temperatura ambiente hasta la mañana siguiente. La reacción se repartió entre EtOAc y HCl acuoso al 10%. Se separó la fase orgánica, se lavó con bicarbonato de sodio ac. sat , agua, se secó y se concentró. El residuo se purificó por cromatografía en columna de gel de sílice usando 2-10% MeOH en diclorometano como eluyente para dar la amida deseada (**284D**; 2,92g).

Paso 5:



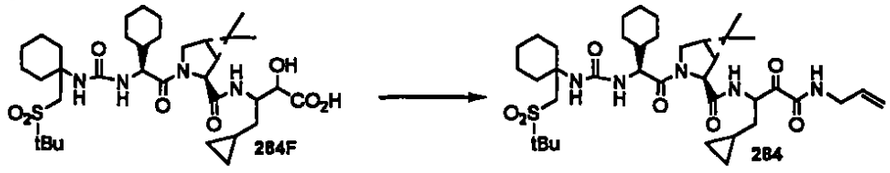
A una solución de la carboxamida (**284D**, 2,92g) en metanol (30 ml) se agregó DMF-DMA (1.12 ml) y la mezcla resultante se agitó a temperatura ambiente durante 3 horas y luego se refluió durante 1,5 horas hasta que la T.L.C. indicó que no quedaba más material de partida Luego de enfriar, la reacción se repartió entre dietil éter y HCl 1N acuoso Se separó la fase orgánica, se secó y se concentró. La cromatografía en columna de gel de sílice del residuo dio el metil éster (**284E**), que se trató como se muestra en el Paso 6, a continuación.

Paso 6.



El metil éster (**284E**) se disolvió en una mezcla de dioxano (30 ml) y agua (10 ml) y se agregó hidróxido de litio monohidrato (0,354g) y la mezcla resultante se agitó durante 3 horas. La reacción se repartió entre EtOAc y HCl acuoso al 10%. Se separó la fase orgánica, se secó y se concentró para proveer el ácido carboxílico (**284F**; 2,80 g).

Pasos 7 y 8.



Paso 7:

Se agregaron alil amina (0,045 ml), reactivo BOP (0,266g) y trietilamina (0,25 ml) a una mezcla de una solución del hidroxiácido (**284F**; 0,348g) en diclorometano (5 ml) y la mezcla resultante se agitó a temperatura ambiente hasta

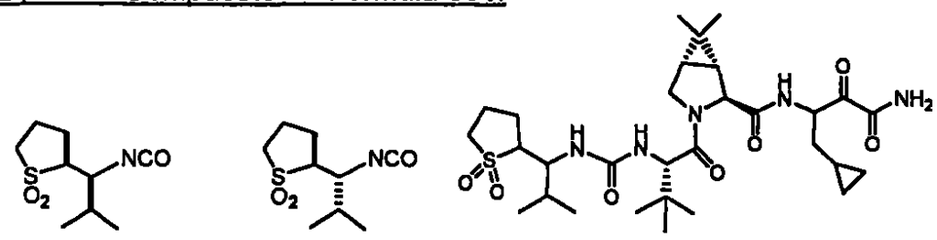
897

la mañana siguiente. La reacción se repartió entre EtOAc y HCl acuoso al 10%. Se separó la fase orgánica, se lavó con bicarbonato de sodio ac. sat., agua, se secó y se concentró para proveer un residuo, usado sin purificación en el Paso 8, a continuación.

Paso 8:

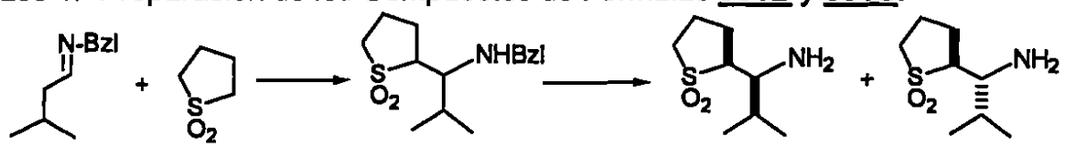
El residuo se disolvió en diclorometano (5 ml) y se agregó Periodinano de Dess-Martin (0,424g) y la mezcla de reacción se agitó a temperatura ambiente durante 3 horas. La reacción se repartió entre EtOAc y sulfito de sodio ac. 5%. Se separó la fase orgánica, se lavó con, bicarbonato de sodio sat. ac., agua, se secó y se concentró. El producto de la reacción en bruto se purificó por cromatografía en columna de gel de sílice para producir la ceto-amida deseada (**284**; 0,296g) MH+, 732,2

Ejemplo de preparación **331** Preparación de los intermediarios de Fórmulas **331D** y **331E** para el Compuesto de Fórmula **331**:



rac-**331D** rac-**331E** **331**

Paso 1. Preparación de los Compuestos de Fórmulas **331B** y **331C**:



331A **331B** **331C**

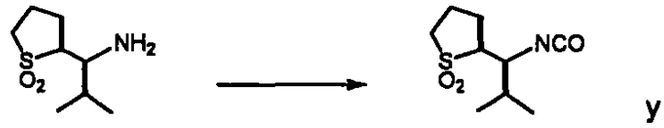
Se hicieron reaccionar N-bencil-4-metilbutanimina (preparada como se describe en: *Synthesis*, **1985**, 679) y tetrahidrotiofeno 1,1-dióxido de la manera descripra en el Ejemplo 336, excepto que fue a -78°C, para obtener el compuesto

898

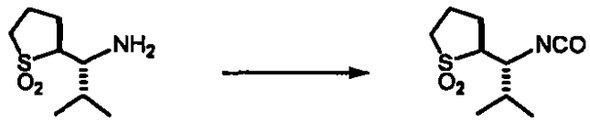
331A, que se sometió a hidrogenólisis de la manera descripta en el Ejemplo 336, excepto que fue a una presión de 101300 Pa (1 atm). El producto en bruto se cromatografió sobre gel de sílice, eluyendo con un gradiente de EtOAc a acetona-EtOAc 1:1 para obtener primero un diastereómero racémico. H^1-RMN ($CDCl_3$) δ 3,2 (m, 1H), 3,1-2,9 (m, 3H), 2,3-2,1 (m, 2H), 2,1-1,9 (m, 1H), 1,9-1,7 (m, 2H), 1.02 (d, 3H), 0,85 (d, 3H).

La posterior elución produjo el otro diastereómero racémico: H^1-RMN ($CDCl_3$) δ 3,2 (m, 1H), 3,2-2,9 (m, 4H), 2,3-2,1 (m, 3H), 2,1-2,0 (m, 1H), 1,78 (sex , 1H), 0,96 (m, 6H).

Paso 2. Preparación de los Compuestos de Fórmulas **331D** y **331E**.



331B **331D**



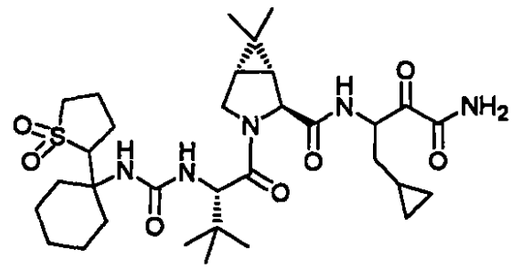
331C **331E**

Los compuestos **331B** y **331C** se hicieron reaccionar separadamente con fosgeno de la manera descripta en el Ejemplo 336 para obtener dos isocianatos diastereómeros:

uno, a partir de la amina de mayor R_f: H^1 -RMN ($CDCl_3$)) δ 3,79 (dd, J_1 = 9,9 Hz, J_2 = 3,0 Hz, 1H), 3,25 (m, 1H), 3,1-3,0 (m, 2H), 2,25 (m, 2H), 2,2-2,0 (m, 1H), 2,0-1,7 (m, 2H), 1,09 (d, J = 6,9 Hz, 3H), 0,93 (d, J = 6,9 Hz, 3H)

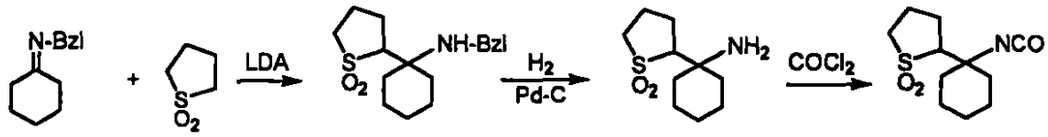
El otro, a partir de la amina de menor R_f: H^1 –RMN ($CDCl_3$)) δ 3,92 (dd, J_1 = 6,6 Hz, J_2 = 4,8 Hz, 1H), 3,3-2,9 (m, 3H), 2,4 (m, 1H), 2,3 (m, 1H), 2,2-2,0 (m, 3H), 1.03 (t, Δv= 6,3, 6H).

Ejemplo de preparación 336 Preparación del Compuesto de Fórmula 336.



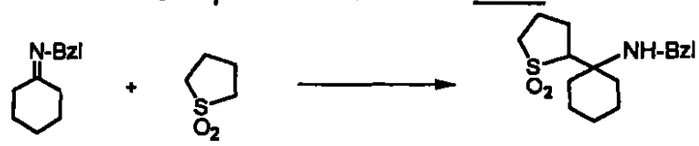
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ESQUEMA 336-1



336A **336B** **336C**

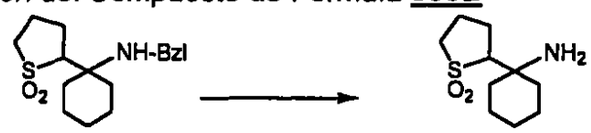
Paso 1. Preparación deL Compuesto de Fórmula **336A**.



336A

Una solución de 20 ml de LDA 2N en hexano-THF se agregó a 60 ml de THF y la solución se enfrió hasta -30°C. Luego se agregaron lentamente 4,80 g de tetrahidrotiofeno 1,1-dióxido (Aldrich Chemical Co) entre -30°C y -10°C, y luego se agitó a -10°C por 10 min adicionales. A -10°C, se agregaron enseguida 7,5 g de N-bencilciclohexilimina (preparada como se describen en: *Síntesis*, **1998**, 1609.). Después de 0,5 h a temperatura ambiente la mezcla se desactivó con $NaHCO_3$ acuoso saturado, y se extrajo con CH_2Cl_2. Los extractos se secaron sobre Mg_2SO_4 anhidro, se filtraron y el filtrado se evaporó. El residuo se cromatografió sobre gel de sílice, eluyendo con EtOAc Hexano (3:7) para obtener 1,3 g del compuesto **336A**: H^1-RMN ($CDCl_3$): δ 7,5-7,2 (m, 5H), 3,76 (ABq, Δv = 230 Hz, J = 12, 2H), 3,41 (m, 1H), 3,13 (m, 1H), 2,94 (m, 1H), 2,4-1,3 (m, 14H).

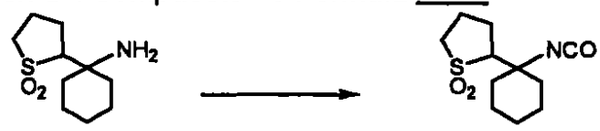
Paso 2. Preparación del Compuesto de Fórmula **336B**



336A **336B**

Una solución de 1,3 g del compuesto **336A**, 30 ml de EtOH, 1,2 ml de solución de HCl/dioxano 4N, y 0,35 g de Pd-C 10%, se hidrogenó a 303900 Pa (3 atm) durante 1,5 h. Se filtró la mezcla, y el filtrado se evaporó. El residuo se trató con NaOH 2N y se extrajo con CH_2Cl_2, el extracto se secó y se evaporó para dejar 0,51 g del compuesto **336B**, que solidificó al reposar H^1-RMN ($CDCl_3$ δ 3,2-2,9 (m, 3H), 2,4-1,8 (m, 6H), 1,7-1,2 (m, 8H).

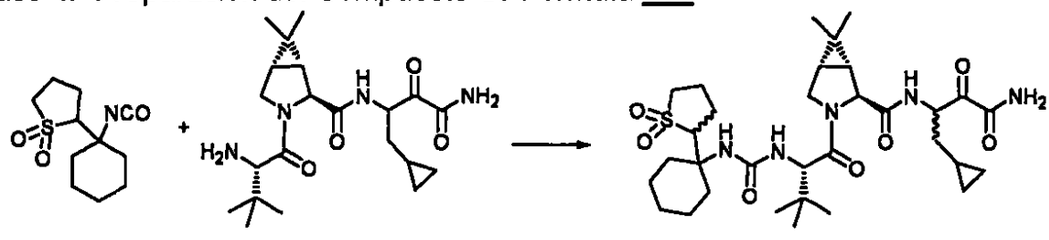
Paso 3. Preparación del Compuesto de Fórmula **336C**



336B **336C**

A una solución de 0,75 g de fosgeno en 30 ml de tolueno a 0°C se agregó lentamente una solución de 0,5 g del compuesto **336B** y 0,80 ml de diisopropil-etilamina en 10 ml de CH_2Cl_2 La mezcla se agitó a temperatura ambiente durante 5 h, se concentró a 15 ml, se filtró, luego se diluyó con tolueno fresco a 18 ml para dar una solución 0,12 M del compuesto **336C**, que se usó para posteriores reacciones

Paso 4. Preparación del Compuesto de Fórmula **336**



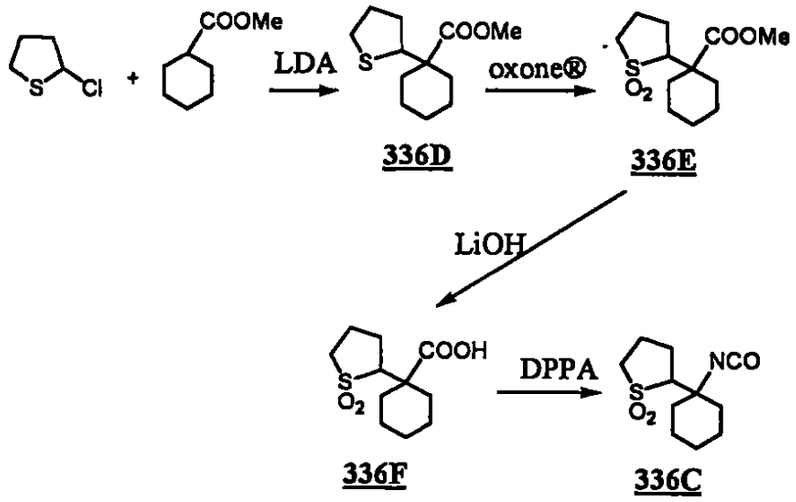
336C **20.10** **336**

901

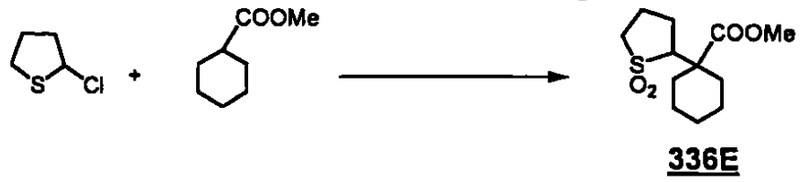
El compuesto **336C** se hizo reaccionar con el compuesto **20.10** de la manera descripta en el ejemplo de preparación 108 para dar el compuesto **336** como una mezcla de diastereómeros H^1-RMN (DMSO-d_6) δ 8,40(m), 8,33 (m), 8,00 (d), 7,75 (s), 6,25 (m), 6,10 (s), 6,01 (s), 4,18 (m), 3,92(m), 3,83 (m), 3,78 (m), 3,13 (m), 2,90 (m) 2,47 (m), 2,1-0,8 (m, Me_A: 1.01; Me_B: 0,82; Bu^t: 0,91), 0,40 (m), 0,19 (m).

Ejemplo **336C** Síntesis Alternativa del compuesto **336C**

ESQUEMA 336-2



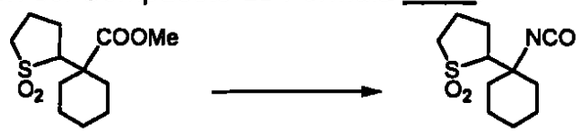
Paso 1 Preparación del Compuesto de Fórmula **336E**.



Se hizo reaccionar 2-clorotetrahidrotiofeno (preparado como se describe en: *Chem. Pharm. Bull.*, ***1986***, *34*(9), 3644) con ácido α-litiociclohexanocarboxílico de la manera descripta en los ejemplos precedentes para obtener el compuesto sulfuro éster **336D** con 39% de rendimiento. El compuesto **336D** se oxidó con oxona® de la manera descripta en los ejemplos precedentes para obtener el compuesto sulfona éster **336E**. H^1 RMN($CDCl_3$) δ 3,73 (s, 3H) 3,3-3,0 (m, 2H), 3,0-2,9 (m, 1H), 2,6-2,4 (m, 1H), 2,4-1,3 (m, 13H)

902

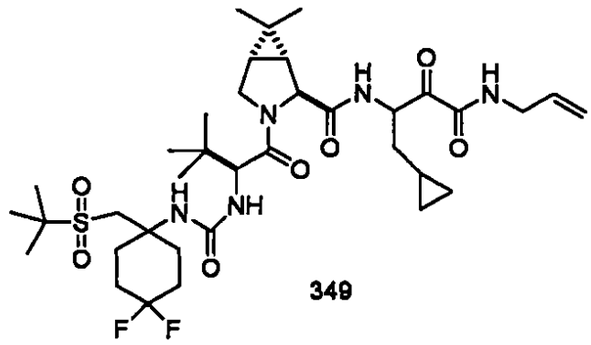
Paso 2. Preparación del Compuesto de Fórmula **336C**.



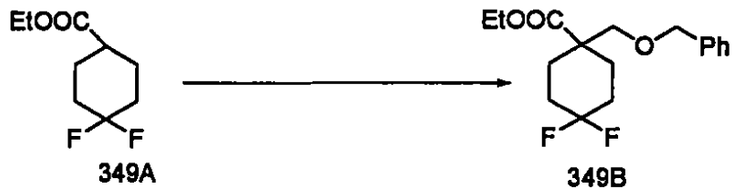
336E **336C**

El compuesto **336E** se hidrolizó con LiOH en agua-dioxano a 100°C de la manera descripta en los ejemplos precedentes para obtener el compuesto ácido sulfona carboxílico **336F**: H^1 RMN($CDCl_3$) δ 3,4-3,2(m, 1H), 3,2-3,1 (m, 1H), 3,1-2,9 (m, 1H), 2,3-2,1 (m, 3H), 2,1-1,8 (m, 3H), 1,8-1,3 (m, 7H) El compuesto **336F** se hizo reaccionar con difenilofosforilazida de la manera descripta en los ejemplos precedentes para obtener el compuesto **336C** como un sólido incoloro: H^1 RMN($CDCl_3$) δ 3,2 (m, 1H), 3,1-2,9 (m, 2H), 2,45 (d, 1H), 2,4-1,9 (m, 4H), 1,85-1,5 (m, 7H), 1,5-1,2 (m, 2H).

Síntesis del Compuesto 349:



349



349A 349B

A una solución del etil éster (**349A**; 10 g; 0,052 mol) en dietil éter (50 ml) a –78°C (temp. del baño) se agregó KHMDS (0,5 M en tolueno; 156,087 ml; 1,5 equiv.). La solución resultante se agitó durante 30 minutos, luego se agregó bencil clorometil éter (11,89 ml, densidad 1 13; 1,65 equiv.). La mezcla de reacción se

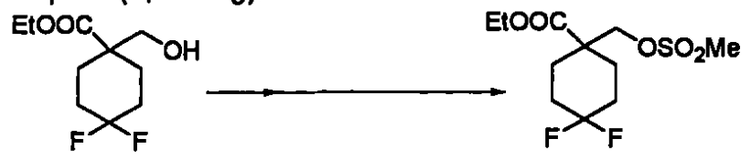
903

agitó desde –78°C hasta T.A. durante 24 h. La reacción se detuvo por agregado de NH_4Cl ac. saturado Luego se diluyó con acetato de etilo y la fase orgánica combinada se lavó con salmuera, se secó sobre Na_2SO_4 y se evaporó hasta sequedad *al vacío* para dar un aceite marrón claro (24,2 g). Se cromatrografió sobre gel de sílice (300 g). La columna se eluyó con 1% - 4% de acetato de etilo en n-hexano dando en algunas de las fracciones **349B** puro (6,54 g).



349B **349C**

Una solución del bencil éter (**239B**; 2,8316 g; 0,0091 mol.) en $CHCl_3$ (49,5 ml) se trató con ácido metan sulfónico (22,65 ml) y la mezcla de reacción se agitó a temperatura ambiente durante ~70 minutos. Se agregó hielo a la mezcla de reacción y se diluyó con acetato de etilo La fase orgánica se lavó con $NaHCO_3$ saturado, se secó sobre Na_2SO_4 y se evaporó hasta sequedad *al vacío* para dar un aceite amarillento (2,86 g). Se cromatografió sobre SiO_2 (65 g) La columna se eluyó con 15% - 25% de acetato de etilo en n-hexano, dando en algunas de las fracciones **349C** puro (1,5913 g).

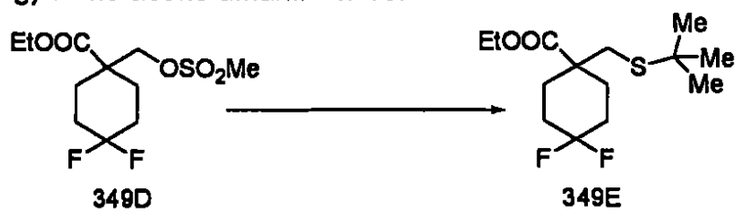


349C **349D**

Una solución agitada del alcohol (**349C**, 1.14 g; 0,0051 mol) en cloruro de metileno (6,4 ml) se enfrió en baño de hielo y se trató con Et_3N (0,7857 ml; densidad 0,726; 1.1 equiv) y cloruro de metansulfonilo (0,4168 ml; densidad 1,48; 1.05 equiv) Después de ~2 hrs la mezcla de reacción se diluyó con cloruro de metileno y se lavó con HCl 6N seguido de $NaHCO_3$ saturado La fase orgánica se

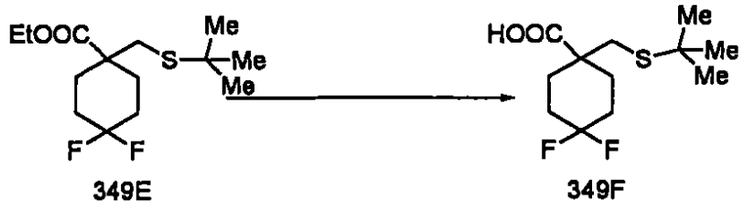
904

secó sobre Na_2SO_4 y se evaporó hasta sequedad *al vacío* para dar el mesilato **349D** (1,5447 g) como aceite amarillo claro.



349D **349E**

Una suspensión agitada de NaH (0,4114 g, dispersión al 60% en aceite mineral; 2 equiv.) en DMF seca se trató con ter-butil tiol (1,16 ml; densidad 0,8; 2 equiv.) con enfriamiento en baño de hielo. La mezcla de reacción se agitó durante 30 minutos, tras lo cual se agregó el mesilato (**349D**; 1,5447 g; 1 equiv.) en DMF seca (8+2 ml). El baño de hielo se retiró y la mezcla de reacción se agitó a temperatura ambiente hasta la mañana siguiente. La mezcla de reacción se acidificó con HCl 6N y se extrajo con acetato de etilo El extracto de acetato de etilo se secó sobre Na_2SO_4 y se evaporó hasta sequedad *al vacío* para dar 349D bruto (2,87 g), que se cromatografió sobre SiO_2 (60 g). La columna se eluyó con acetato de etilo al 3%, dando en algunas de las fracciones **349E** puro (1,38 g) como un aceite incoloro.



349E **349F**

Una solución del etil éster (**349E**; 1,38 g; 0,00468 mol.) en etanol (16 ml) y agua (4,13 ml) se trató con perlas de KOH (2,63 g; 10 equiv.). La solución resultante se reflujó durante 7 h y luego se dejó enfriar hasta la temperatura ambiente hasta la mañana siguiente. Se evaporó el etanol *al vacío* y el residuo se repartió entre CH_2Cl_2/agua, se acidificó con HCl 6N hasta pH 1. Se separó la fase orgánica y la fase acuosa se extrajo tres veces con CH_2Cl_2. La fase orgánica

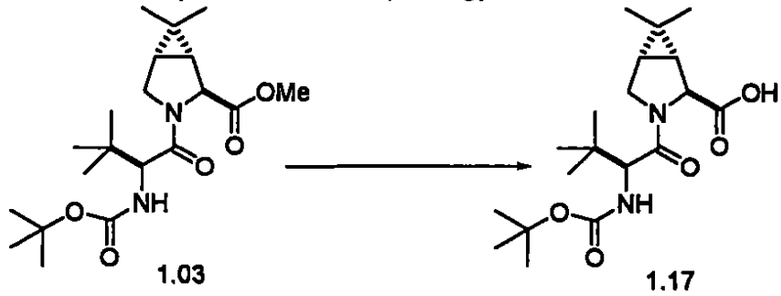
905

cpmbinada se secó sobre Na_2SO_4 y se evaporó hasta sequedad *al vacío* para dar **349F** (1.19 g) como un sólido blancuzco, p.f. 93-95°C.



349F 349G

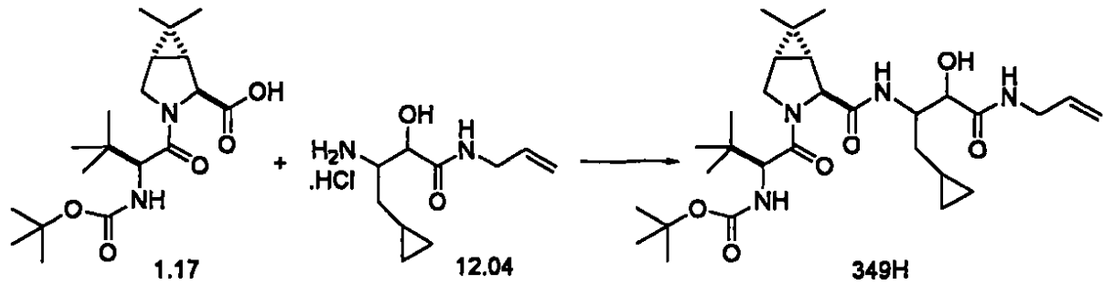
Se agregó la oxona (8,24 g; 3 equiv) disuelta en agua (31 ml) a una solución agitada del sulfuro (**349F**; 1,19 g; 1 equiv.) en metanol (31 ml) a 0°C (temp. del baño). La reacción se agitó desde 0°C hasta T.A. durante el fin de semana. Los solventes se evaporaron al vacío y el residuo se repartió entre CH_2Cl_2/agua. La fase orgánica se separó y la fase acuosa se extrajo dos veces con CH_2Cl_2. La fase orgánica combinada se secó sobre Na_2SO_4 y se evaporó hasta sequedad *al vacío* para dar **349G** (1,29 g) como sólido cristalino, p.f. 212°C.



1.03 1.17

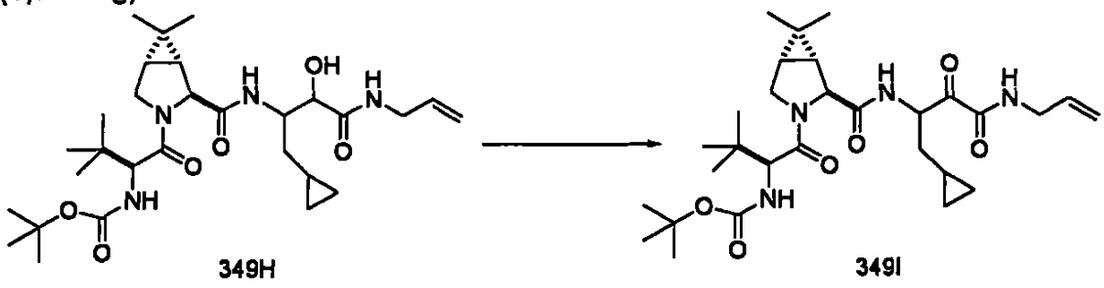
A una solución fría (baño de hielo) del éster (**1.03**; 4,56 g, 0,0119 mol.) en dioxano (18,23 ml) se agregó con agitación LiOH 1,0 N (18,23 ml). La mezcla de reacción se agitó durante 2 hrs La TLC indicó algún material de partida remanente, de modo que se agregó 2+1 ml de LiOH 1,0 N y se agitó hasta la mañana siguiente. La reacción se verificó completa mediante TLC. Se agregó HCl 6N para acidificar la mezcla de reacción hasta pH 1 y se agregó acetato de etilo (150 ml). Después de agitar, la fase acetato de etilo se separó y la fase acuosa se extrajo con acetato de etilo. La fase acetato de etilo combinada se lavó una vez con salmuera, se secó (Na_2SO_4) y se evaporó hasta sequedad *al vacío* para dar **1.17** como sólido amorfo (4,7805 g; solvente ocluído).

906



1.17 12.04 349H

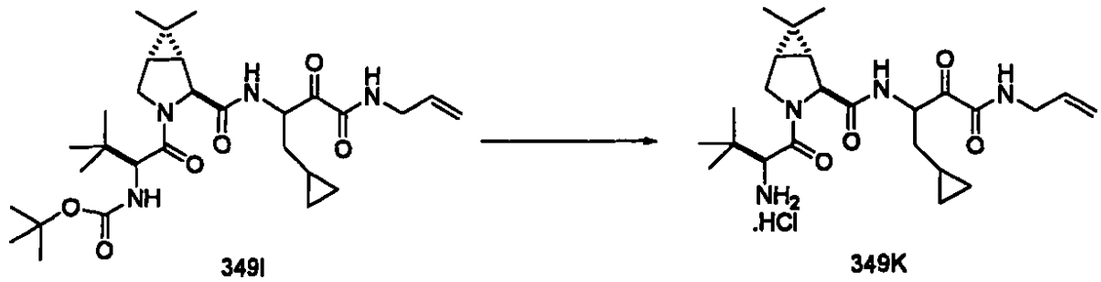
A una solución a –20°C solución del ácido **1.17** (0,7079 g; 0,00192 mol.) y la sal de amina (**12.04**; 0,5231 g; 1,16 equiv.) en CH_2Cl_2 (10 ml) se agregó HATU (0,77 g; 1.05 equiv.) seguido de diisopropiletilamina (0,8913 g; 1,2 ml; 3,59 equiv.) La mezcla de reacción se agitó a –20°C durante ~16 hrs. Luego se diluyó con EtOAc (~150 ml) y se lavó sucesivamente con $NaHCO_3$ sat , ácido cítrico 10% y se secó sobre Na_2SO_4 La evaporación del solvente *al vacío* dio un sólido amorfo que se cromatografió sobre SiO_2 (42 g). La elución de la columna con 50%-60% de EtOAc en n-hexano dio en algunas de las fracciones **349H** puro (0,7835 g)



349H 349I

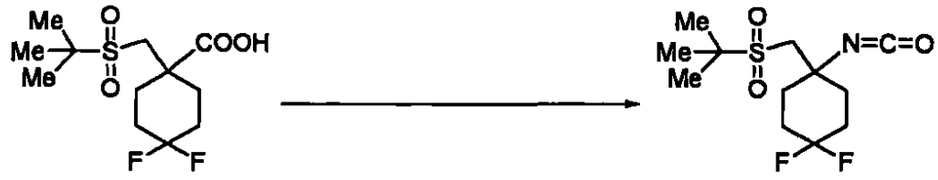
Una solución de la hidroxiamida **349H** (0,7835 g, 0,00142 mol.) en cloruro de metileno seco (32 ml) se trató con agitación y enfriamiento (baño de hielo) con reactivo Dess-Martin (1,5134 g; 2,5 equiv.) Se retiró el baño de hielo y la mezcla de reacción se dejó agitar a temperatura ambiente durante 2,5 hrs. Se agregó $Na_2S_2O_3$ saturado (32 ml) para destruir el exceso de oxidante y se continuó la agitación hasta que la solución turbia se convirtió en un sistema transparente bifásico. La mezcla de reacción se diluyó luego con CH_2Cl_2 (~100 ml), la fase orgánica se separó y se lavó una vez con $NaHCO_3$ sat , agua luego se secó La evaporación hasta sequedad *al vacío* dio **349I** (0,7466 g) como sólido amorfo.

907



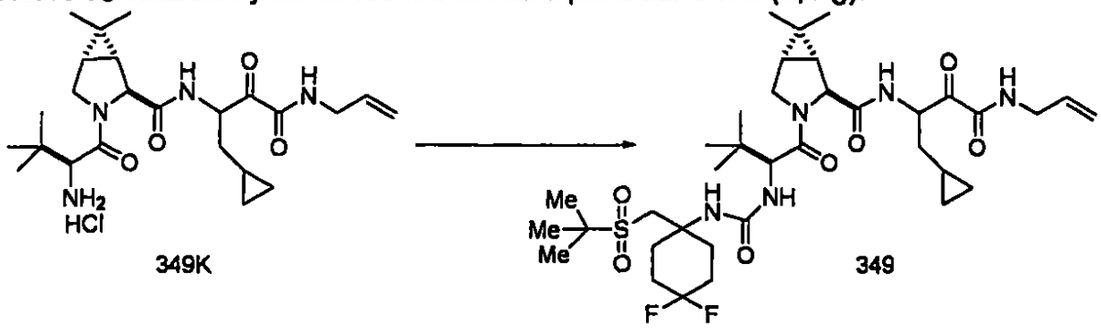
3491 349K

El ter-butilcarbamato **3491** (0,7466 g) se trató con HCl 4M/dioxano (20 ml) y se dejó en un matraz con tapón durante 45 minutos. La mayor parte del dioxano se evaporó al vacío y el residuo se evaporó con n-hexano dos veces; el residuo remanente se trituró con éter, dejando **349K** (0,6341 g) como sólido de libre fluencia.



349G 349J

A una solución en tolueno (7,5 ml) del ácido **349G** (0,1 g; 0,0003351 mol.) se agregó Et_3N (0,0467 ml, 46,7 µl; 1 equiv.) seguida de difenilofosforil azida (0,072, 72 µl; 1equiv). La mezcla de reacción se reflujó durante 1 h. Después de enrriar, se trató con acetato de etilo (~50 ml), la fase orgánica se lavó con $NaHCO_3$ saturado y se concentró *al vacío* para dar **349J** (0,1 g).



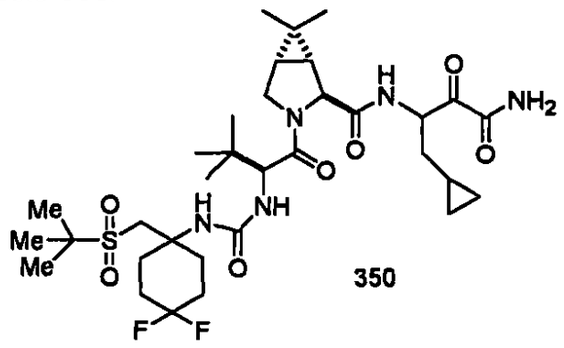
349K 349

A una suspensión agitada del clorhidrato de amina **349K** (0,1 g; 0,000207 mol.) en cloruro de metileno (5 ml) se agregó diisopropiletilamina (0,135 g; 5 equiv.). Luego de 1 minuto se agregó el isocianato **349J** (0,1 g, 0,0003385 mol.)

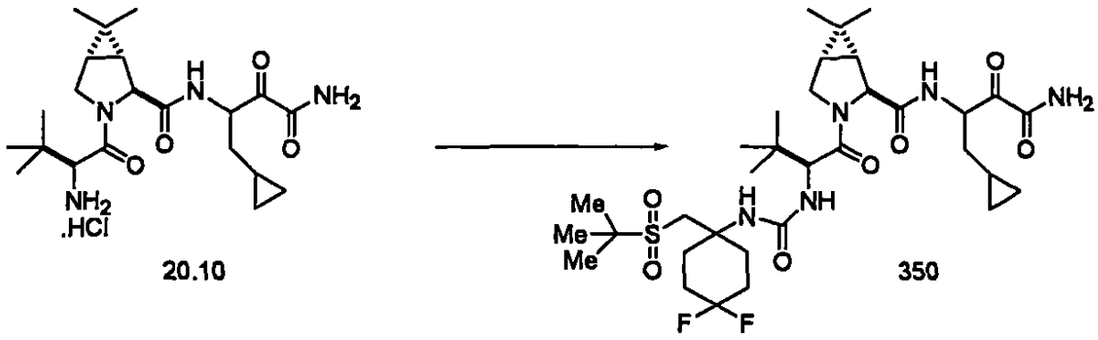
908

La mezcla de reacción se agitó a temperatura ambiente durante 2 hrs. Luego se diluyó con EtOAc y se lavó con HCl 1N, $NaHCO_3$ sat., se secó sobre Na_2SO_4 y finalmente se evaporó hasta sequedad al vacío para dar un sólido amorfo. Se sometió a TLC preparativa en placas de gel de sílice usando acetona 40% en n-hexano como eluyente. La banda positiva al UV se extrajo con acetona 60% en cloruro de metileno para dar **349** (0,122 g) como sólido amorfo.

Síntesis del Compuesto 350.



350



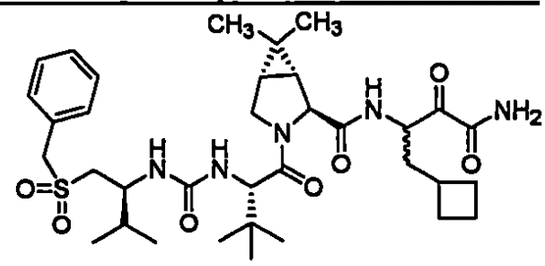
20.10 350

A una suspensión agitada del clorhidrato de amina **20.10** (0,0966 g; 0,000223 mol.) en cloruro de metileno (5 ml) se agregó diisopropiletilamina (0,144 g, 5 equiv.) Después de 1 minuto se agregó el isocianato **349H** (0,1 g, 0,0003385 mol.). La mezcla de reacción se agitó a temperatura ambiente durante 2 hrs Luego se diluyó con EtOAc (~100 ml), luego se lavó con HCl 1N, $NaHCO_3$ sat , se secó sobre Na_2SO_4 y finalmente se evaporó hasta sequedad *al vacío* para dar un sólido blanco amorfo (0,1731 g). Se sometió a TLC preparativa sobre gel de sílice usando acetona 40% en n-hexano como eluyente. La banda positiva al UV se

909

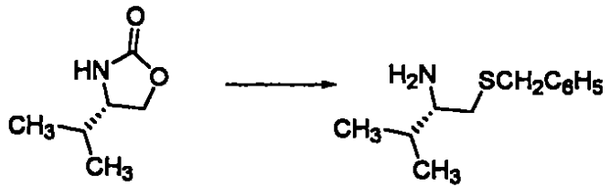
extrajo con acetona 60% en cloruro de metileno para dar **350** (0,0671 g) como sólido amorfo.

Ejemplo 145. Preparación del compuesto de fórmula I45



145

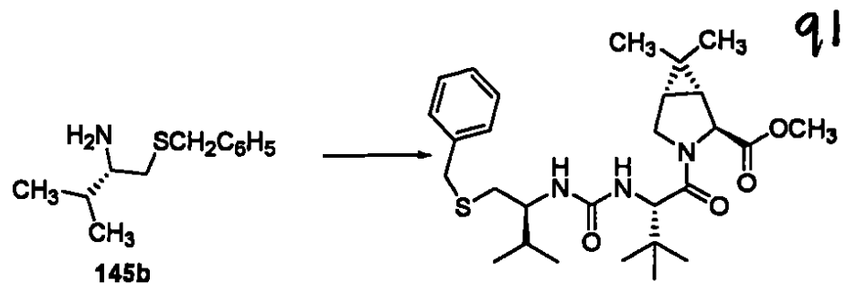
Paso 1



145a **145b**

Se trató 1-propanol con sodio metálico (361 mg, 15,7 mmol) y se agitó a temperatura ambiente durante 1 h. Luego de la completa disolución del sodio, se agregó benciltiol (2,74 ml, 23,2 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 0,5 h. Se agregó (S)-4-isopropil-oxazolidinona (Aldrich, 1g, 7,74 mmol) y la mezcla de reacción se calentó a reflujo durante 16 h. La mezcla de reacción se concentró al vacío y la mezcla bruta mixture se diluyó con agua fría y se extrajo con éter (3x150 ml). Las fases orgánicas combinadas se secaron, se filtraron y concentraron al vacío para producir la amina **145b.** Se convirtió en el clorhidrato con HCl 4 M y se secó en alto vacío para producir **145b.HCl** (1,9 g).

Paso 2

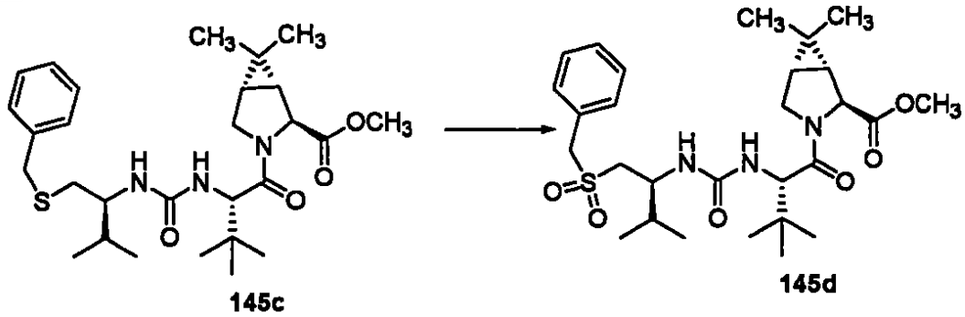


145b **145c**

Una solución de **145b.HCl** (1 g, 4,07 mmol) en CH_2Cl_2 (50 ml) y $NaHCO_3$ sat. (70 ml) a 0°C se trató con fosgeno (15% en tolueno, 10 ml) y se agitó a 0°C durante 3 h. La mezcla de reacción se vertió en una ampolla de decantación y se separó la fase orgánica. La fase orgánica se lavó con $NaHCO_3$ frío, salmuera y se secó ($MgSO_4$). Se concentró y usó tal cual en el próximo paso.

El clorhidrato de amina (**1.04**; 865 mg, 2,7 mmol) se disolvió en CH_2Cl_2/DMF 1:1 y se enfrió hasta 0°C. La mezcla se trató con $(C_2H_5)_3N$ (682 mg, 6,75 mmol) e isocianate preparado como anteriormente (950 mg, 4,07 mmol) y se agitó a temperatura ambiente hasta la mañana siguiente. El solvente se evaporó y el residuo se disolvió en EtOAc. La fase orgánica se lavó con HCl acuoso, NaHCO3 ac , salmuera. La mezcla de reacción se secó, se filtró y se concentró al vacío. El residuo se purificó por cromatografía (SiO_2, EtOAc/Hexanos 1:3) para producir **145c** (880 mg).

Paso 3



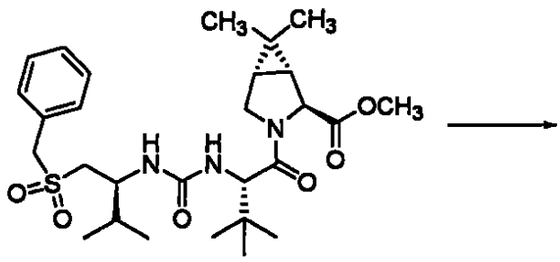
145c **145d**

Una solución de **145c** (500 mg, 0,9 mmol) en 1,2 dicloroetano (10 ml) se trató con MCPBA (70%, 500 mg,) a 0°C y se diluyó con éter y solución ac. de $Na_2S_2O_3$ La fase orgánica se separó y se lavó extensamente con $NaHCO_3$

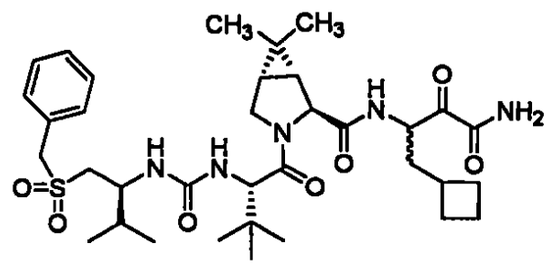
911

acuoso saturado y salmuera La mezcla de reacción se secó (MgSO4), se filtró, se concentró al vacío y se purificó por cromatografía (SiO_2, EtOAc/Hexano 2:3) para producir **145d** (530 mg). MS (ESI) 550 [$(M+1)^+$, 100], 381 (95), 353 (20).

Paso 4



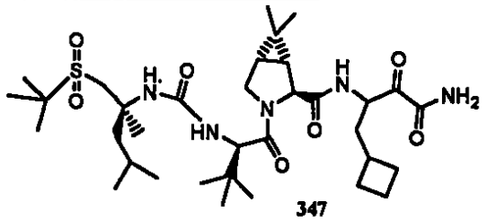
145d



145

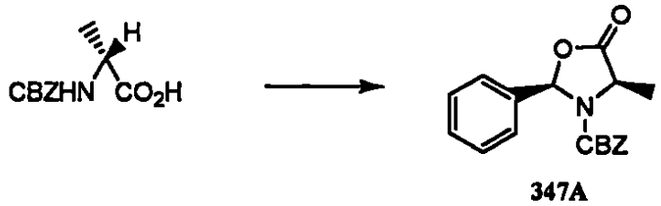
La conversión de **145d** a **145** fue idéntica al procedimiento descripto en la conversión de **284B** a **284D** y **108D** a **108** MS (ESI) 690 [$(M+1)^+$, 100), 381 (30).

Preparación del Intermediario de Fórmula 347:



347

Paso1·



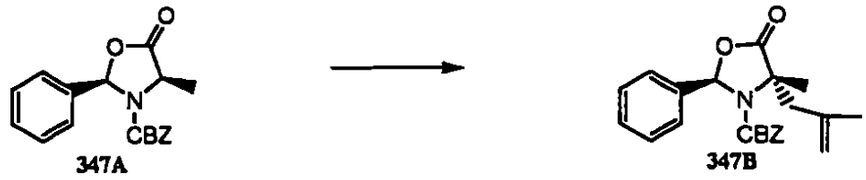
347A

Se agregó dimetil benzaldehído acetal (10.0 ml, 67,2 mmol) a una solución fría de CBZ-*D*-alanina (15,0 g, 67,2 mmol) en Et_2O (180 ml), seguido de $BF_3.Et_2O$ (50,6 ml, 403,2 mmol) a lo largo de 15 min. La mezcla de reacción se agitó a

912

-20°C durante 4 días y se desactivó por agregado de $NaHCO_3$ saturado (350.0 ml) enfriado con hielo. La fase orgánica se diluyó con Et_2O (500 ml), se separó, se lavó con $NaHCO_3$ (solución acuosa al 5%), salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El producto bruto se recristalizó usando Et_2O/Hexano para producir **347A** (13,6 g, 65%).

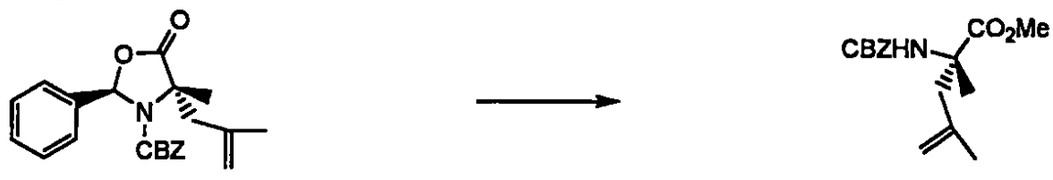
Paso 2



347A **347B**

Se agregó THF(48,0 ml) a un matraz secado a la llama y se enfrió a -35°C. Se agregó al mismo KHDMS(solución 0,5 M en PhMe, 42,0 ml, 21 mmol), seguido del agregado gota a gota de una mezcla de **347A** (6,22g, 20 0 mol) y 3-bromo-2-propeno (2,02 ml, 20 mmol), manteniendo la temperatura interna entre -30 y -35°C. La mezcla de reacción se agitó a -35°C durante 2 h, luego se dejó entibiar a lo largo de 2,5 h, se desactivó por agregado de $NaHCO_3$ saturado enfriado con hielo (400,0 ml). La fase orgánica se diluyó con Et_2O (600 ml), se separó, se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El producto bruto se purificó sobre SiO_2 usando CH_2Cl_2 para producir **347B** (14,2 g, 90%).

Paso 3

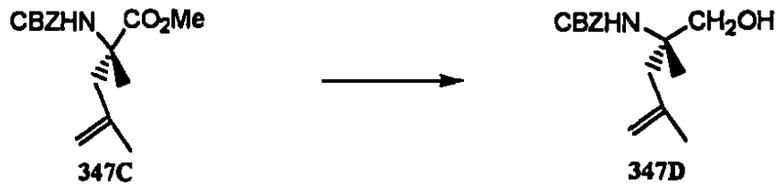


347B **347C**

A una solución de **347B** (10,7 g, 29,4 mmol) en MeOH (200 ml) se agregó LiOH (4N, 15 ml) y se agitó a temperatura ambiente durante 30 min, se diluyó con H_2O (500 ml), se extrajo con EtOAc (4 x 400 ml), se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El producto bruto se purificó sobre SiO_2 usando CH_2Cl_2 para producir **347C** (8,65 g, 88%).

913

Paso 4



347C 347D

A una solución enfriada en hielo de **347C** (8,56 g, 29,4 mmol) en EtOH (100 ml) se agregó $LiBH_4$ (960 mg, 44,1 mmol) y se agitó a temperatura ambiente durante 12h, se le agregó otra porción de $LiBH_4$ (960 mg) a 5°C y se agitó a temperatura ambiente durante 4h, se diluyó con H_2O (100 ml) y MeOH (100 ml), se evaporó hasta sequedad, se disolvió en H_2O (100 ml), se extrajo con EtOAc (500 ml), se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El producto bruto se purificó sobre SiO_2 usando EtOAc (1-8%) en CH_2Cl_2 para producir **347D** (4,7 g, 60%).

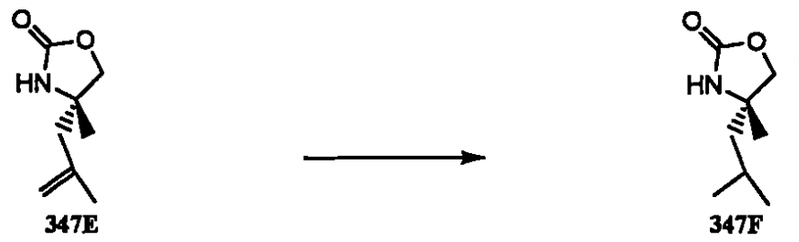
Paso 5



347D 347E

Se agregó *t*-BuOK (1M en THF, 3,85 ml) a una solución fría (-5°C) de **347D** (4,06 g, 15,4 mmol) en THF (20 ml) y se agitó a esa temperature durante 2h. La mezcla de reacción se concentró, se redisolvió en EtOAc (250 ml) y NaOH (2N, 50 ml). La fase orgánica se diluyó con EtOAc (600 ml), se separó, se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El producto bruto se purificó sobre SiO_2 usando CH_2Cl_2 10% en EtOAc para producir **347E** (1,4 g).

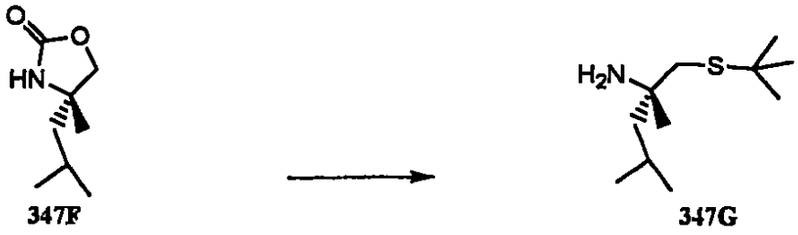
Paso 6



347E 347F

Se disolvió **347E** (1,37 g, 8,82 mmol) en EtOH (25 ml) y se le agregó Pd-C (10% en peso, 275,0 mg). La mezcla de reacción se agitó bajo atmósfera de hidrógeno durante 12h, se filtró, se concentró y purificó sobre SiO_2 usando CH_2Cl_2 10% en EtOAc para producir **347F** (1,04g, 75%).

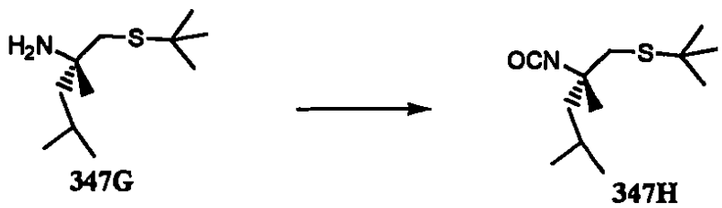
Paso 7



347F 347G

Se disolvió **347F** (2,58 g, 16,4 mmol) en PrOH (40 ml) y se le agregó NaSBu-*t* (10,2 g, 82 mmol). La mezcla de reacción se reflujó durante 136 h, se enfrió, se evaporó y redisolvió en EtOAc, se lavó con H_2O y la fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró El producto bruto se purificó sobre SiO_2 usando acetona 30% en CH_2Cl_2 para producir **347G** (0,6 g, 19%) y **347F** (1,1g).

Paso 8



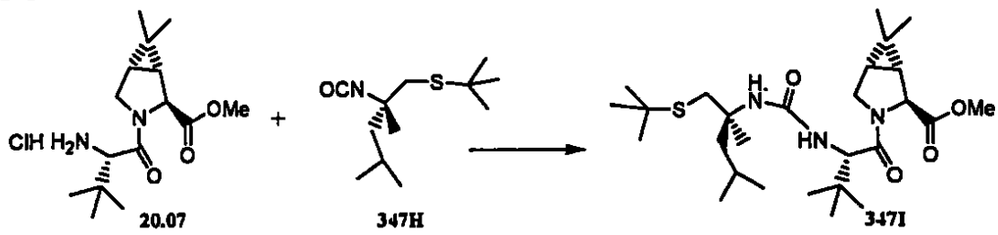
347G 347H

Se agregó $NaHCO_3$ saturado a una solución enfriada en hielo de **347G** (0,6 g, 3,0 mmol) en CH_2Cl_2 (30 ml). La mezcla de reacción se agitó vigorosamente durante 10 min. y se le agregó $COCl_2$ (solución 1,85 M en PhMe, 4,51 ml) y se continuó agitando a temperatura ambiente durante 1h La fase orgánica se secó

915

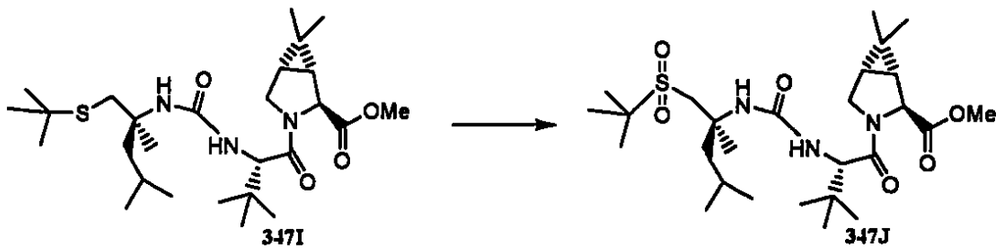
sobre MgSO4, se filtró y se concentró a la mitad del volumen para producir **347H** como solución en CH_2Cl_2.

Paso 9



A una solución fría (0°C) de **347H** (685 mg, 3,0 mmol) en DMF (10,0 ml) se agregó **20.07** (1,05 g, 3,34 mmol), seguida de DIPEA (1,45 ml, 8,35 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1,2 h, se diluyó con acetato de etilo, se lavó con ácido cítrico 3%, salmuera, se secó sobre $MgSO_4$, se filtró, se concentró y purificó sobre SiO_2 usando acetona/CH_2Cl_2 (1:9) para producir **347I** (1,57g).

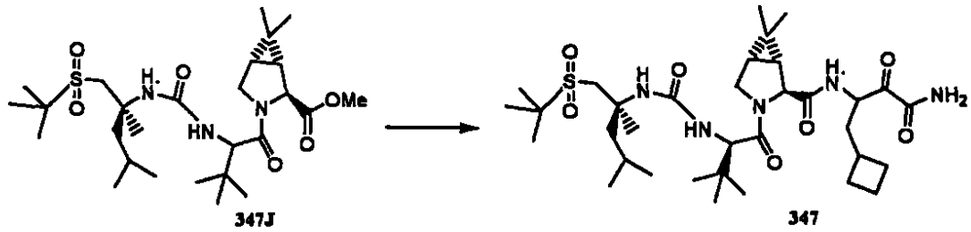
Paso 10



A una solución fría (0°C) de **347I** (1,5 g, 3,34 mmol) en CH_2Cl_2 (100,0 ml) se agregó ***m*-CPBA** (2,51g, 10,02 mmol). La mezcla de reacción se entibió hasta la temperatura ambiente a lo largo de 12 h, se diluyó con CH_2Cl_2 (300,0 ml), se lavó con salmuera, se secó sobre $MgSO_4$, se filtró, se concentró y purificó sobre SiO_2 usando acetona/CH_2Cl_2 (1·9) para producir **347J** (1,57g).

Paso 11

916



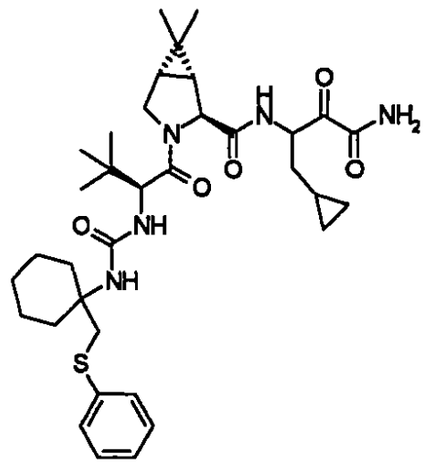
347J 347

La conversión de **347J** a **347** fue similar en procedimiento a los descriptos en la conversión de **284B** a **284D** y **108D** a **108** MS(LCMS) calc. 681,94, experimental (MH^+) 683,2.

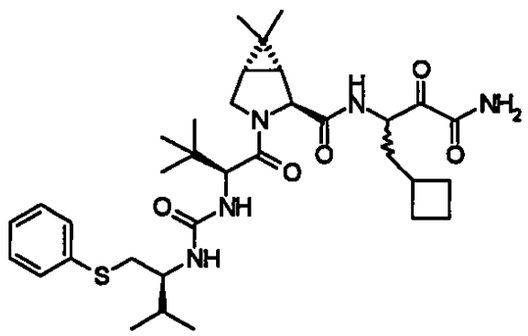
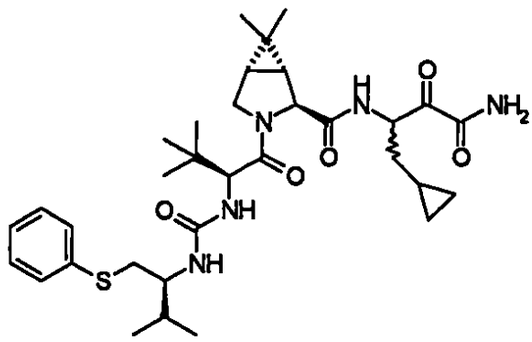
La **Tabla 3** enumera algunos de los compuestos de la invención y sus rangos de actividad inhibitoria de la serina proteasa del VHC, determinados por el ensayo descripto más adelante. La actividad se muestra como rangos de Ki* (nanoMolar), que son: A = <75 nM; B = 75 - 250 nM; y C = >250 nM.

Tabla 3

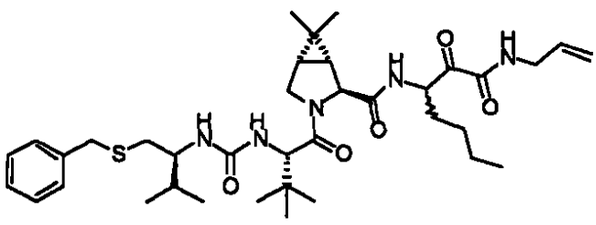
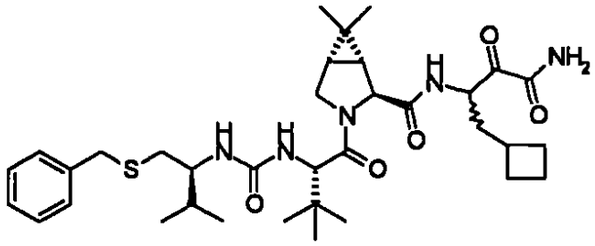
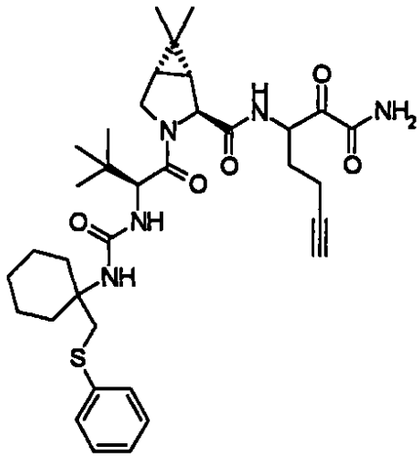
Compuestos con Grupo Sulfuro

Ej. de Prep.	COMPUESTO	Datos de Espect. de masa selecc.	Rango de Ki*
	[Los rangos de Ki* son: A = <75 nM; B = 75 - 250 nM; C = >250 nM]		
102		CLEM; MH^+, 654,1	A

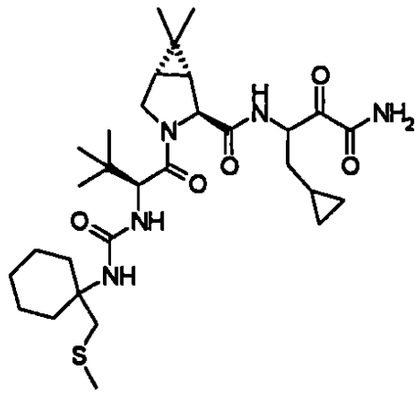
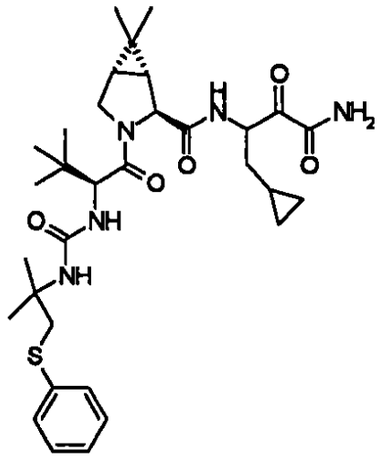
917

Ej. de Prep	COMPUESTO	Datos de Espect. de masa selecc.	Rango de Ki*
103			B
104			A

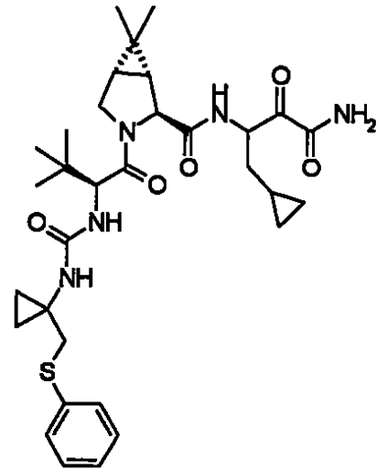
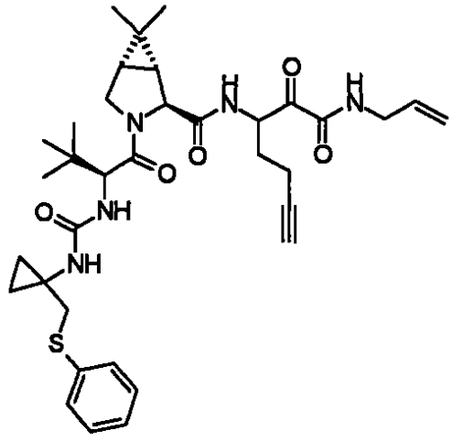
918

Ej. de Prep	COMPUESTO	Datos de Espect. de masa selecc.	Rango de Ki*
105			C
106			B
107		FABMS, $(M+TG)^+$, 760,5. TG= tioglicerol	A

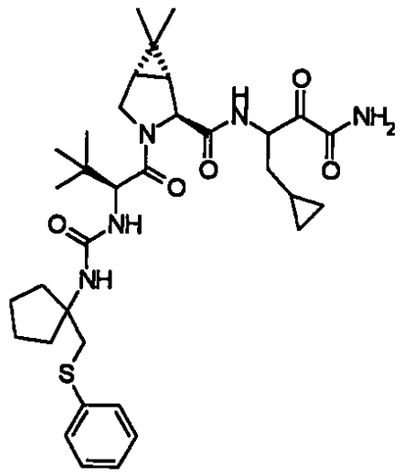
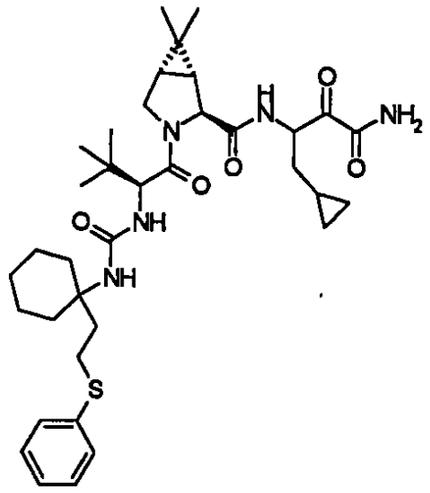
919

Ej. de Prep.	COMPUESTO	Datos de Espect. de masa selecc.	Rango de Ki*
108			A
109			A

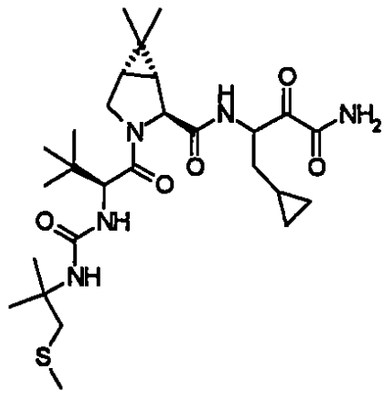
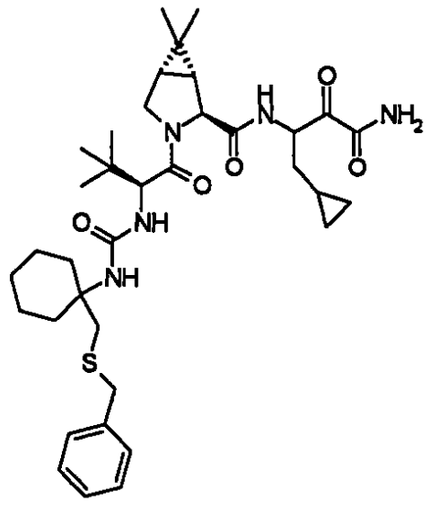
920

Ej. de Prep	COMPUESTO	Datos de Espect. de masa selecc	Rango de Ki*
110			A
111		FABMS (MH)+, 650,3.	B

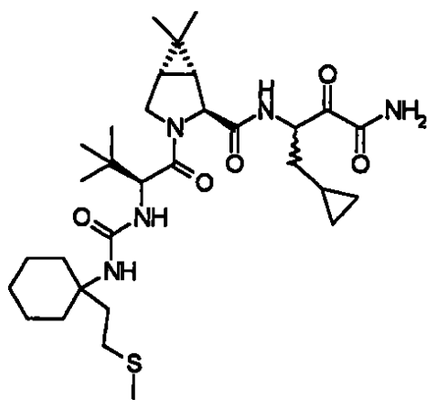
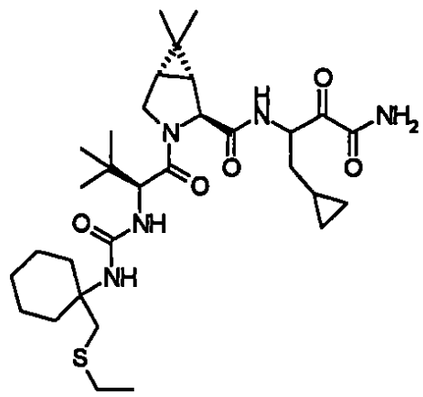
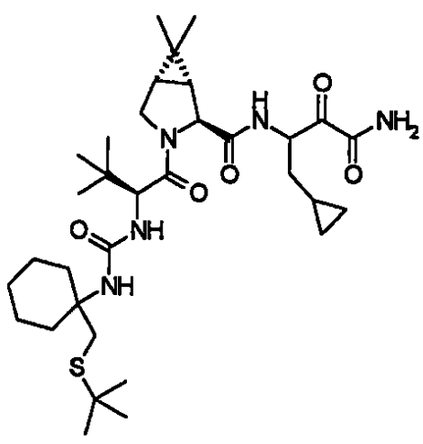
921

Ej. de Prep	COMPUESTO	Datos de Espect. de masa selecc.	Rango de Ki*
112			A
113		FABMS: $(MH)^+$,668,3	A

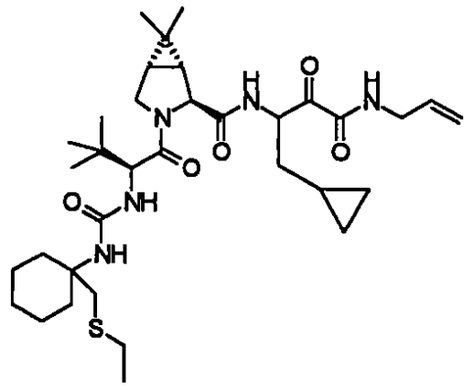
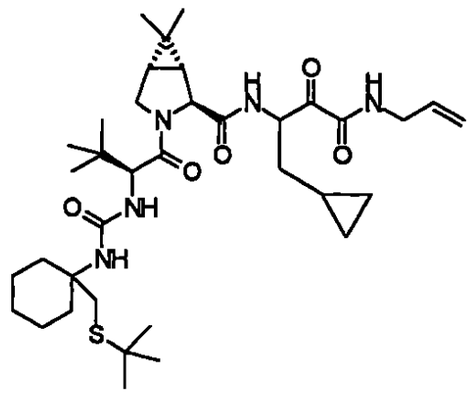
922

Ej. de Prep.	COMPUESTO	Datos de Espect de masa selecc.	Rango de Ki*
114			A
115			A

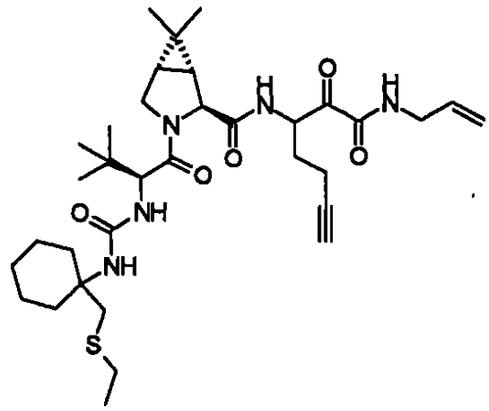
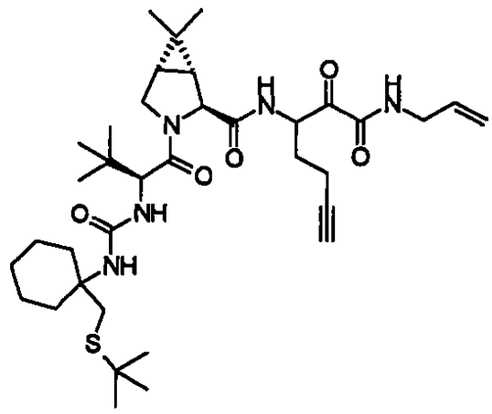
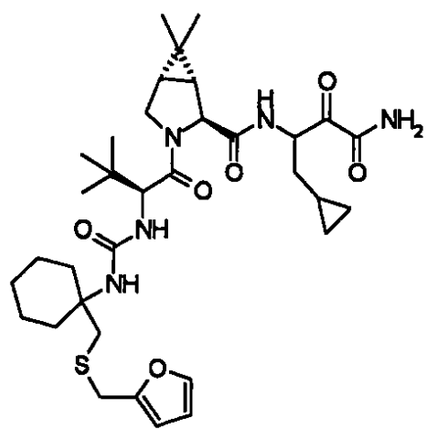
923

Ej. de Prep.	COMPUESTO	Datos de Espect. de masa selecc.	Rango de Ki*
116		CLEM; MH+, 606,1.	A
117			A
118			A

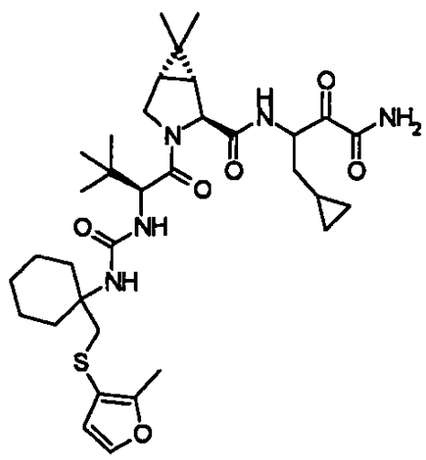
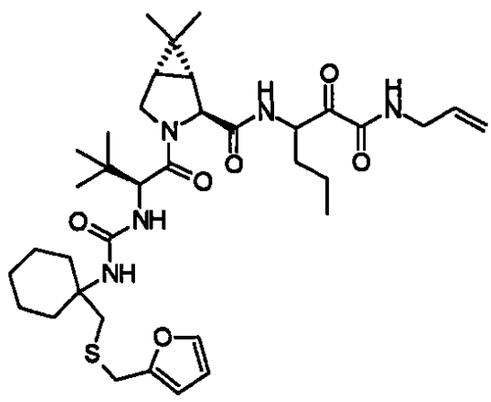
929

Ej. de Prep.	COMPUESTO	Datos de Espect. de masa selecc.	Rango de Ki*
119			B
120			C

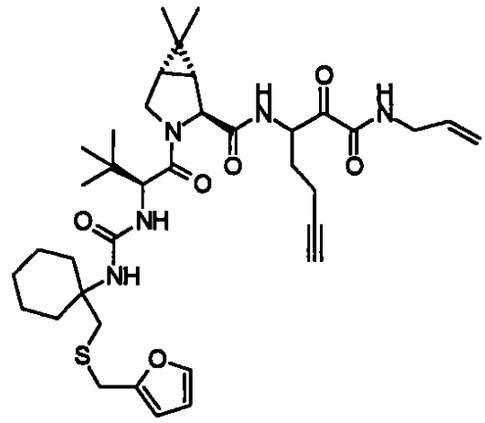
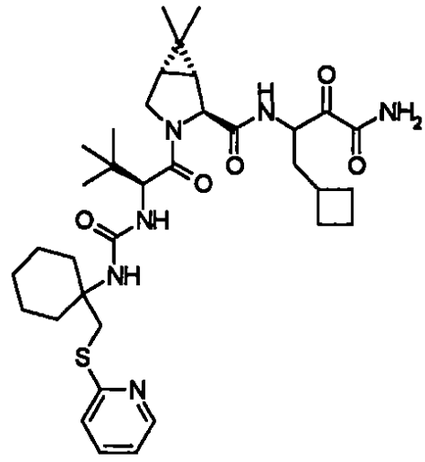
925

Ej. de Prep.	COMPUESTO	Datos de Espect. de masa selecc.	Rango de Ki*
121		FABMS; MH^+, 644,2	A
122		FABMS; MH^+, 672,5.	A
123			A

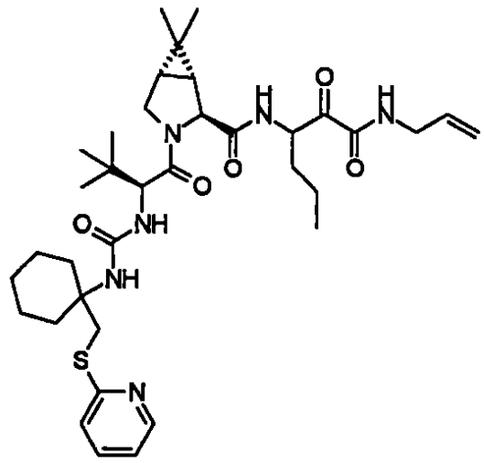
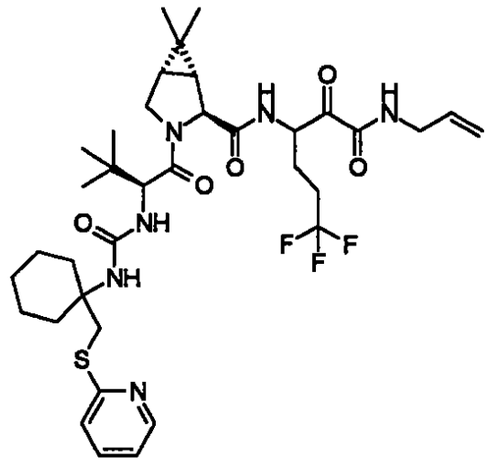
926

Ej. de Prep.	COMPUESTO	Datos de Espect. de masa selecc.	Rango de Ki*
124			B
125			B

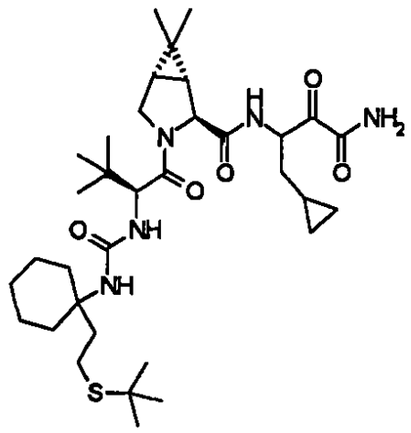
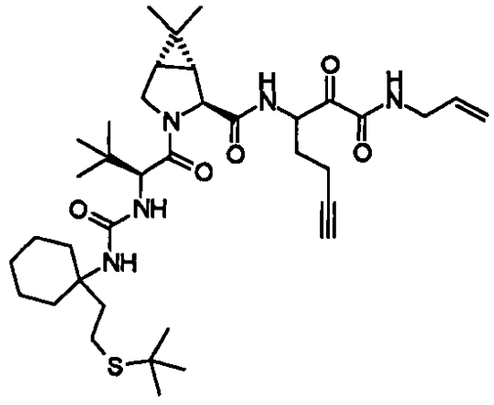
927

Ej. de Prep.	COMPUESTO	Datos de Espect. de masa selecc.	Rango de Ki*
126			A
127			A

928

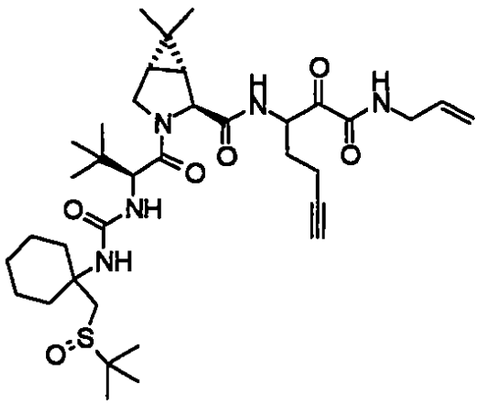
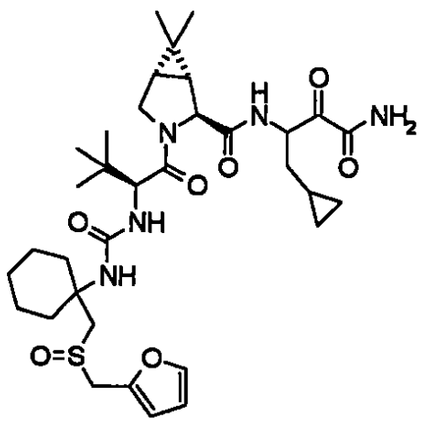
Ej. de Prep	COMPUESTO	Datos de Espect de masa selecc.	Rango de Ki*
128			B
129			C

929

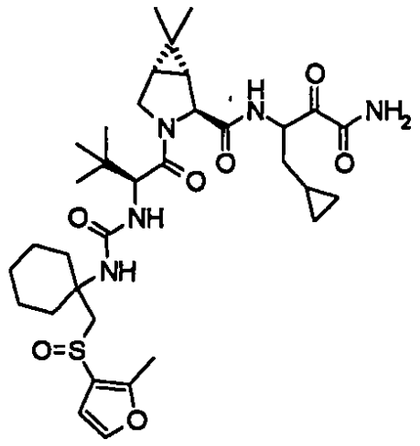
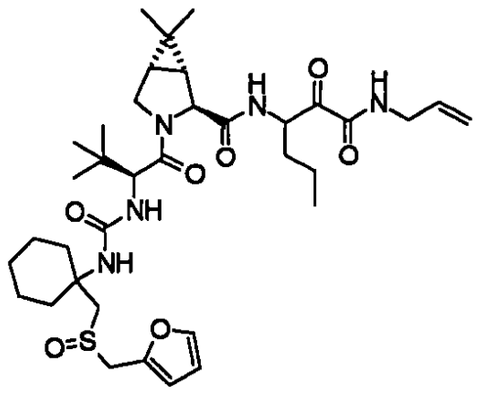
Ej. de Prep	COMPUESTO	Datos de Espect. de masa selecc.	Rango de K_i*
130			B
131			B

930

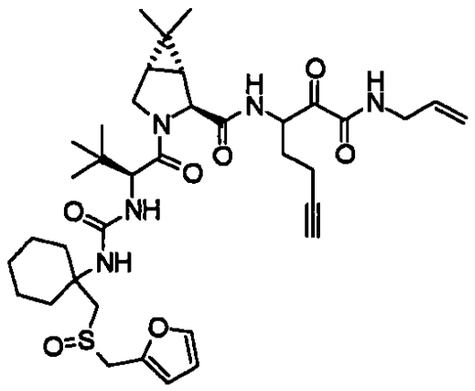
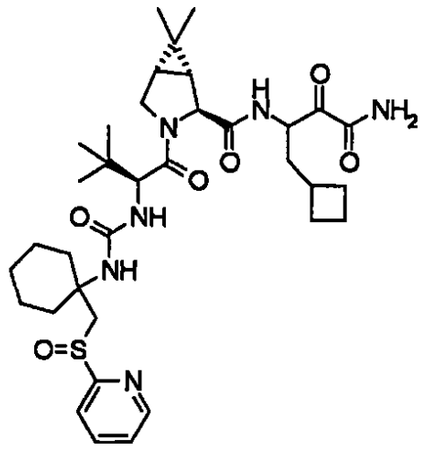
Compuestos Sulfóxido

Ej. de Prep	COMPUESTO	Datos Espectrales de Masa Selec.	Rango de Ki*
	[Los rangos de Ki* son A = <75 nM; B = 75 - 250 nM; C = >250 nM]		
132		FABMS; MH^+, 688,5	A
133			A

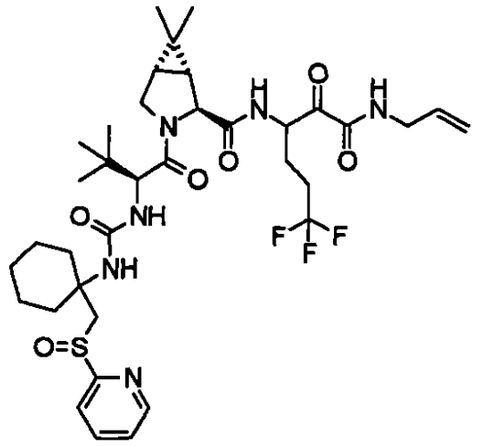
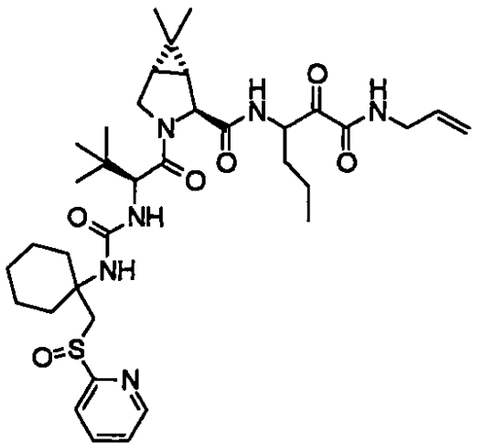
931

Ej. de Prep	COMPUESTO	Datos Espectrales de Masa Selec.	Rango de Ki*
134			A
135			A

932

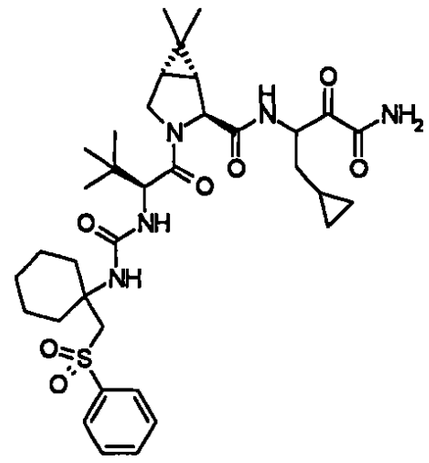
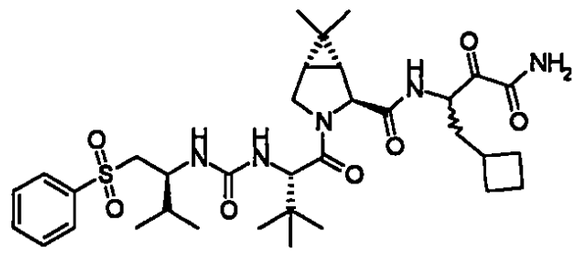
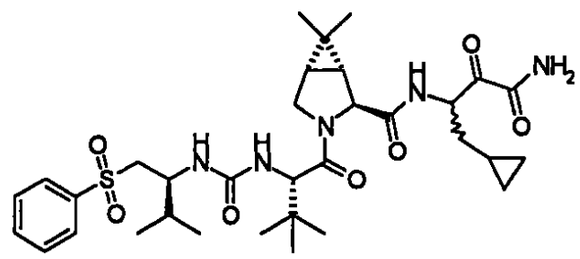
Ej. de Prep	COMPUESTO	Datos Espectrales de Masa Selec	Rango de Ki*
136			A
137			A

933

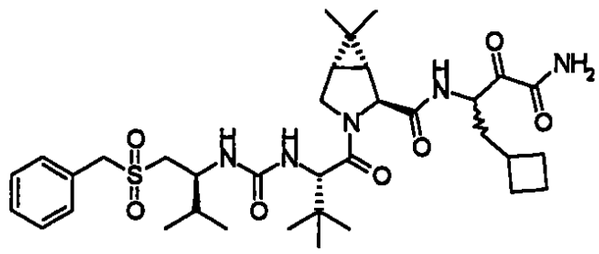
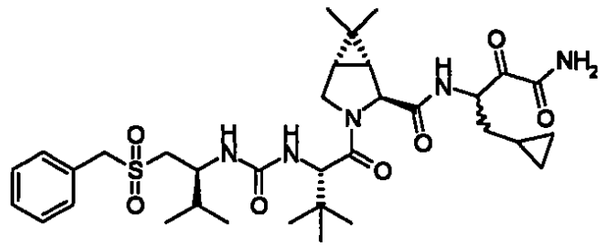
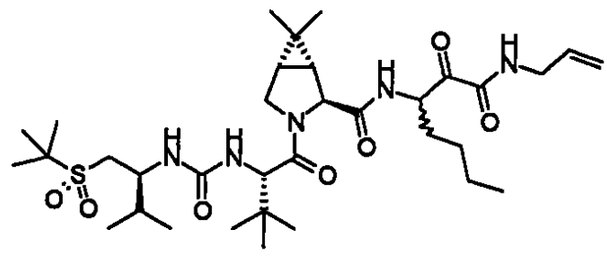
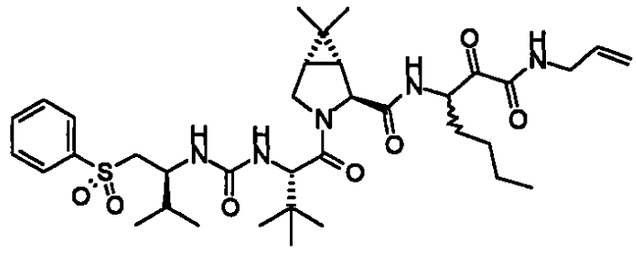
Ej. de Prep	COMPUESTO	Datos Espectrales de Masa Selec.	Rango de Ki*
138			B
139			A

934

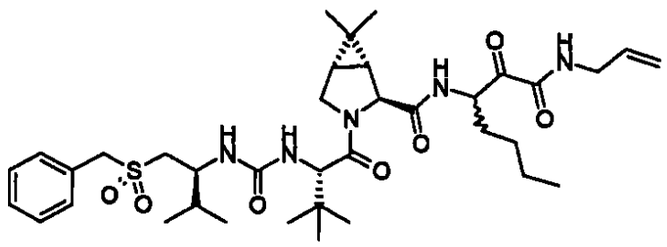
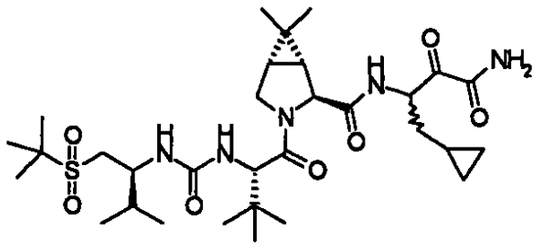
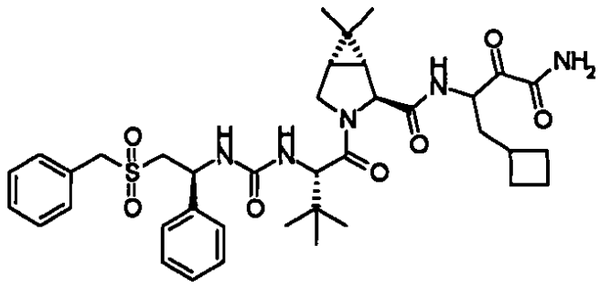
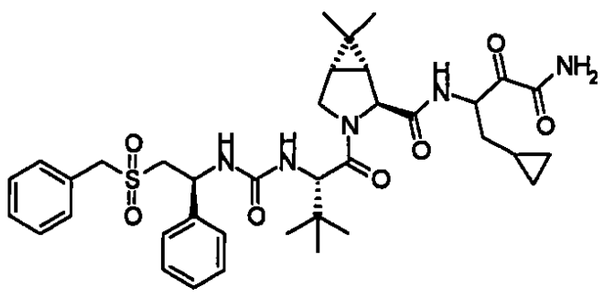
Compuestos Sulfona

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
	[Los rangos de Ki* son: A = <75 nM; B = 75 - 250 nM, C = >250 nM]		
142		CLEM. MH^+, 686,1.	A
143			A
144			A

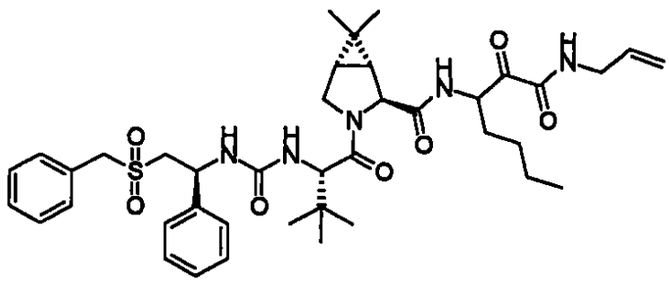
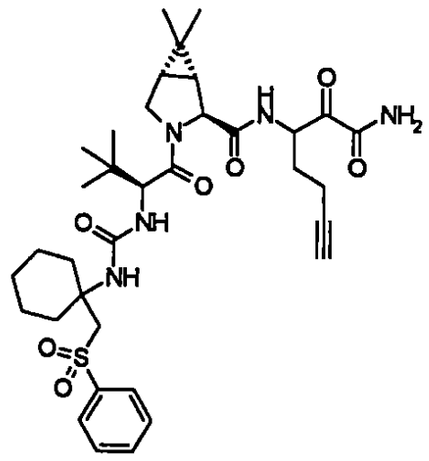
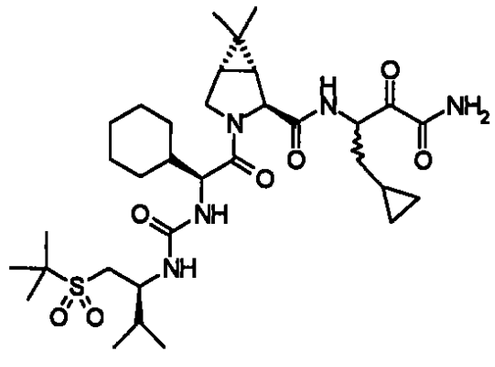
935

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
145			A
146			A
147			B
148			B

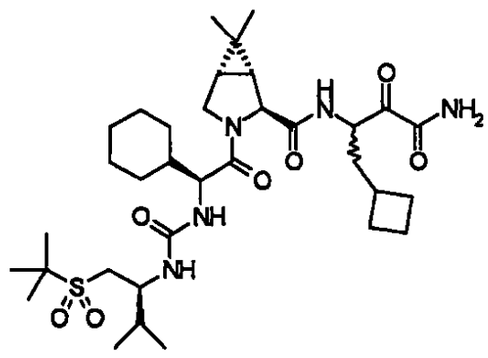
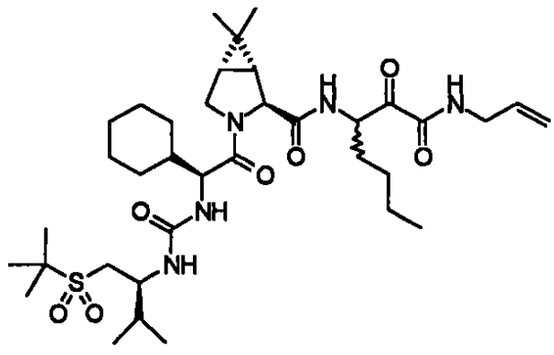
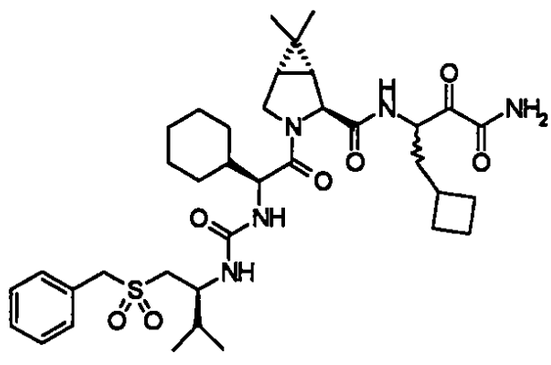
936

Ej de Prep.	COMPUESTO	Datos de espec. de masa. selec	rango de Ki*
149			B
150			A
151			B
152			B

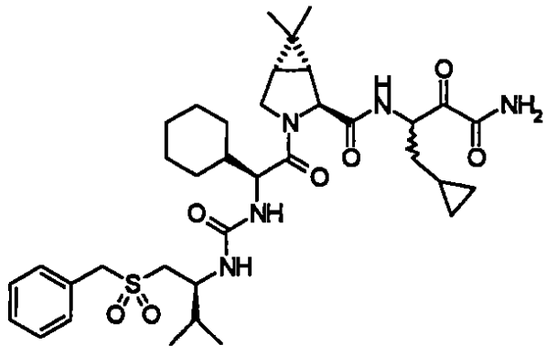
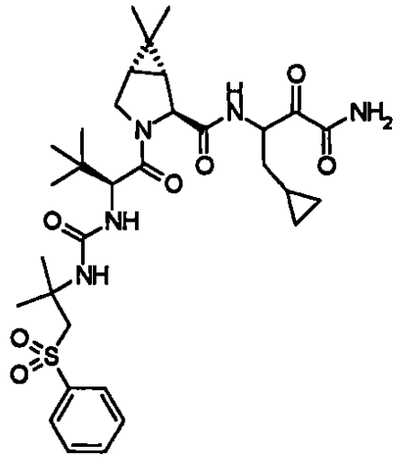
937

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
153			C
154		FABMS, MH^+, 684,2	A
155			A

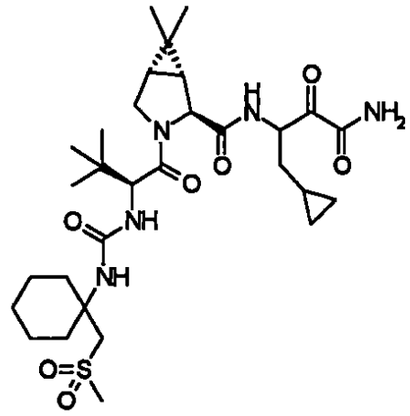
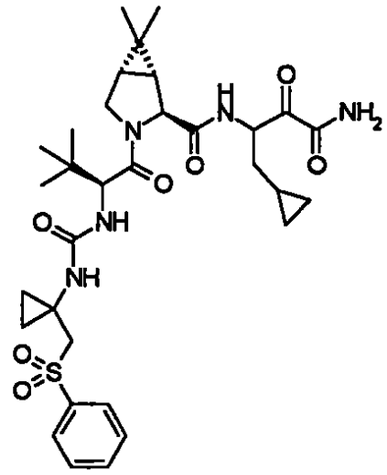
938

Ej. de Prep	COMPUESTO	Datos de espec de masa. selec.	rango de Ki*
156			A
157			A
158			A

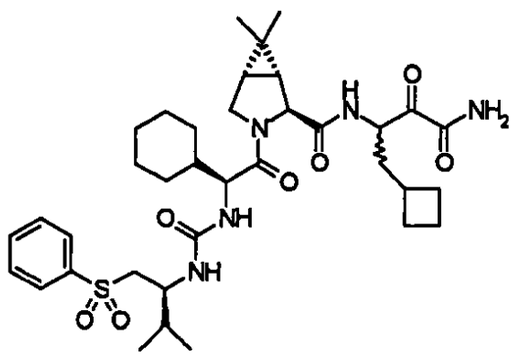
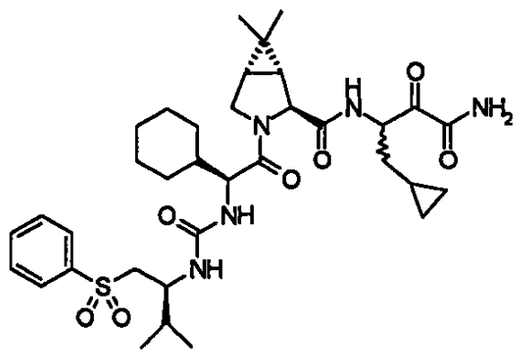
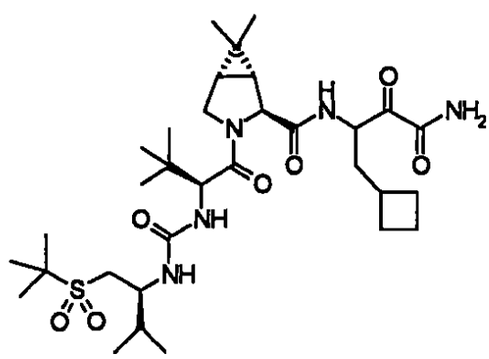
939

Ej de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
159			A
160			A

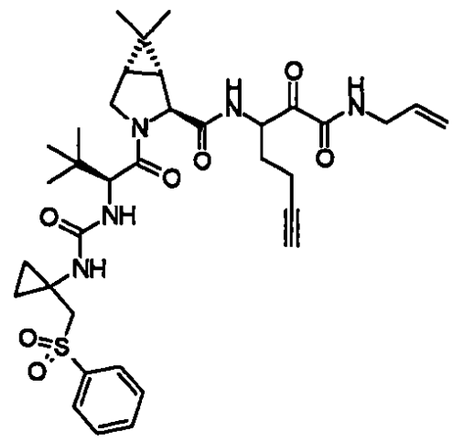
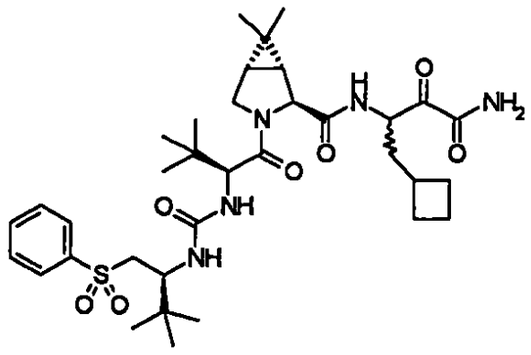
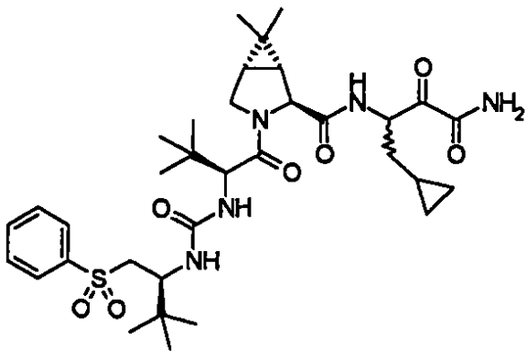
940

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
161			A
162			A

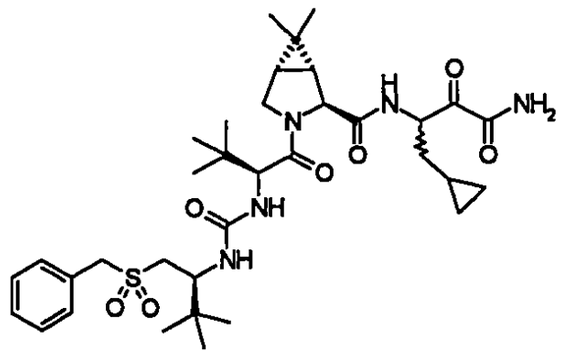
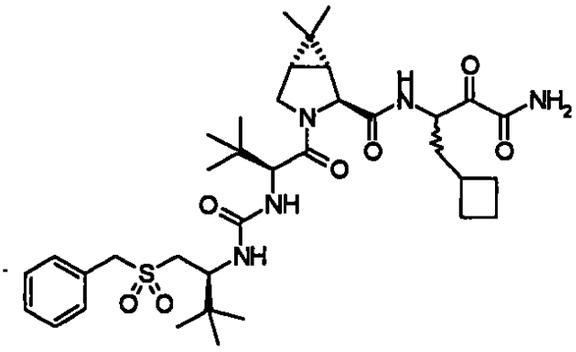
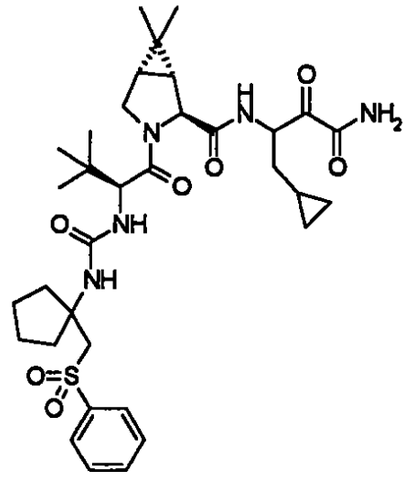
941

Ej. de Prep	COMPUESTO	Datos de espec. de masa. selec	rango de Ki*
163			A
164			A
165			A

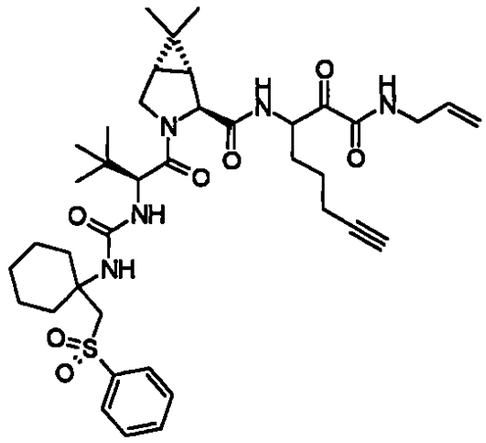
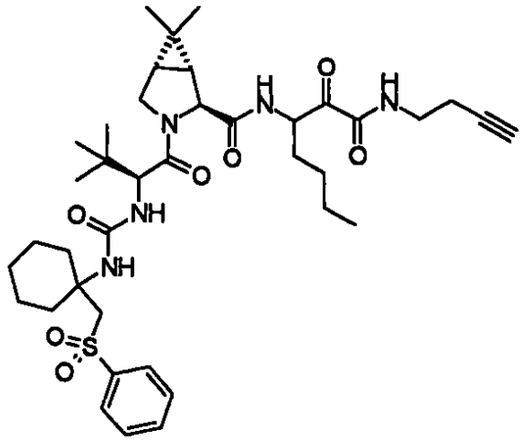
942

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
166		FABMS; MH^+, 682,3.	B
167			A
168			A

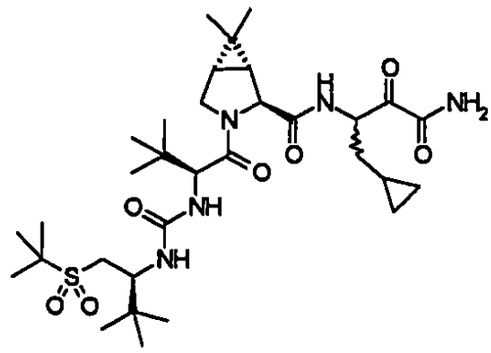
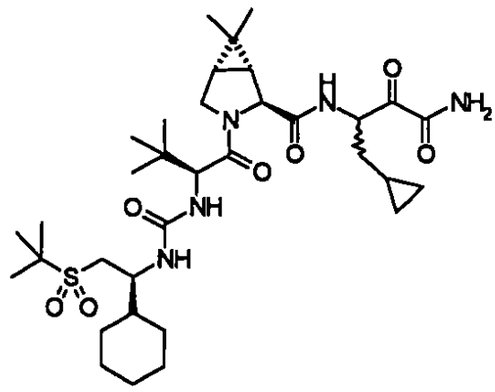
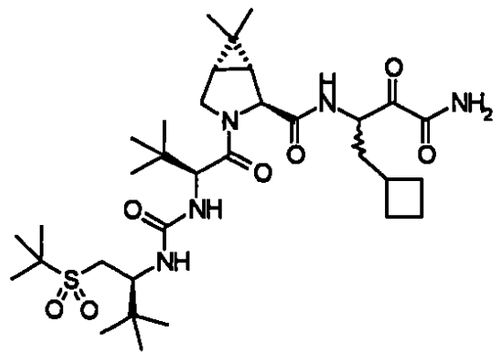
943

Ej. de Prep.	COMPUESTO	Datos de espec. de masa selec.	rango de Ki*
169			A
170			A
171			A

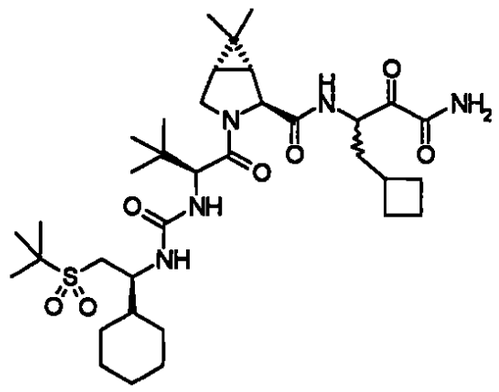
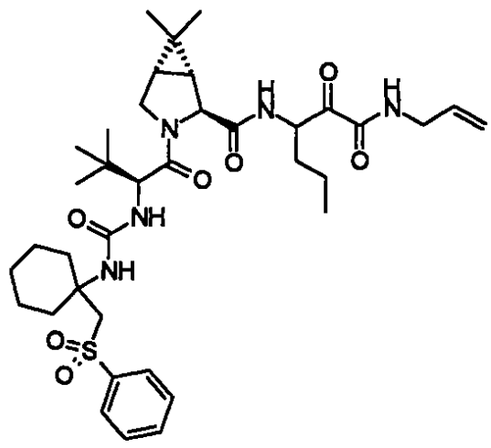
944

Ej. de Prep.	COMPUESTO	Datos de espec de masa. selec.	rango de Ki*
172		CLEM; MH^+, 738,2	B
173			A

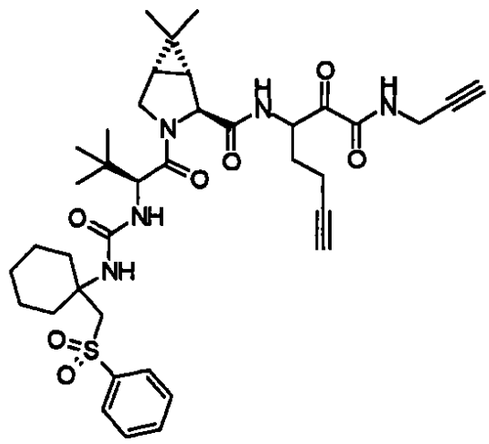
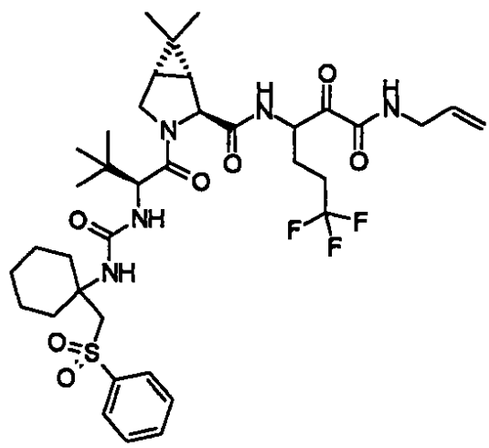
945

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
174			A
175			A
176			A

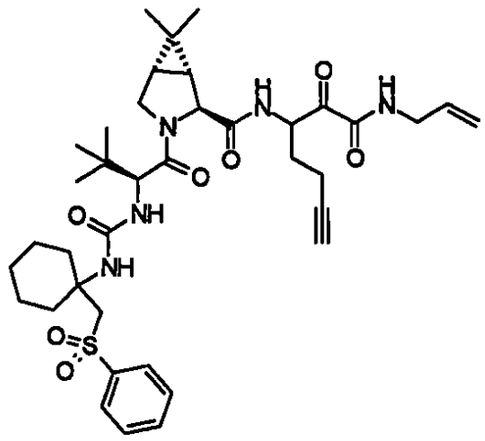
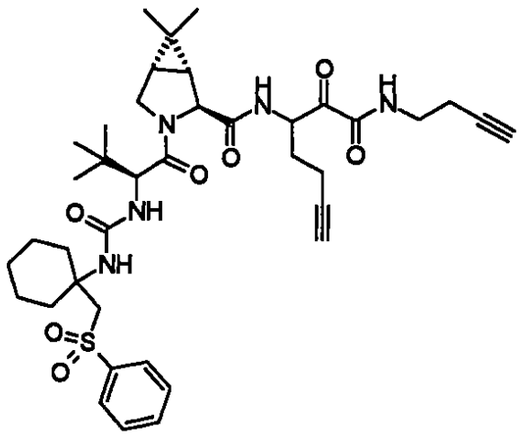
946

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
177			A
178		CLEM; MH^+, 714,1.	A

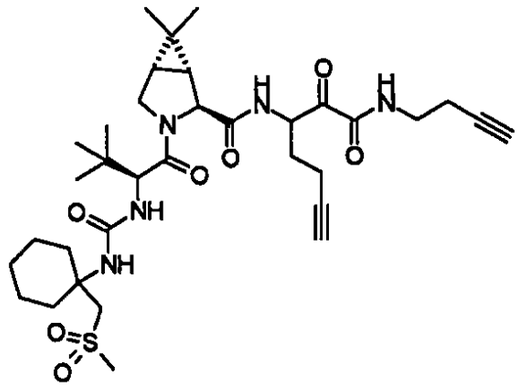
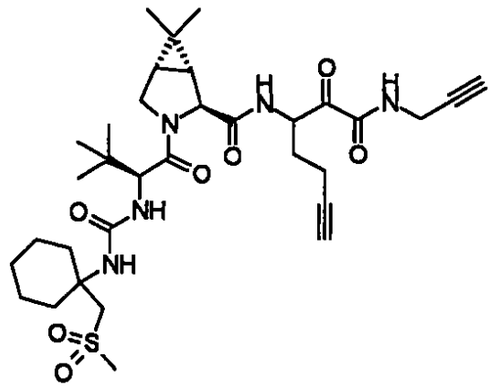
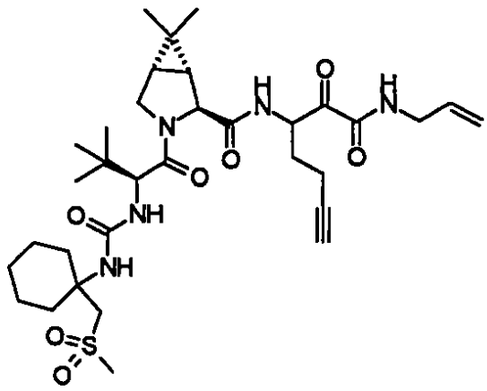
947

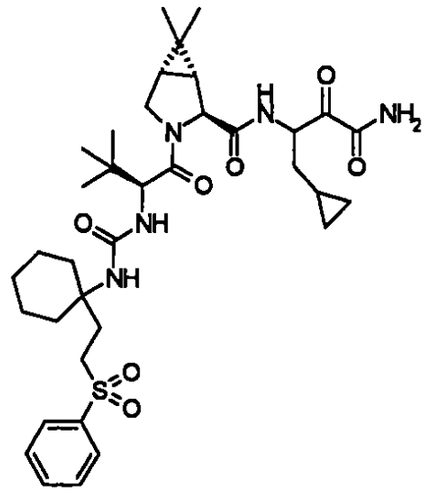
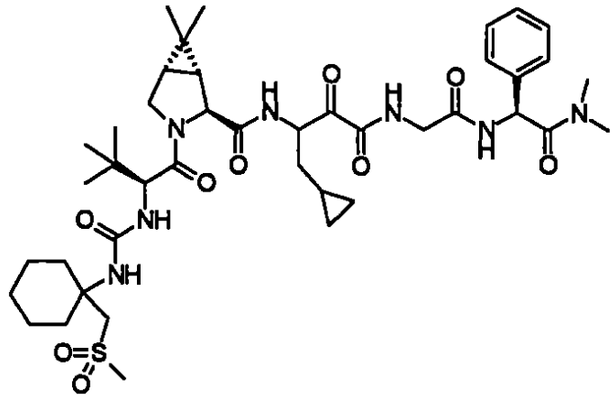
Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
179			A
180			A

948

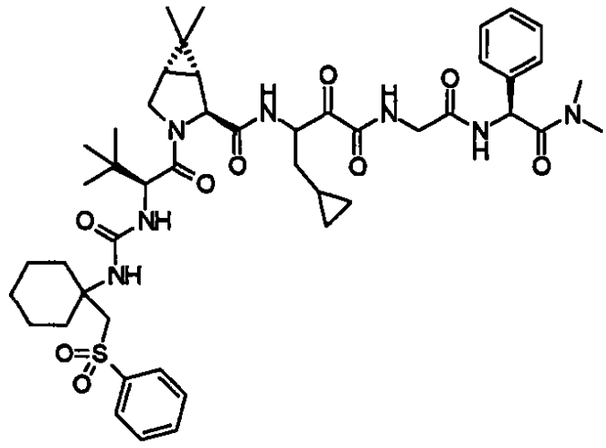
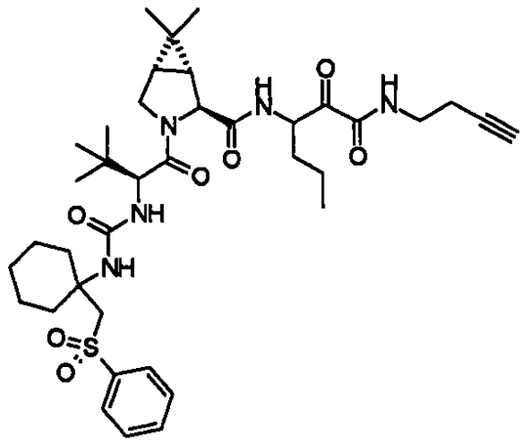
Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
181		FABMS; MH^+, 724,6.	A
182		FABMS; MH^+, 736,5.	A

949

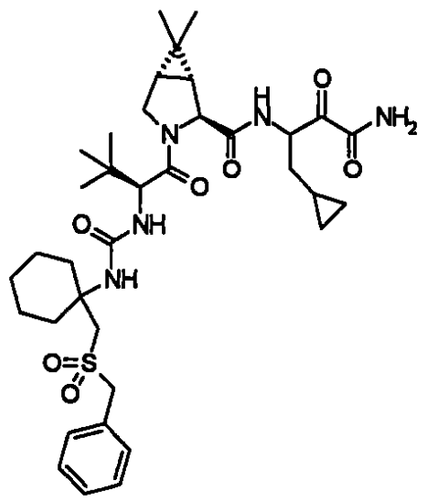
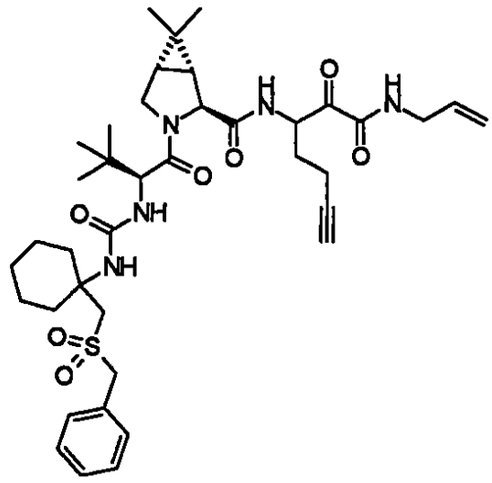
Ej. de Prep.	COMPUESTO	Datos de espec. de masa selec.	rango de Ki*
183			A
184			A
185		FABMS; MH^+, 662,5.	A

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
186		FABMS; MH^+, 700,3.	A
187			A

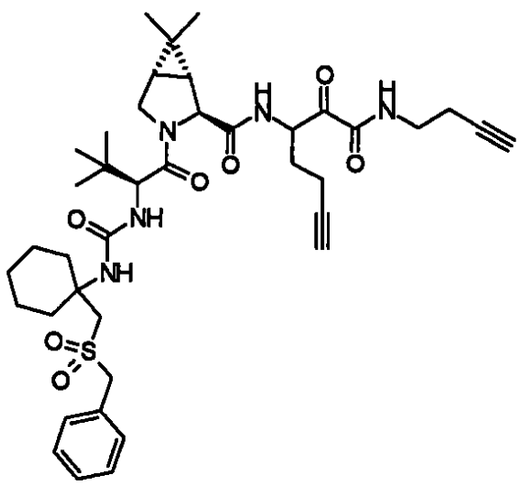
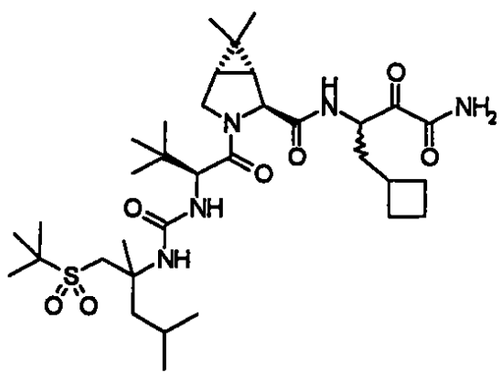
951

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
188			A
189			A

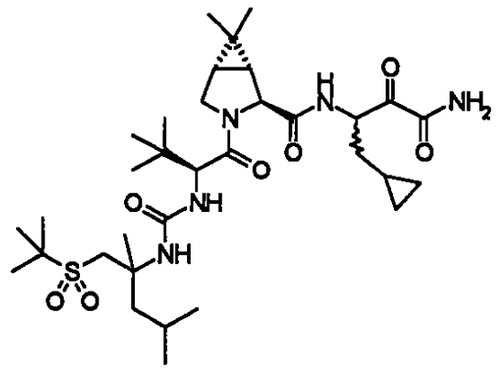
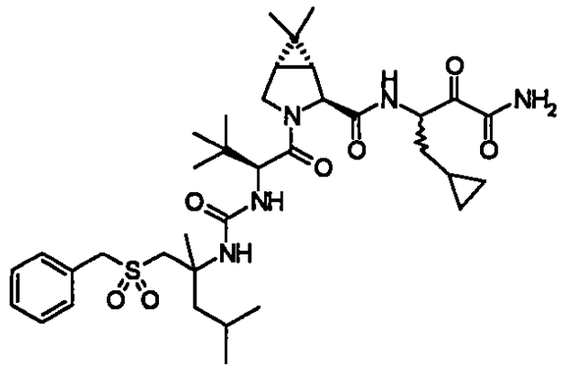
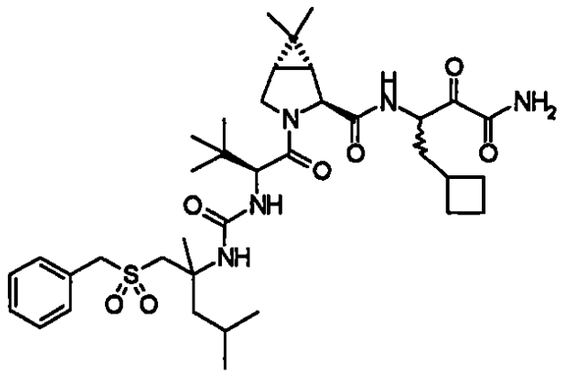
952

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
190			A
191		FABMS, MH^+, 738,4.	A

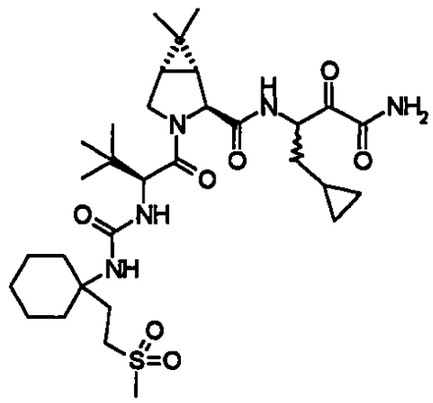
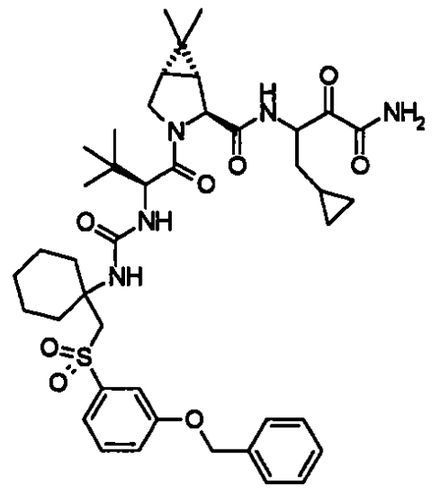
953

Ej. de Prep.	COMPUESTO	Datos de espec. de masa selec	rango de Ki*
192			A
193			A

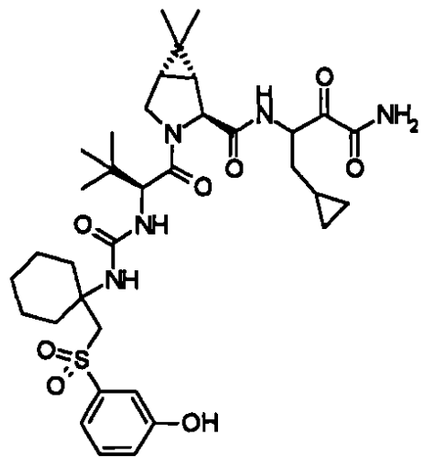
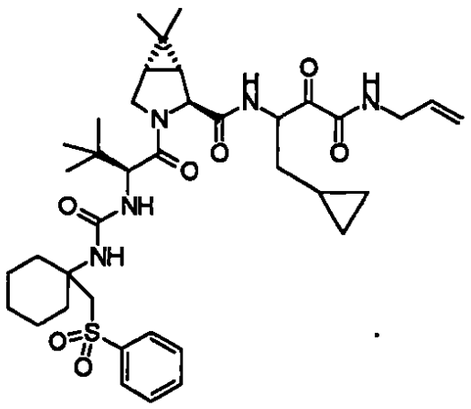
954

Ej. de Prep	COMPUESTO	Datos de espec. de masa selec.	rango de Ki*
194			A
195			A
196			A

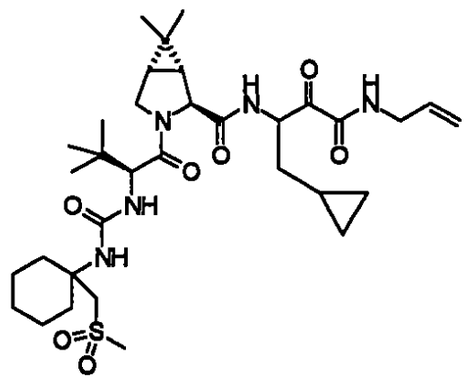
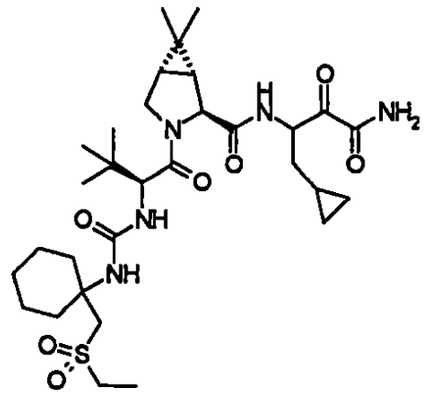
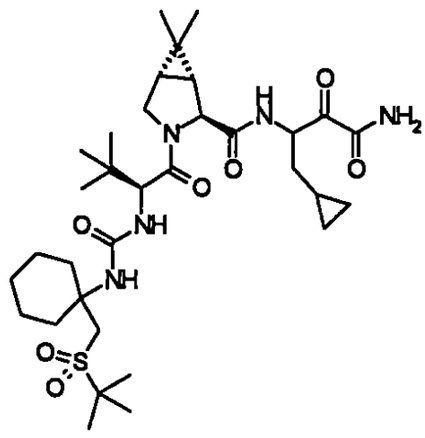
955

Ej. de Prep.	COMPUESTO	Datos de espec de masa selec.	rango de Ki*
197		FABMS; MH^+, 638,3.	A
198		CLEM; MH^+, 792,2.	A

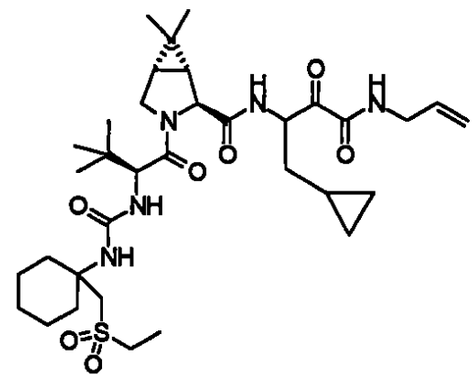
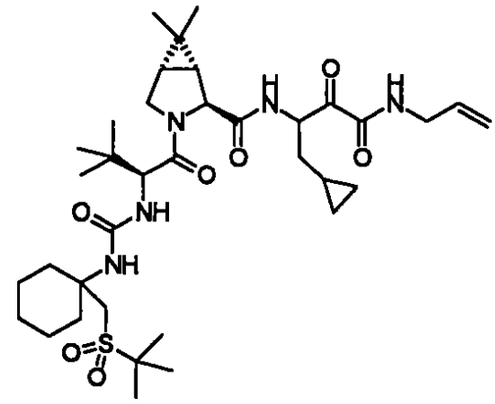
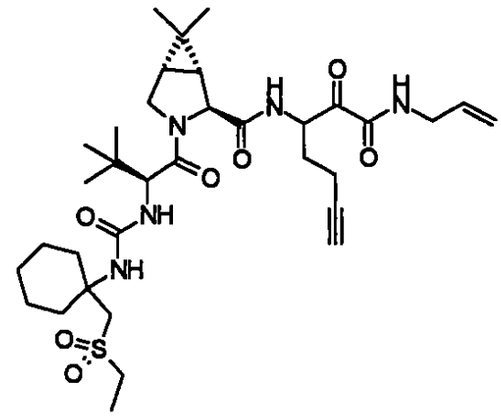
956

Ej. de Prep	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
199		CLEM: MH^+, 702,2.	A
200		FABMS; MH^+, 726,5.	A

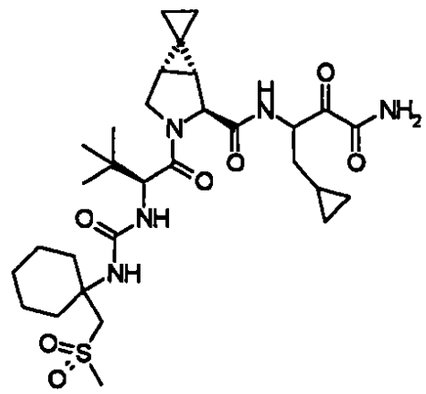
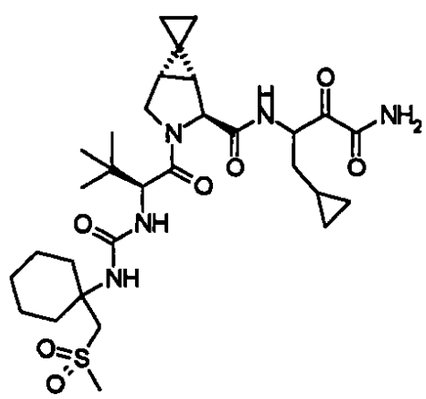
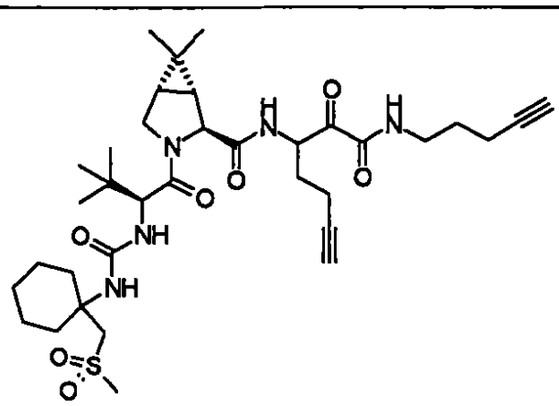
957

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec	rango de Ki*
201			A
202			A
203			A

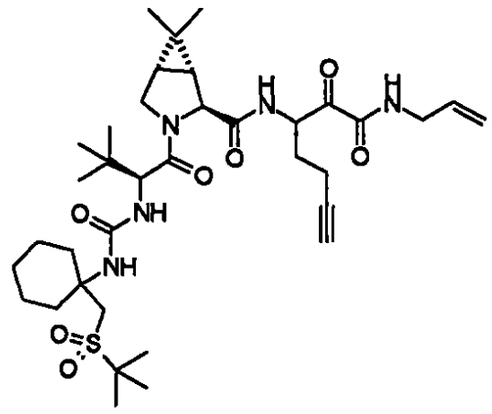
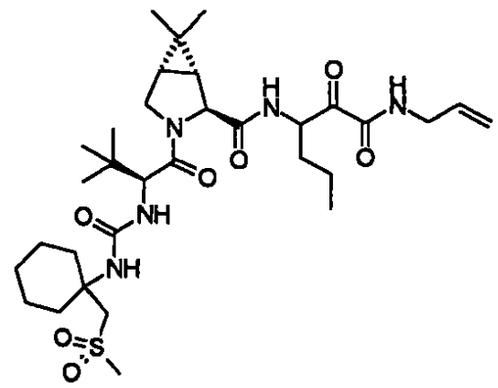
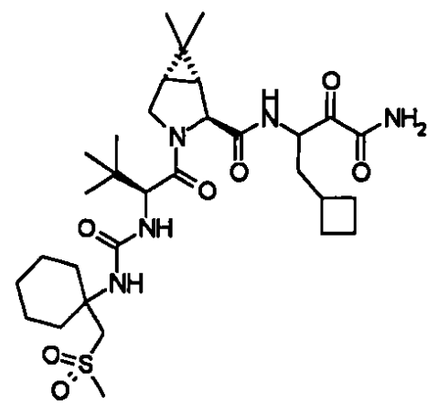
958

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
204			A
205			A
206		FABMS; MH^+, 676,7.	A

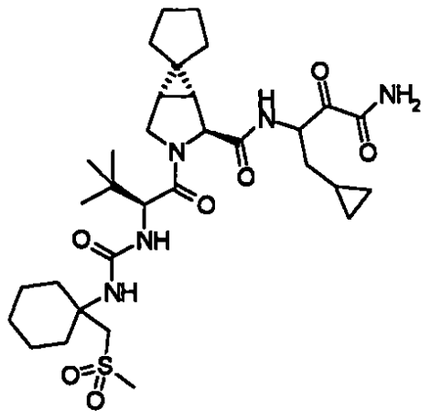
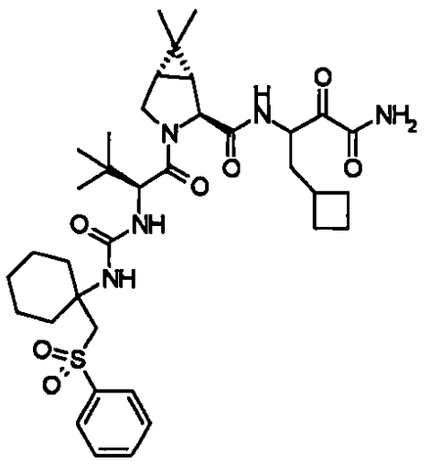
959

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
207			A
208			A
209		FABMS, MH^+, 688,3.	A

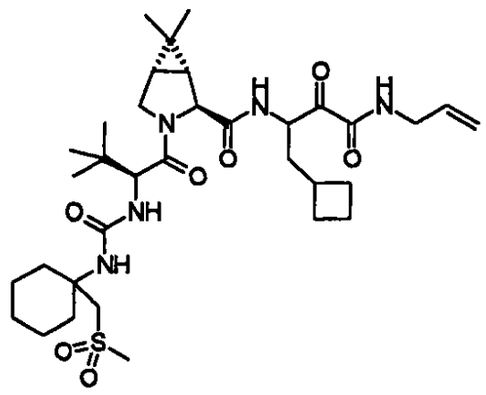
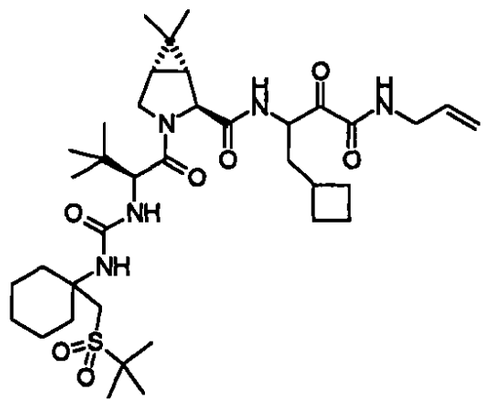
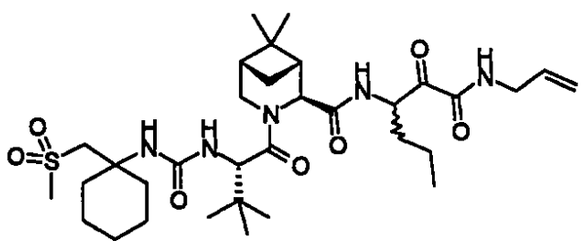
960

Ej. de Prep.	COMPUESTO	Datos de espec. de masa selec.	rango de Ki*
210		FABMS; MH^+, 704,4.	A
211			A
212			A

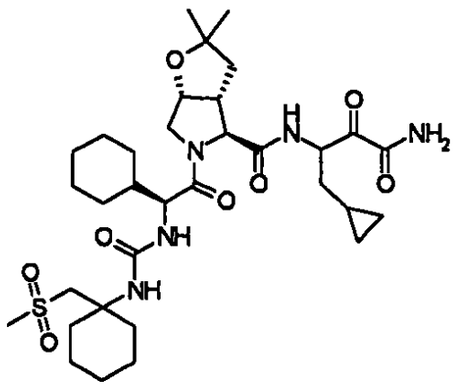
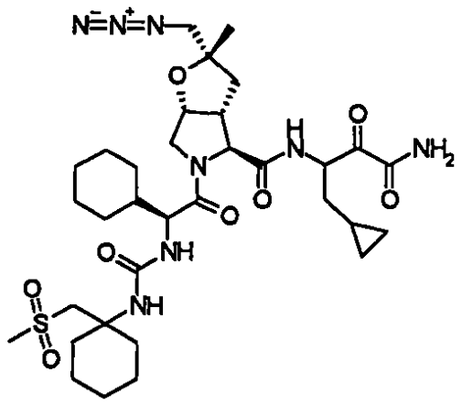
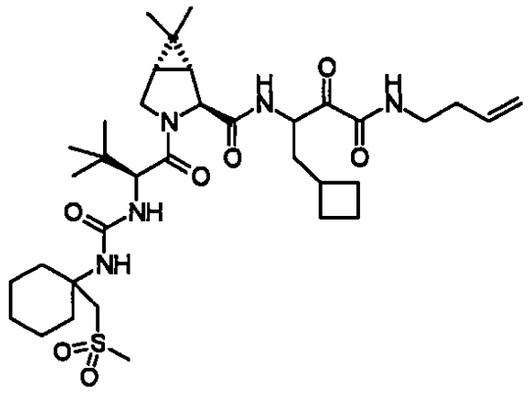
961

Ej. de Prep	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
213			A
214			A

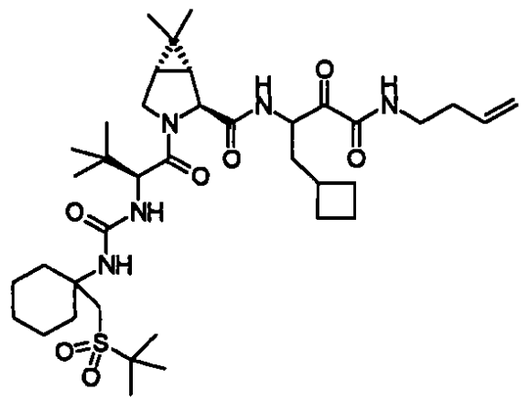
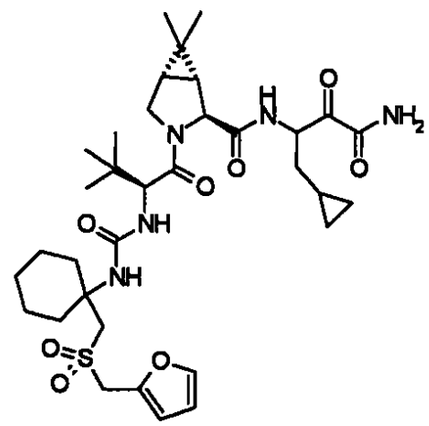
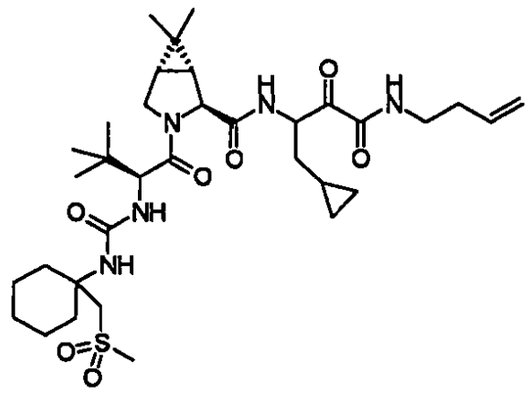
962

Ej. de Prep	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
215		FABMS, MH^+, 678,6.	A
216		FABMS, MH^+, 720,6.	A
217			A

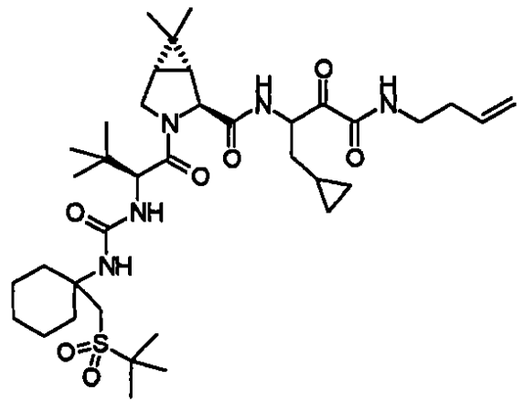
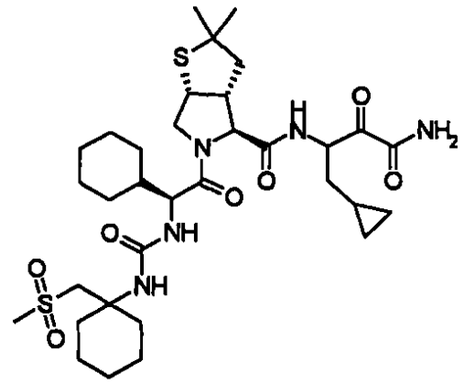
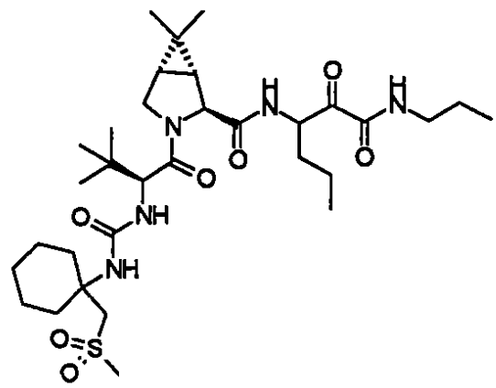
963

Ej de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
218			A
219			A
220		FABMS; MH^+, 692,5.	A

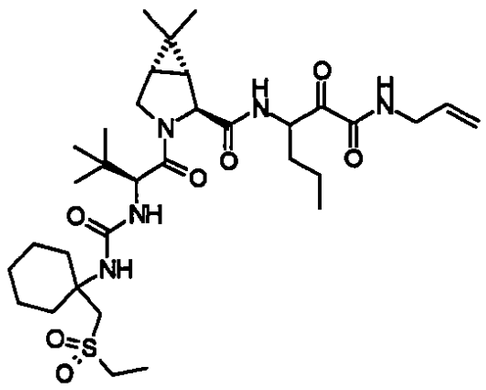
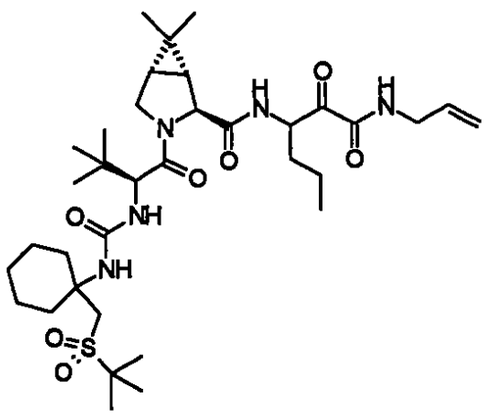
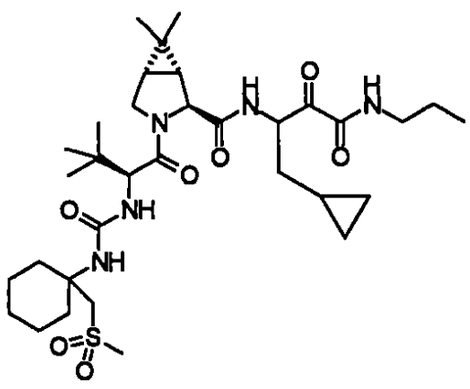
964

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
221		FABMS; MH^+, 734,5.	A
222			A
223		FABMS; MH^+, 678,4.	A

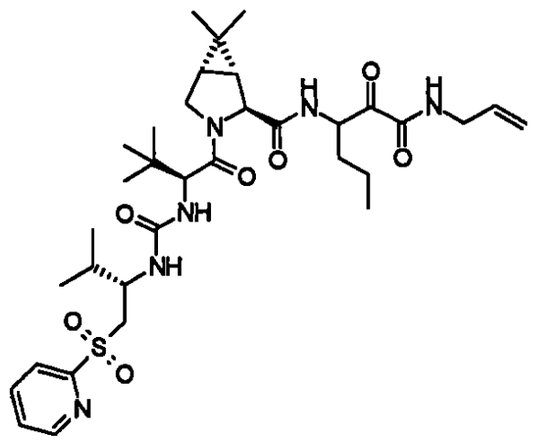
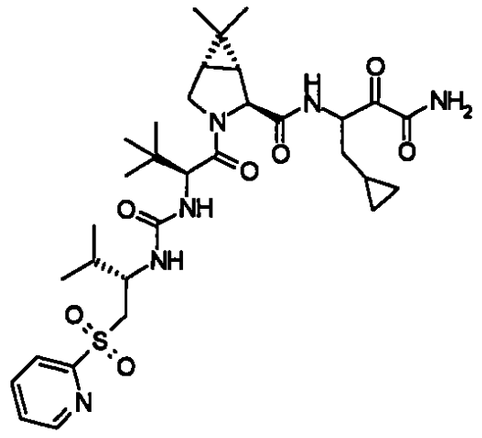
965

Ej. de Prep	COMPUESTO	Datos de espec de masa. selec.	rango de Ki*
224		FABMS; MH^+, 720,8.	A
225			B
226		CLEM; MH^+, 654,1.	A

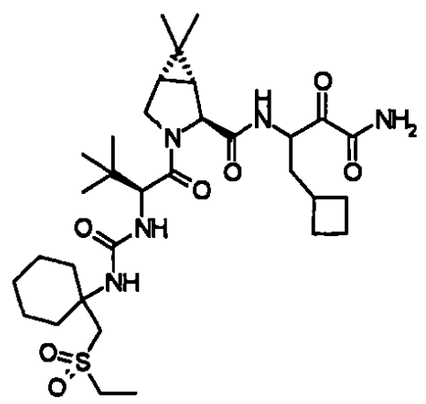
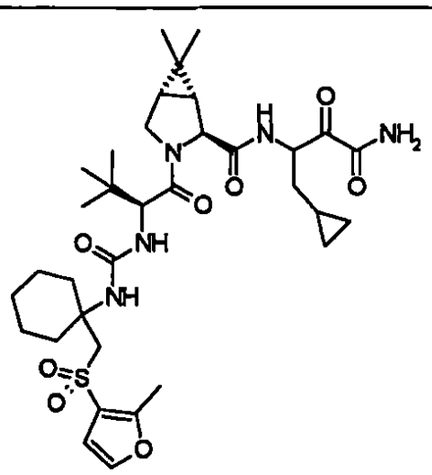
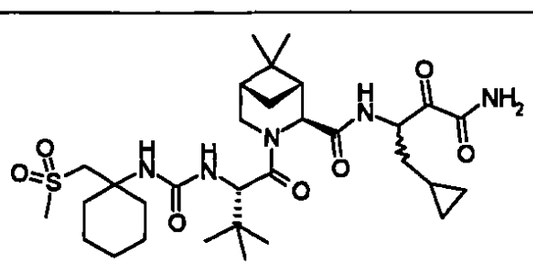
966

Ej. de Prep.	COMPUESTO	Datos de espec de masa. selec.	rango de Ki*
227			A
228			A
229		FABMS; MH+, 666,5.	A

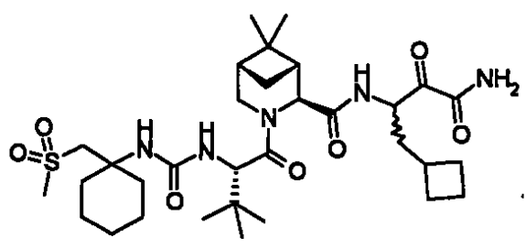
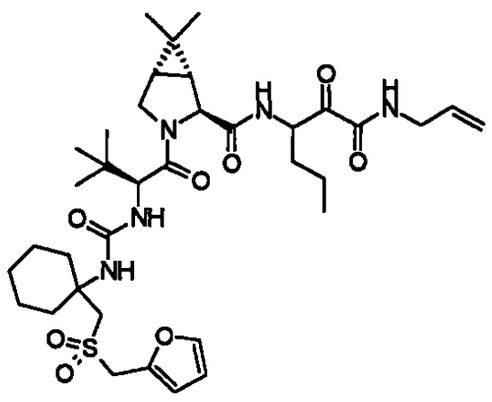
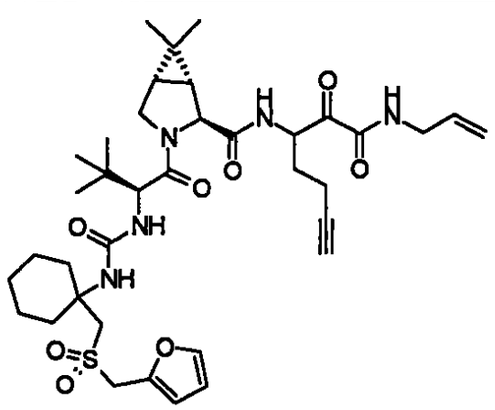
967

Ej. de Prep	COMPUESTO	Datos de espec de masa. selec.	rango de Ki*
230			C
231			A

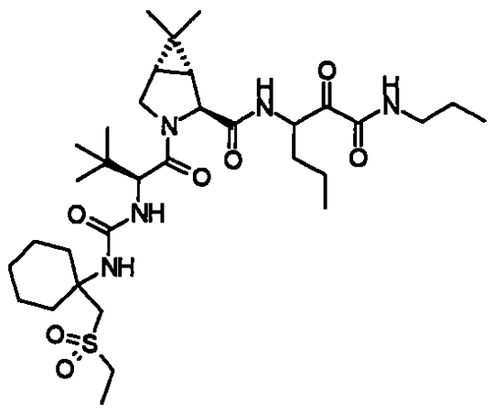
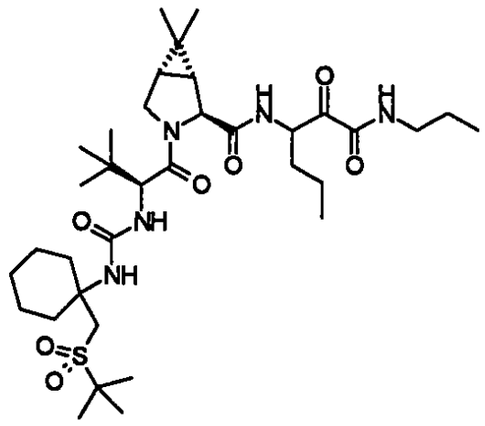
968

Ej de Prep.	COMPUESTO	Datos de espec. de masa selec.	rango de Ki*
232			A
233			A
234			C

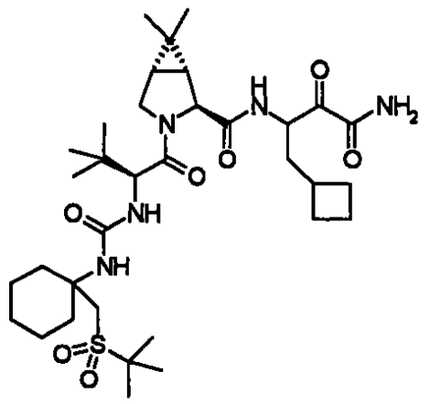
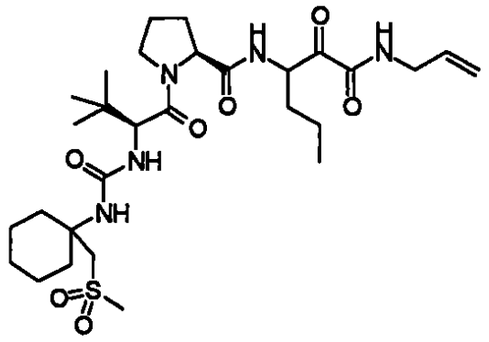
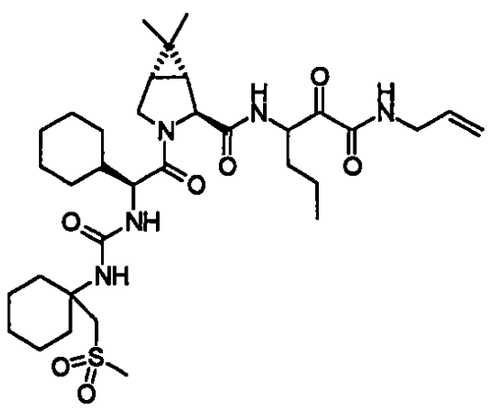
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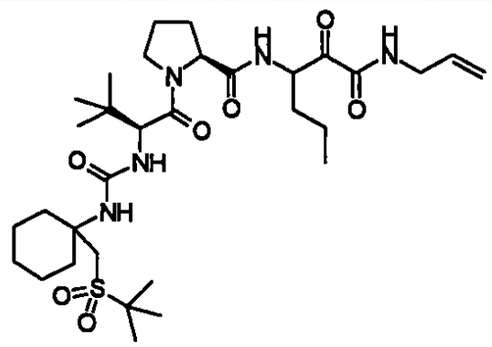
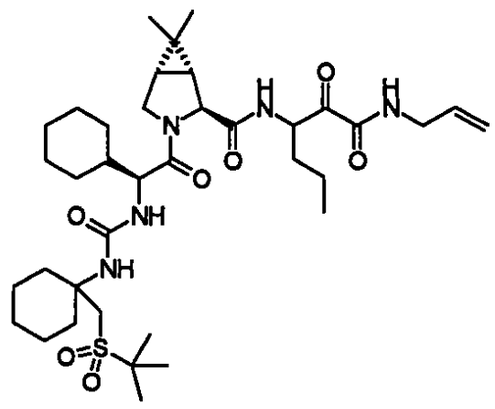
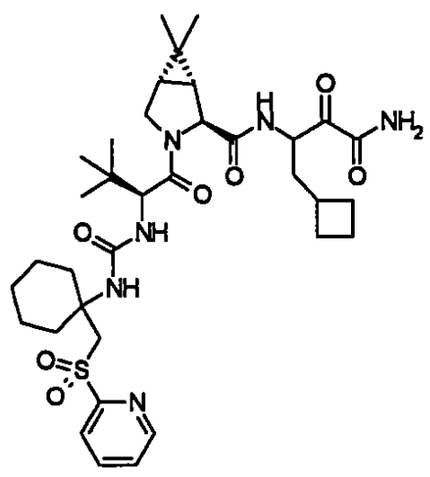
Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
235			A
236			A
237			A

970

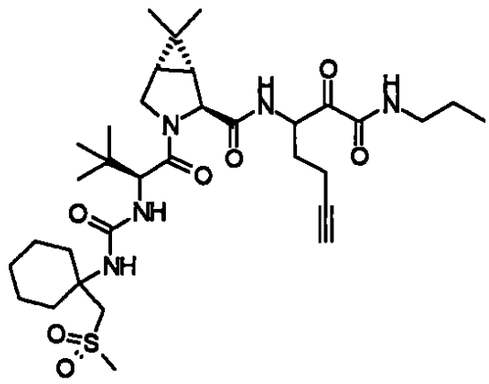
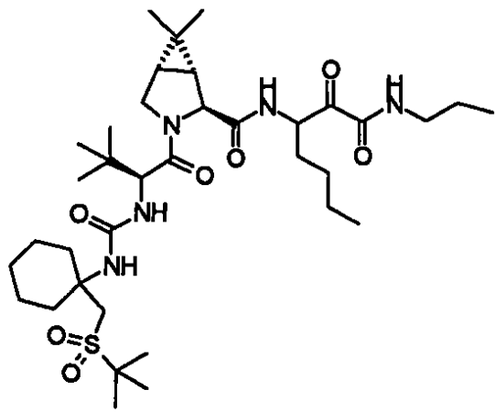
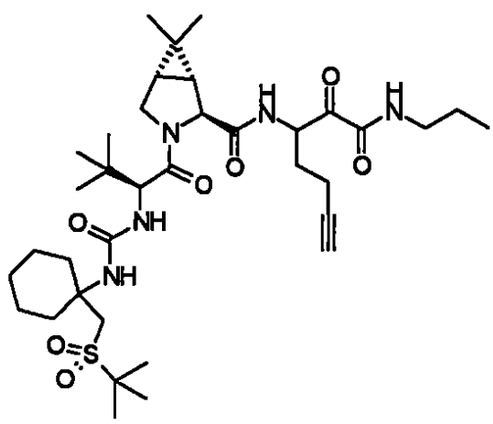
Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
238			A
239			A

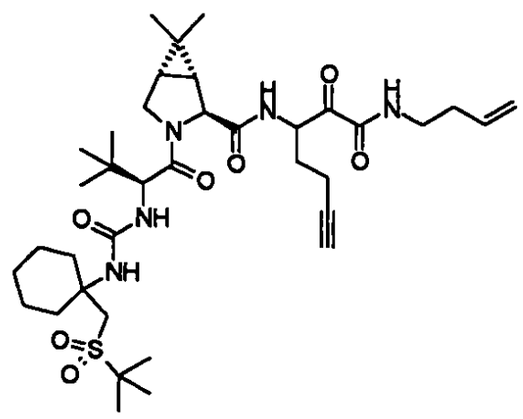
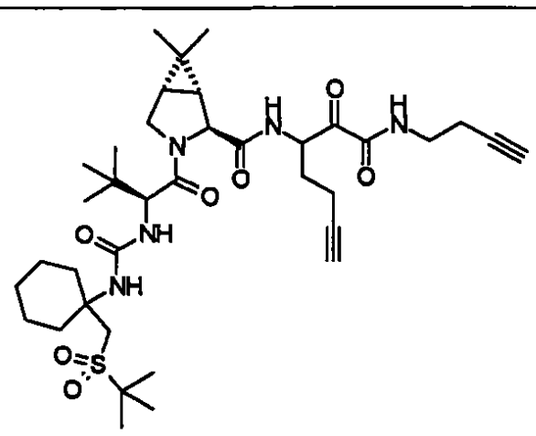
971

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
240			A
241			C
242			A

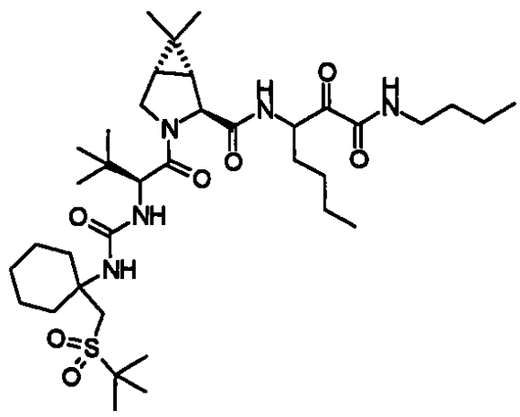
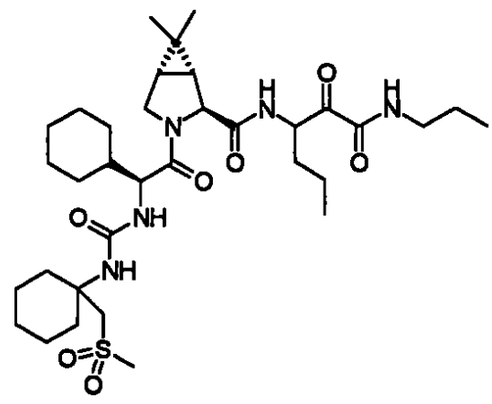
Ej de Prep	COMPUESTO	Datos de espec de masa selec.	rango de Ki*
243			C
244			A
245			A

973

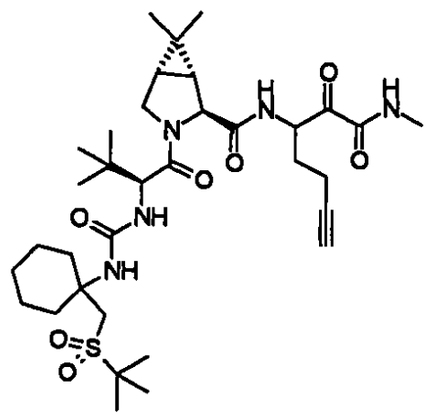
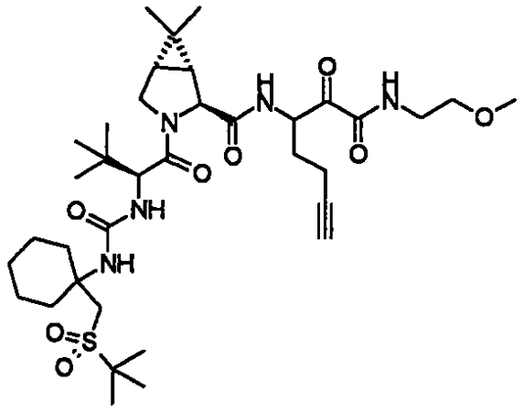
Ej. de Prep.	COMPUESTO	Datos de espec. de masa selec.	rango de Ki*
246		FABMS; MH^+, 664,2.	A
247		FABMS; MH^+, 710,3.	A
248		FABMS; MH^+, 706,5	A

Ej de Prep.	COMPUESTO	Datos de espec de masa. selec.	rango de Ki*
249		FABMS; MH^+, 718,2.	A
250			A

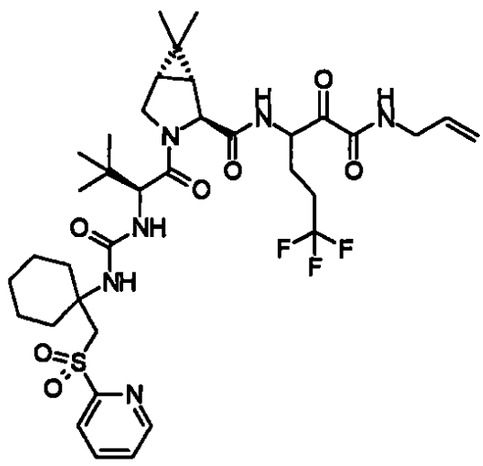
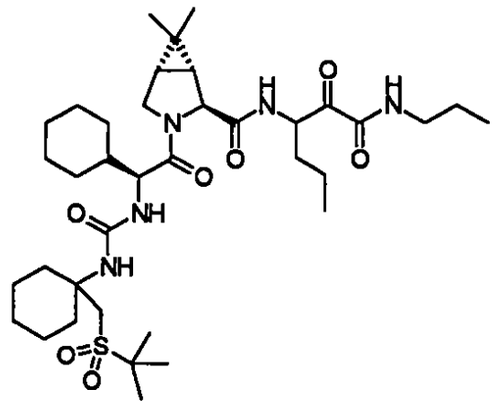
975

Ej. de Prep	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
251		FABMS; MH^+, 724,5.	A
252		FABMS, MH^+, 680,4.	A

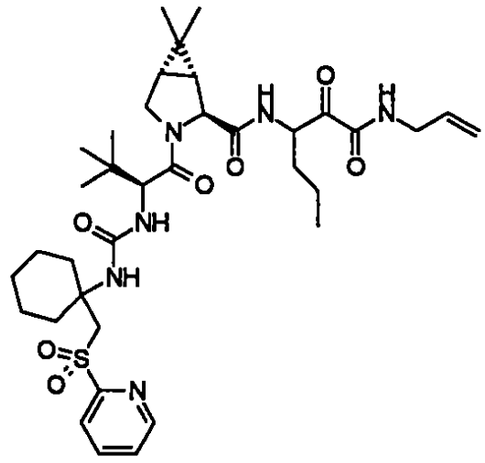
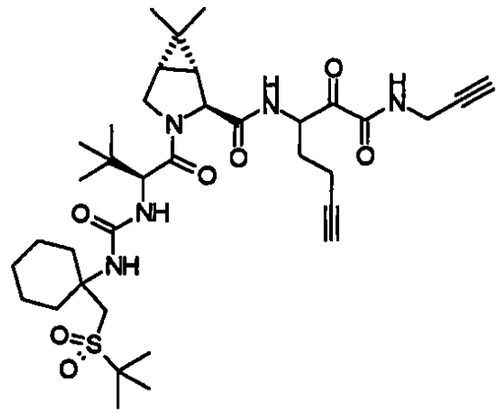
976

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
253			A
254		FABMS; MH^+, 722,1.	A

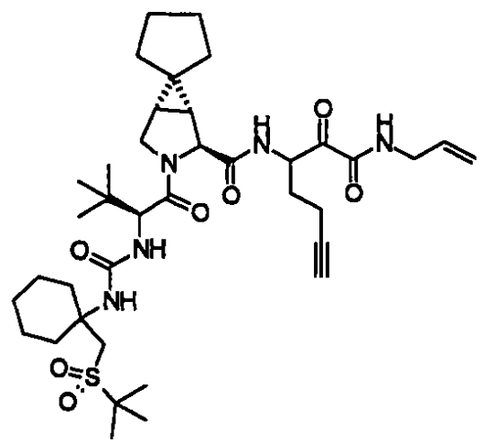
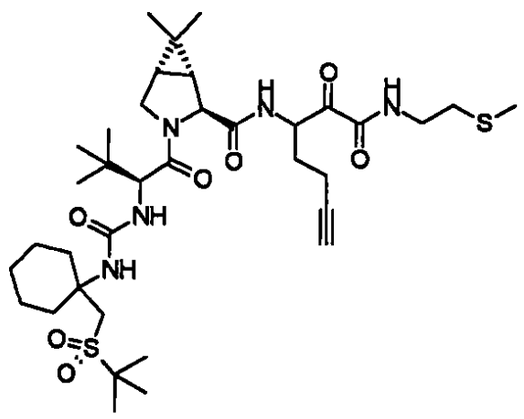
977

Ej. de Prep	COMPUESTO	Datos de espec. de masa selec.	rango de Ki*
255			A
256			A

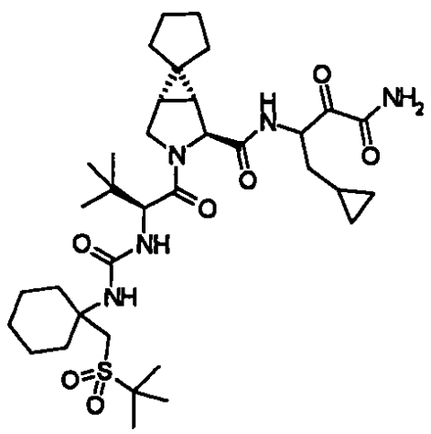
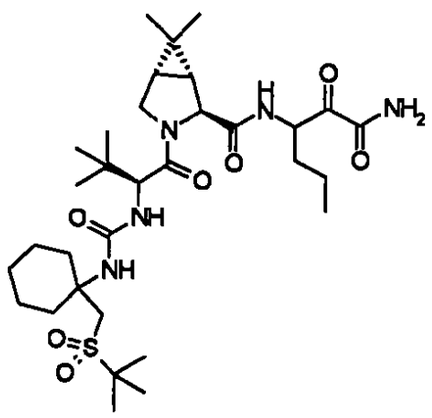
978

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
257			A
258		FABMS; MH+, 702,3.	A

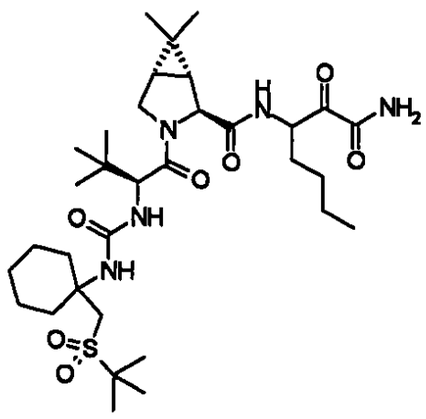
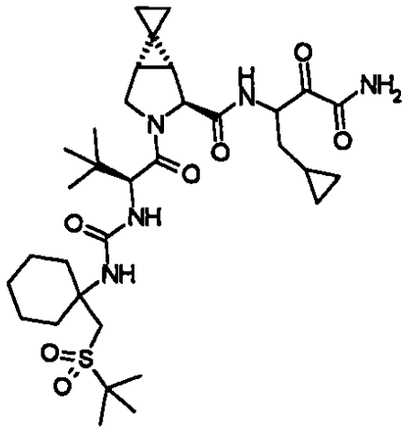
979

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
259		FABMS; MH^+, 730,5	A
260		FABMS; MH^+, 738,4.	A

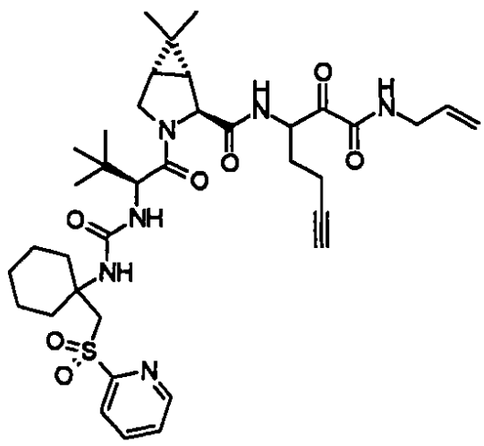
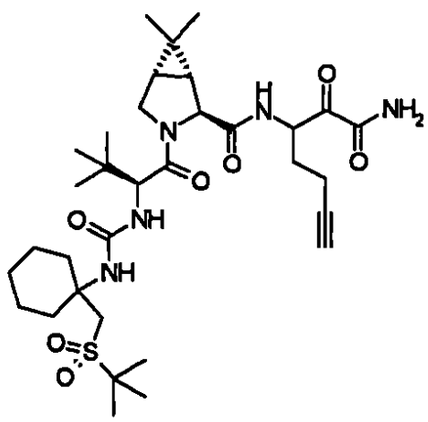
980

Ej de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
261		FABMS; MH^+, 692,5.	A
262			A

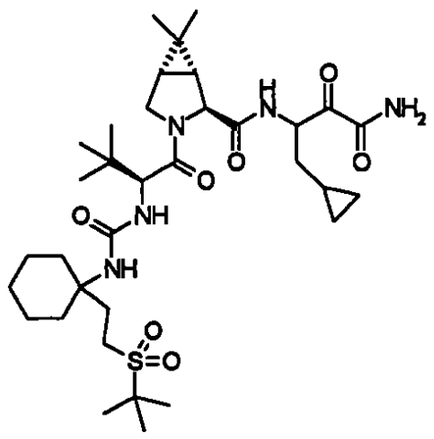
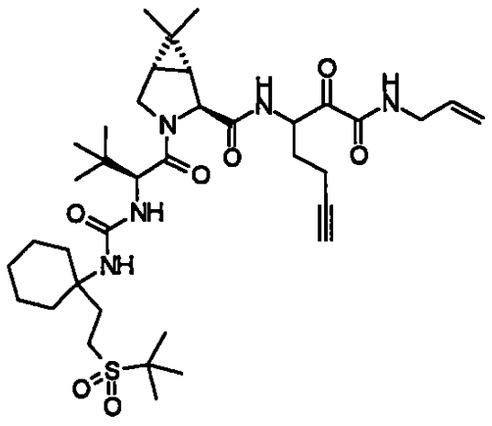
981

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
263			A
264		FABMS; MH^+, 664,4.	A

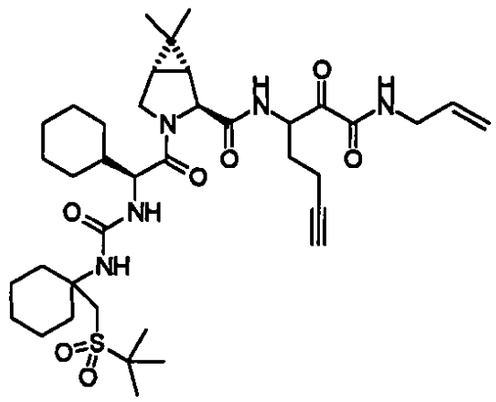
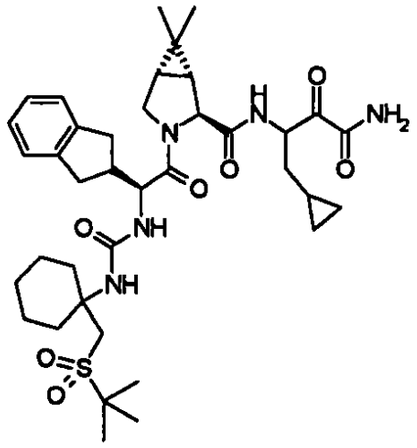
982

Ej. de Prep	COMPUESTO	Datos de espec de masa. selec.	rango de Ki*
265			A
266		FABMS; MH^+, 664,2.	A

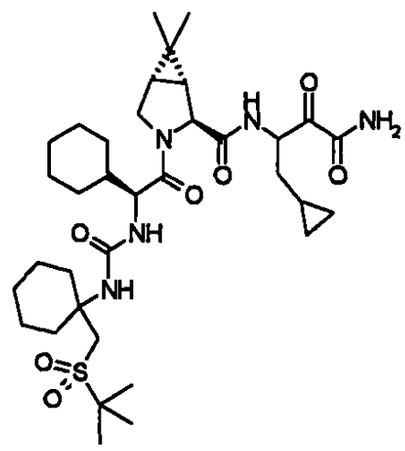
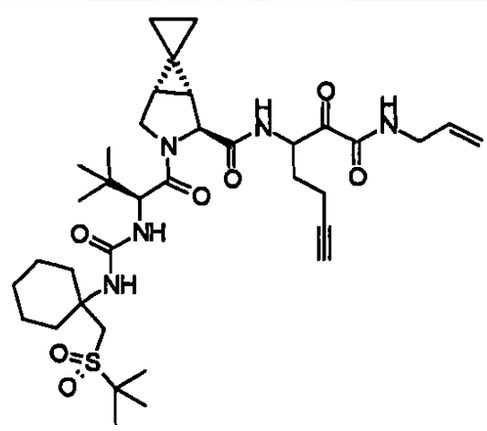
983

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
267			B
268			B

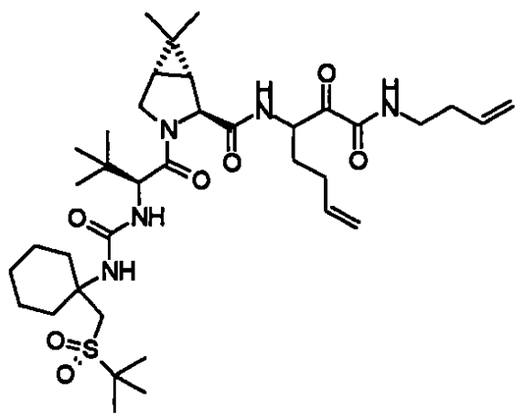
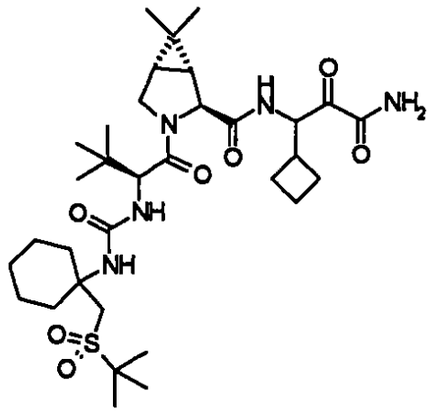
984

Ej de Prep.	COMPUESTO	Datos de espec. de masa. selec	rango de Ki*
269			A
270			A

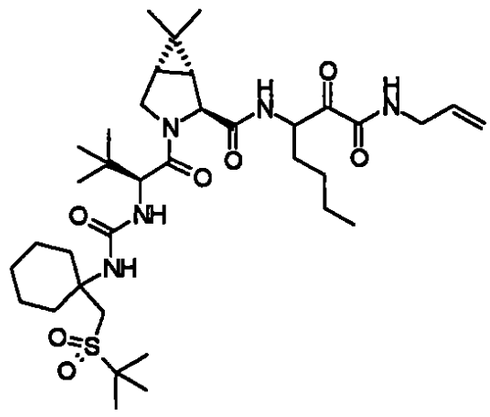
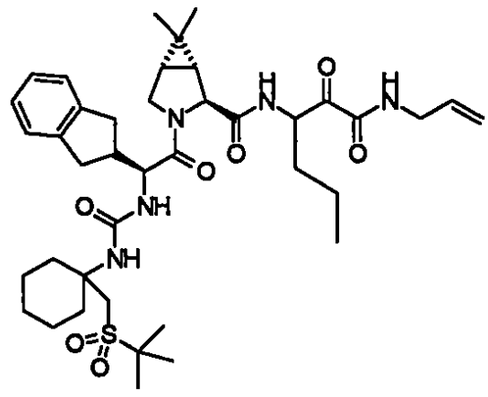
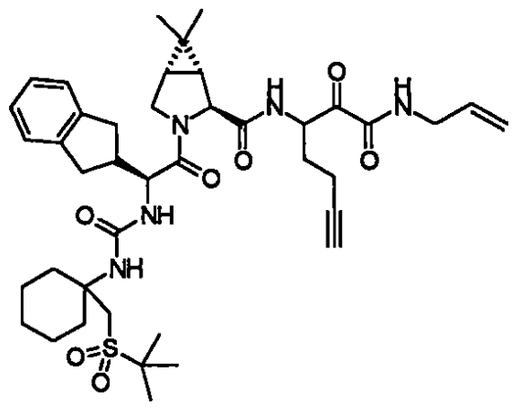
985 1082

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
271			A
272		FABMS; MH^+, 702,3.	A

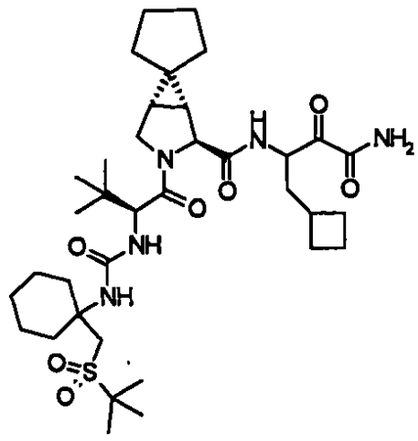
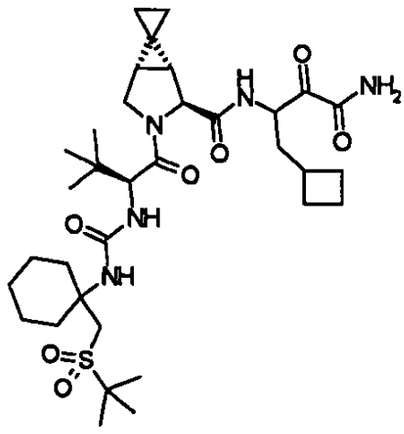
986

Ej de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
273		FABMS; MH^+, 720,5.	A
274			A

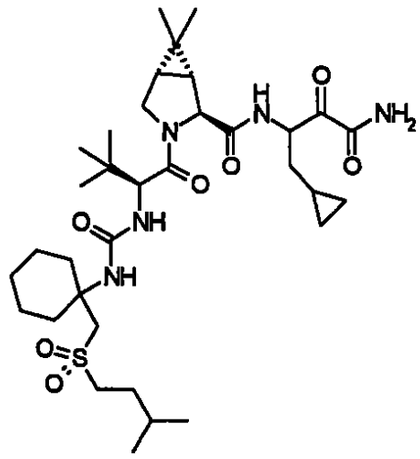
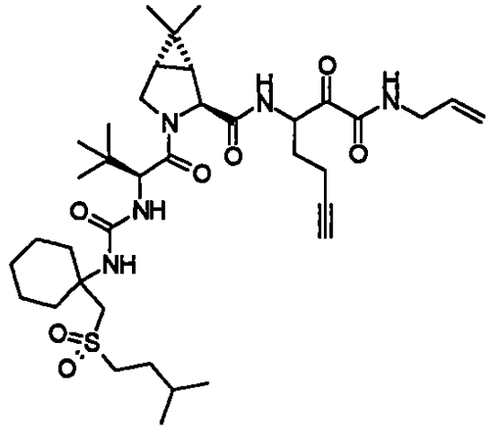
987

Ej. de Prep	COMPUESTO	Datos de espec. de masa selec.	rango de Ki*
275			A
276			A
277		FABMS; MH^+, 764,8.	A

988

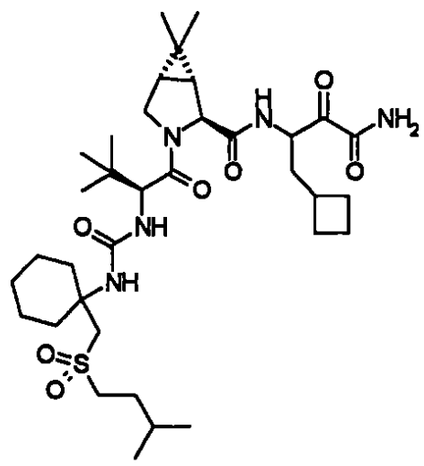
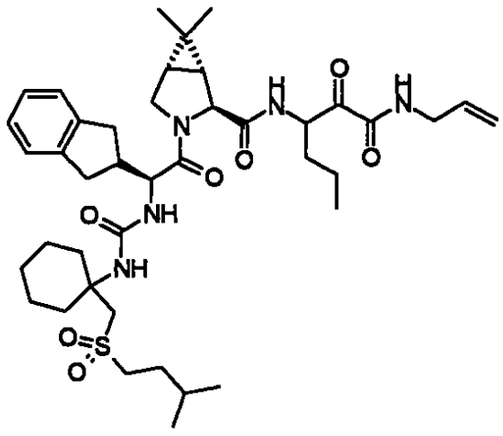
Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec	rango de Ki*
278		CLEM; MH^+, 706,2.	A
279		FABMS; MH^+, 678,2.	A

989

Ej. de Prep.	COMPUESTO	Datos de espec de masa. selec	rango de Ki*
280			A
281			A

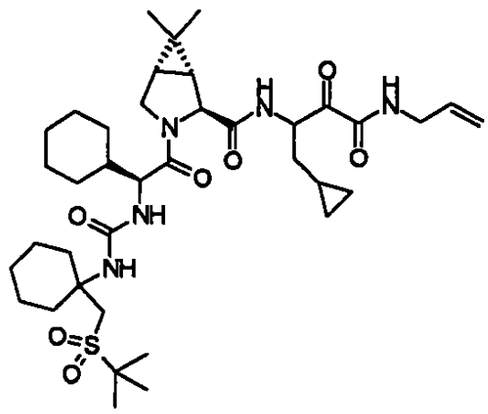
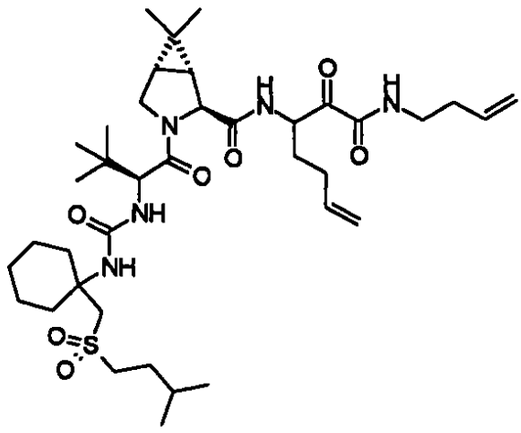
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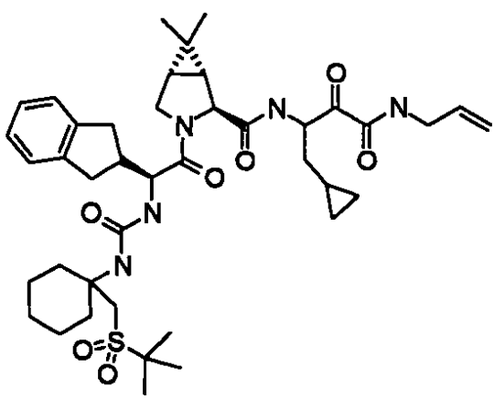
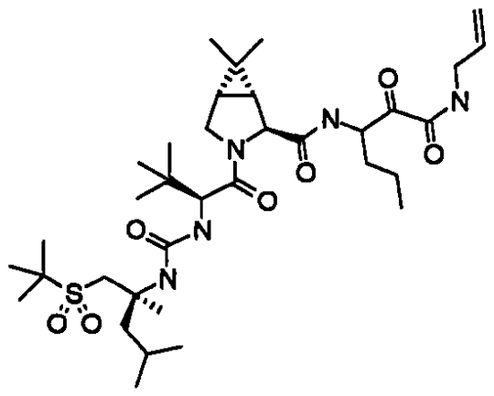
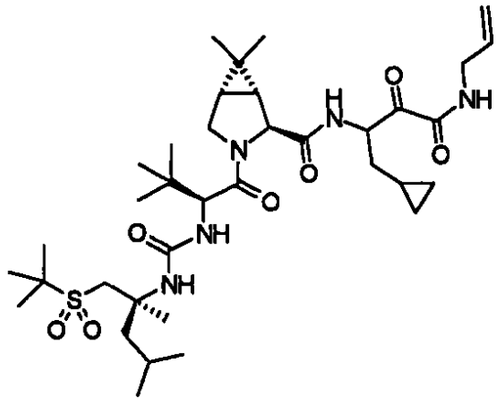
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Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
282			A
283			A

1008

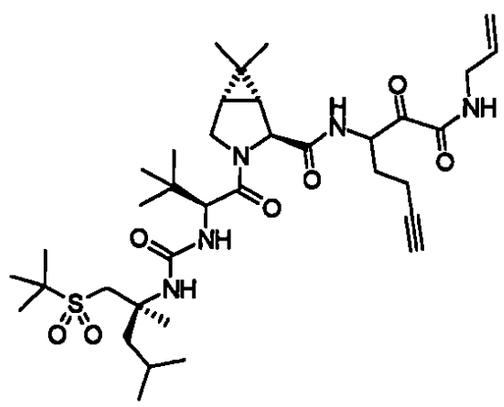
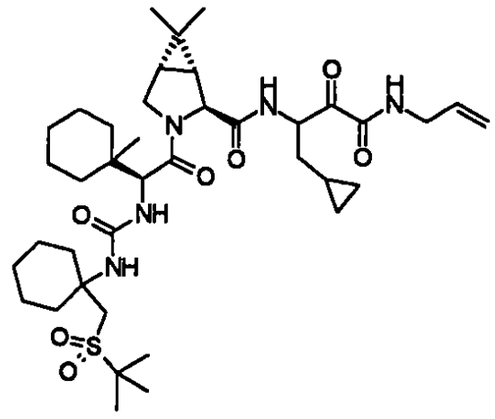
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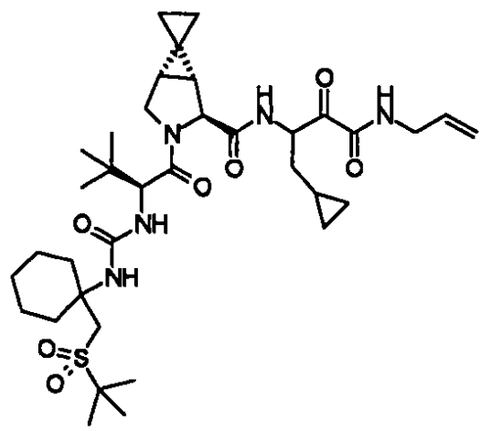
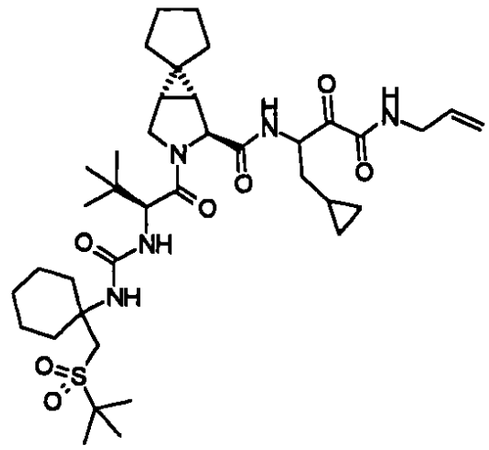
Ej. de Prep.	COMPUESTO	Datos de espec de masa. selec.	rango de Ki*
284			A
285			A

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec	rango de Ki*
286		CLEM, MH^+, 766,2	A
287			C
288			C

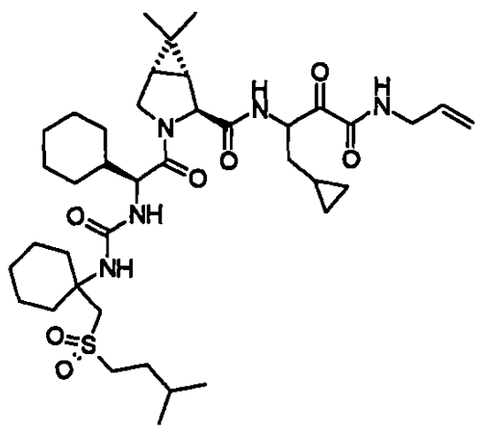
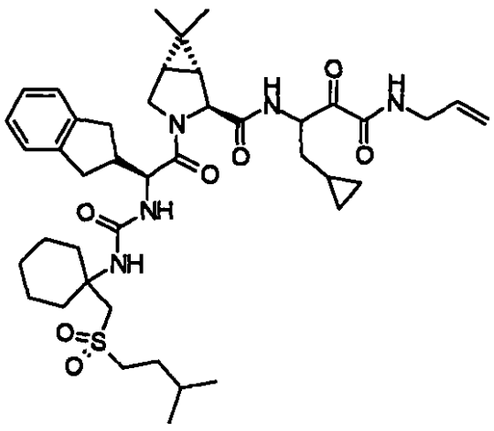
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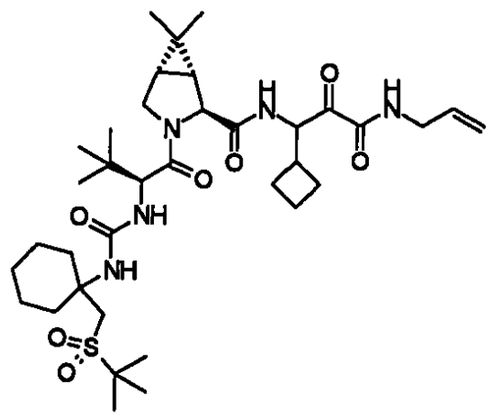
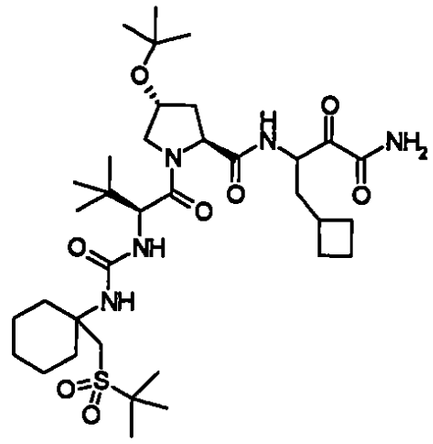
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Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
289			B
290			A

Ej de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
291			A
292			A

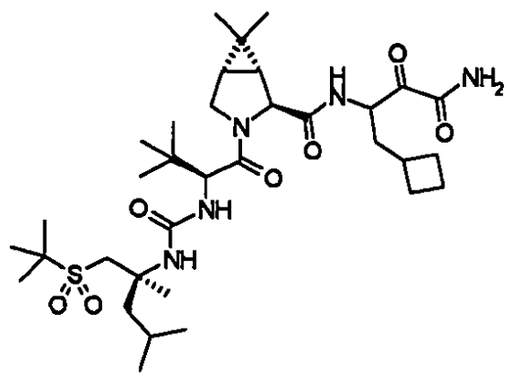
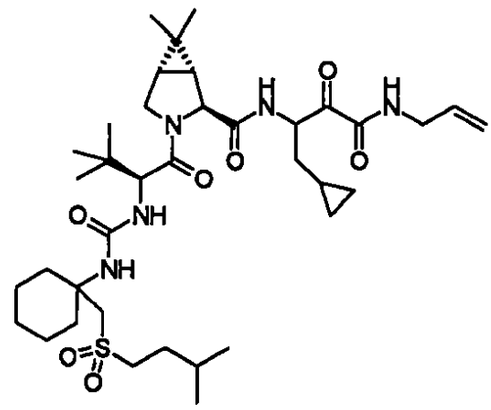
995

Ej. de Prep	COMPUESTO	Datos de espec. de masa. selec	rango de Ki*
293			A
294			A

Ej de Prep.	COMPUESTO	Datos de espec de masa. selec.	rango de Ki*
295			B
296		CLEM; MH^+, 712,3.	A

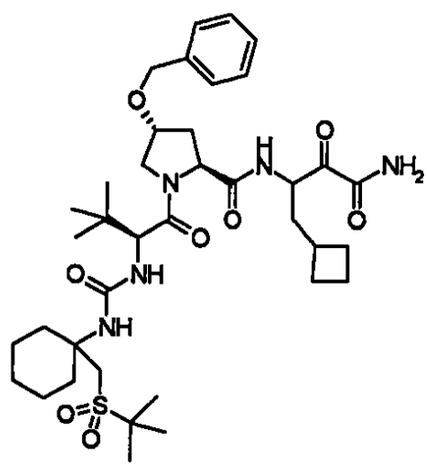
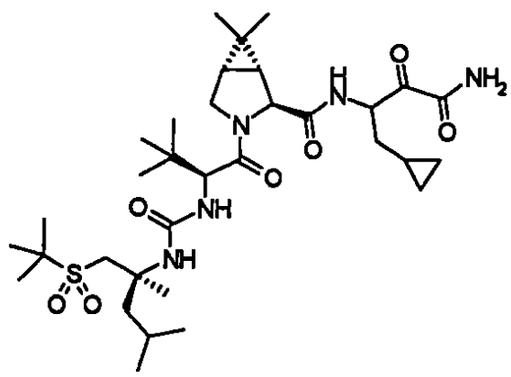
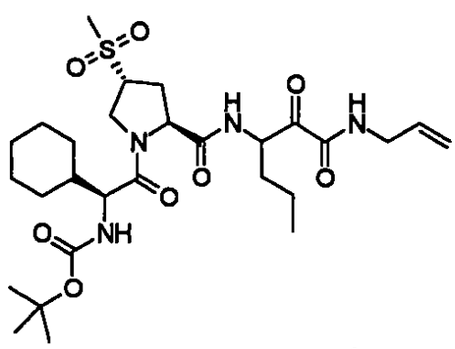
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997

Ej. de Prep	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
297			A
298			A

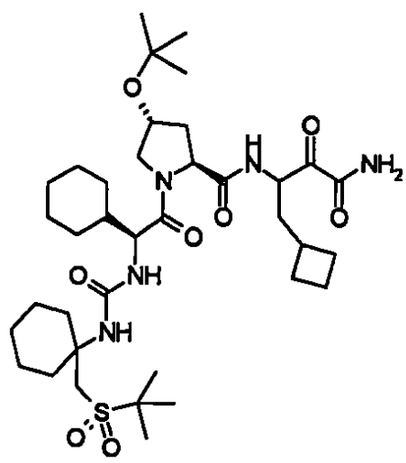
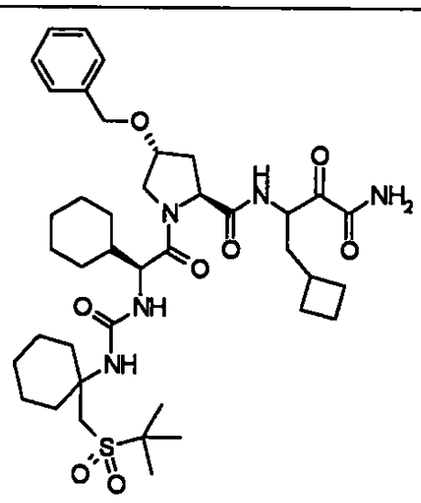
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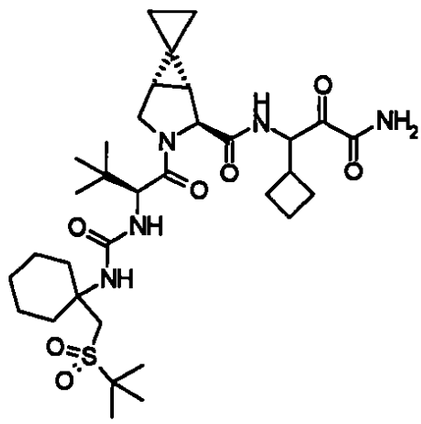
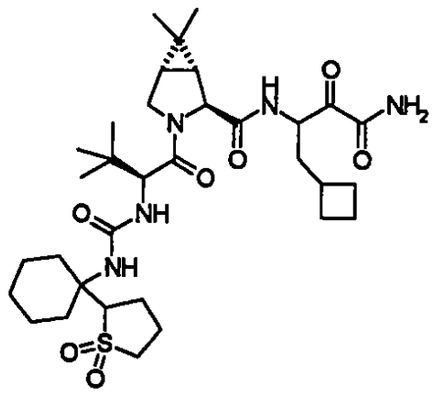
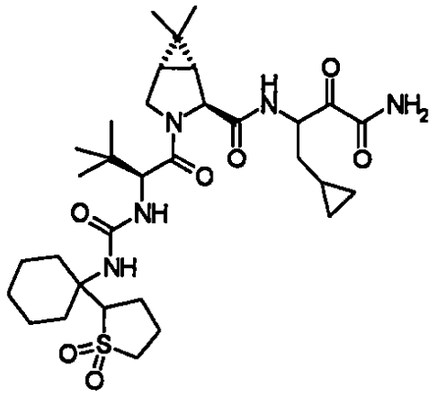
998

Ej. de Prep	COMPUESTO	Datos de espec. de masa. selec	rango de Ki*
299		CLEM; MH^+, 746,2.	A
300			B
301			A

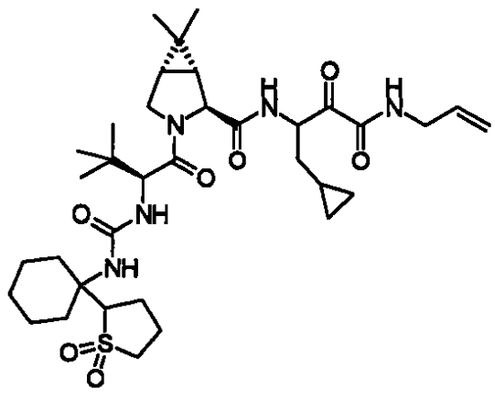
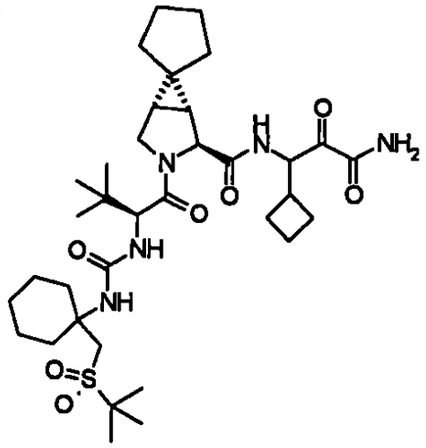
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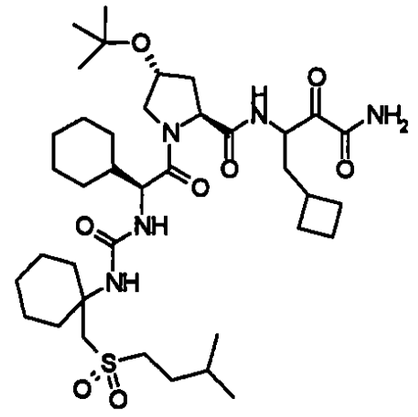
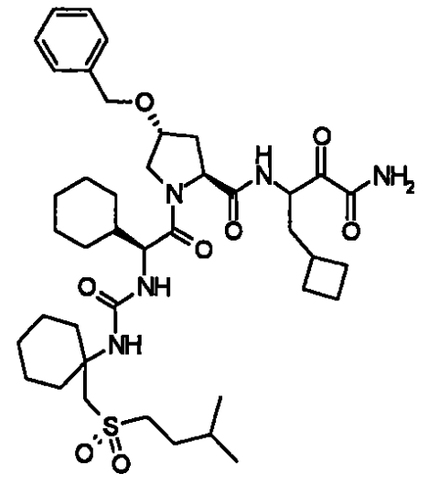
Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
302			A
303			B

Ej de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
304		CLEM; MH^+, 664,1.	C
305			B
306			A

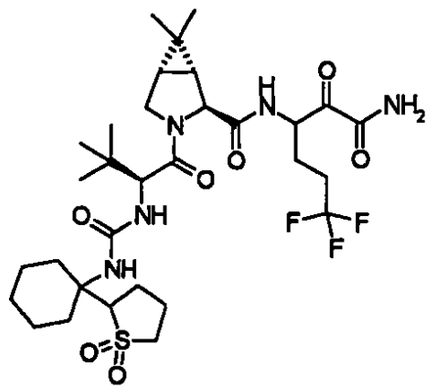
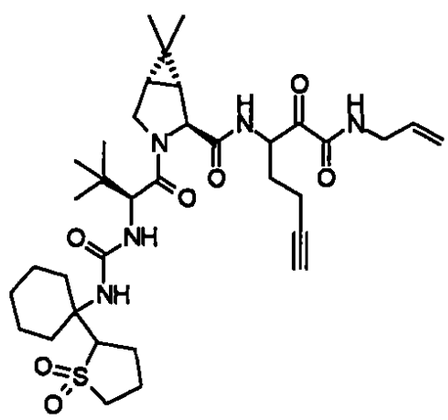
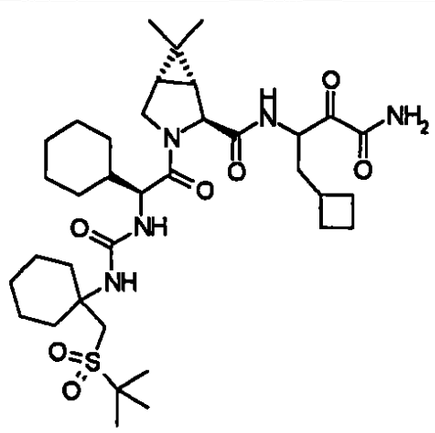
1001

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
307			A
308		CLEM, MH^+, 692,1.	A

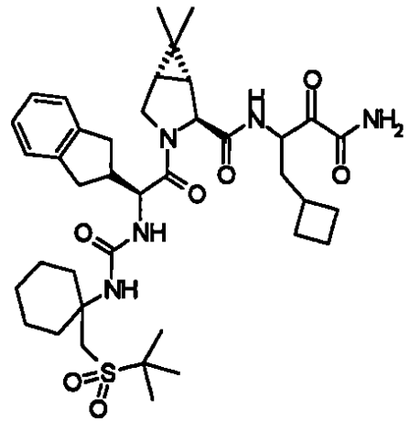
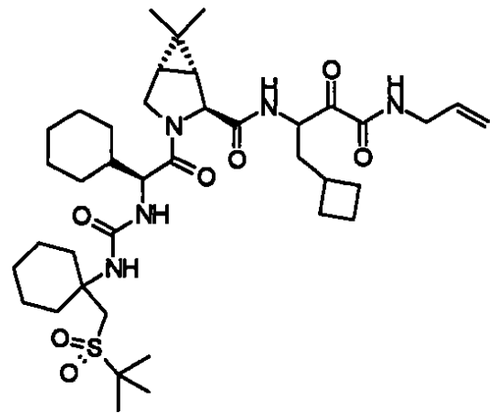
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Ej de Prep.	COMPUESTO	Datos de espec. de masa selec.	rango de Ki*
309			A
310			A

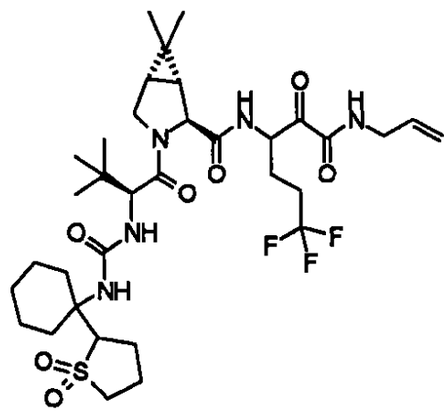
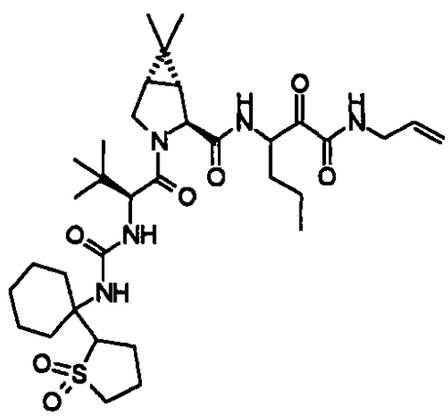
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Ej. de Prep	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
311			A
312			A
313			A

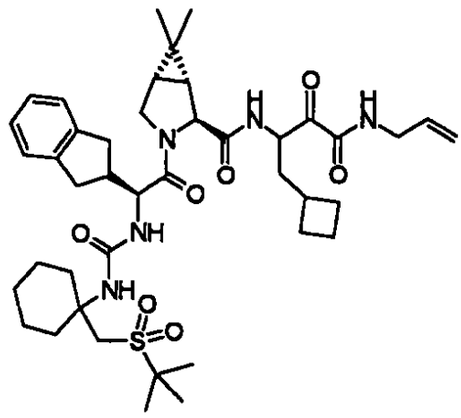
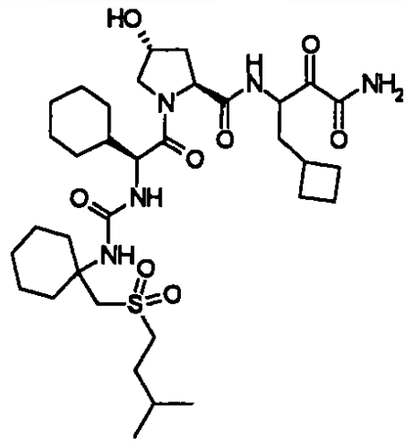
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Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
314			A
315			A

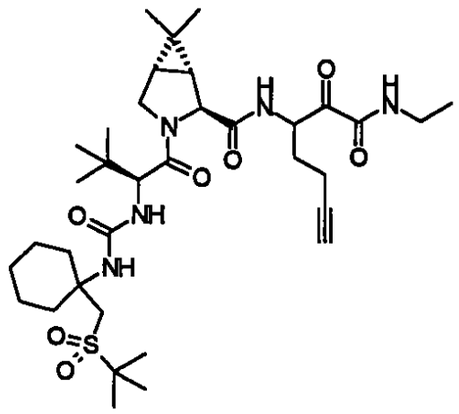
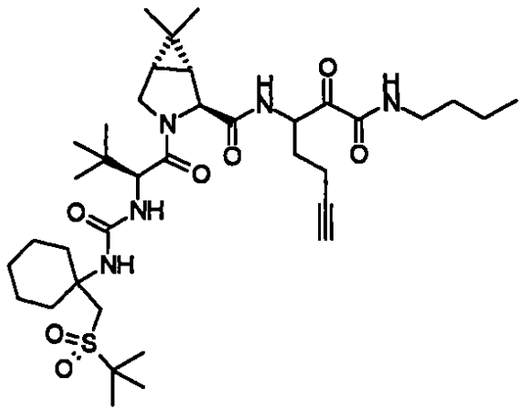
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Ej. de Prep.	COMPUESTO	Datos de espec. de masa selec.	rango de Ki*
316			A
317			A

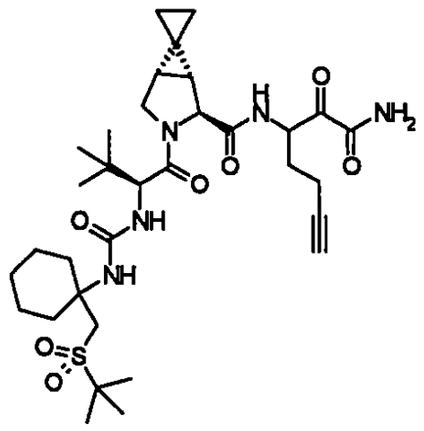
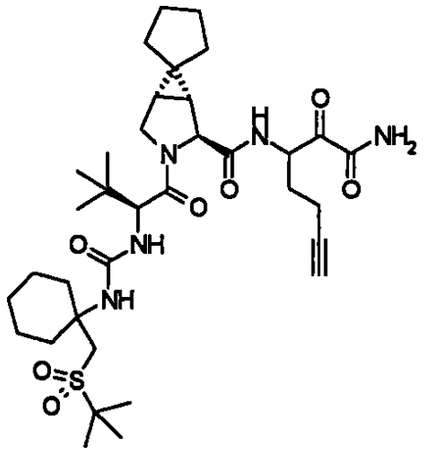
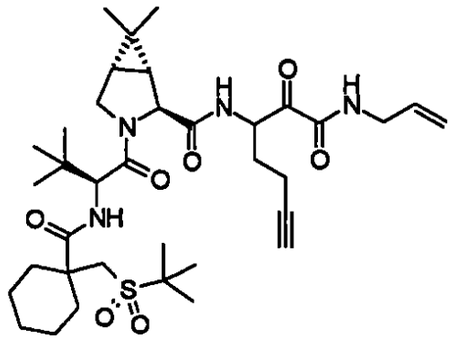
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Ej de Prep.	COMPUESTO	Datos de espec. de masa. selec	rango de Ki*
318			A
319			A

1007 1024

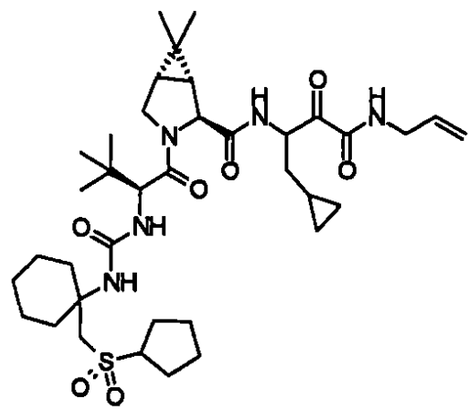
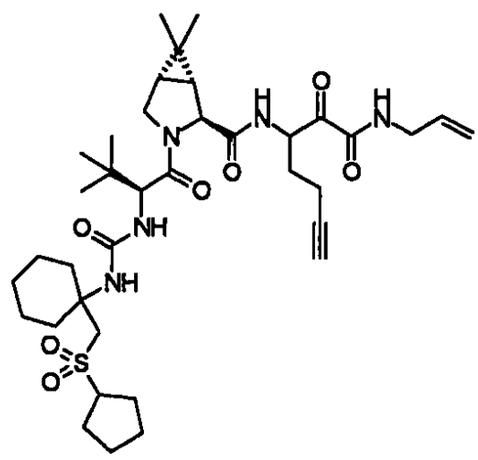
Ej de Prep.	COMPUESTO	Datos de espec. de masa selec.	rango de Ki*
320		692,3CLEM; MH^+, 692,2.	A
321		CLEM; MH^+, 720,2.	B

1008 1025

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
322			B
323			A
324			A

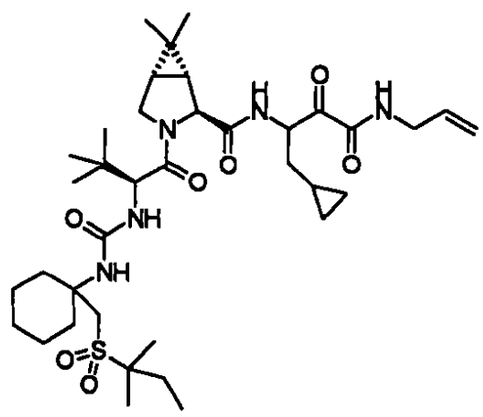
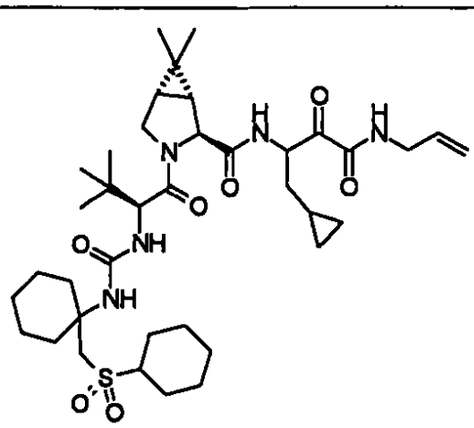
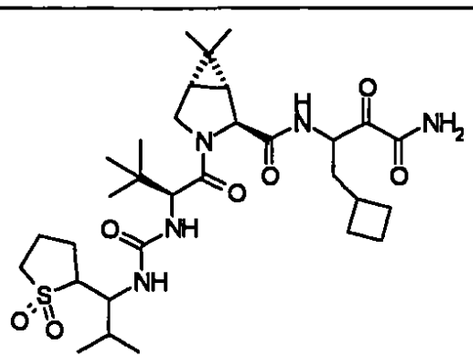
1026

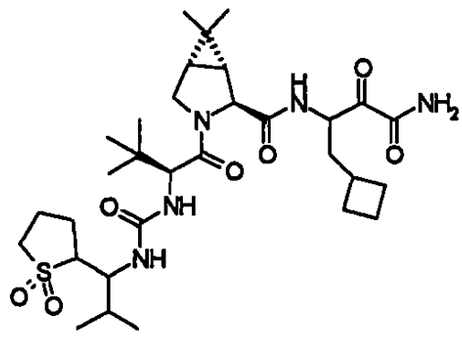
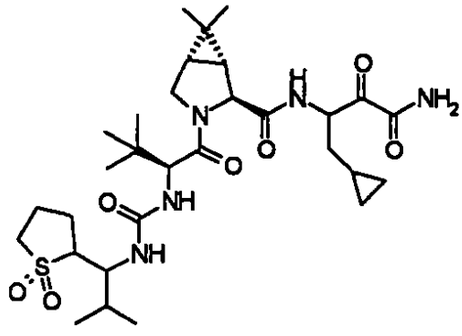
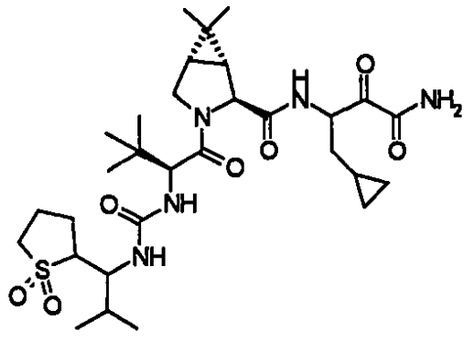
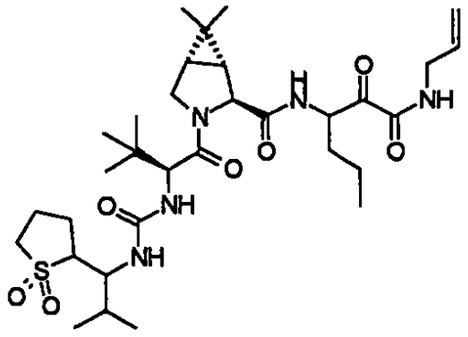
1009

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
325			A
326			A

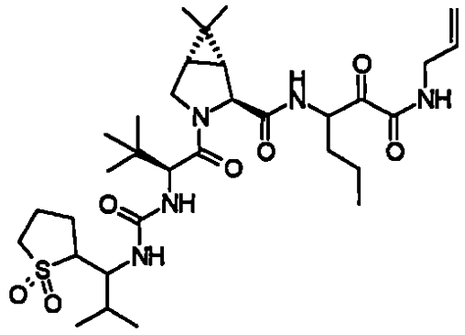
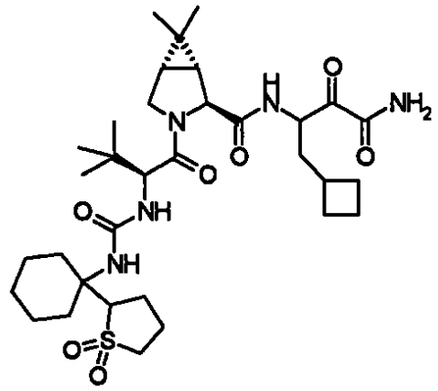
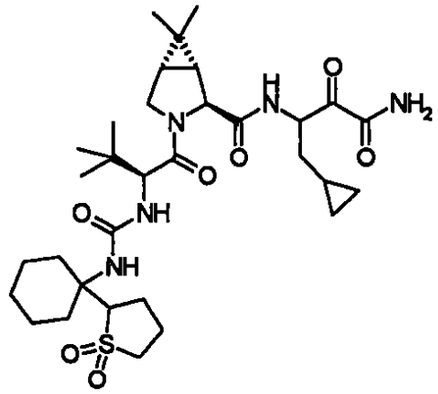
1029

1010

Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
327		CLEM; MH^+, 720,2.	C
328			NA
329			A

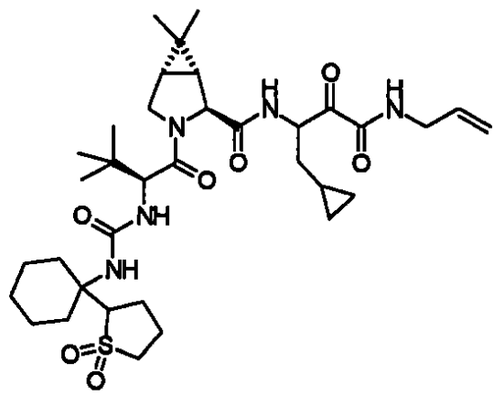
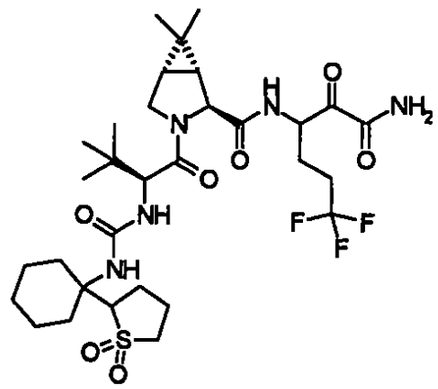
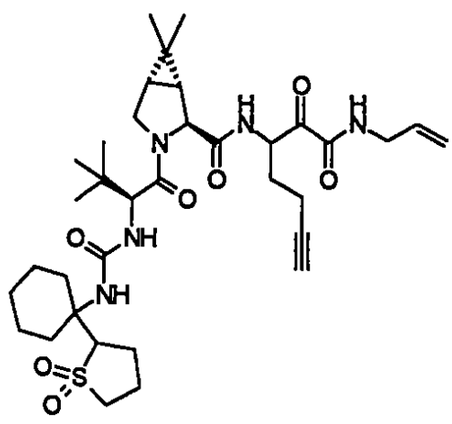
Ej. de Prep	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
330			C
331			A
332			C
333			C

1012

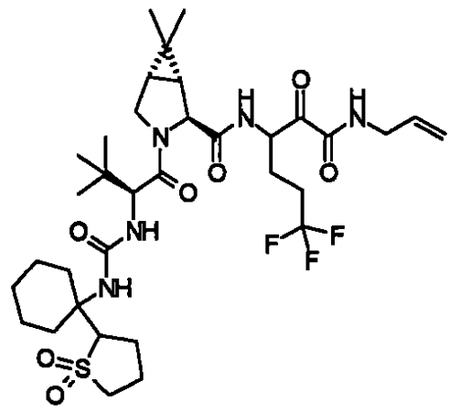
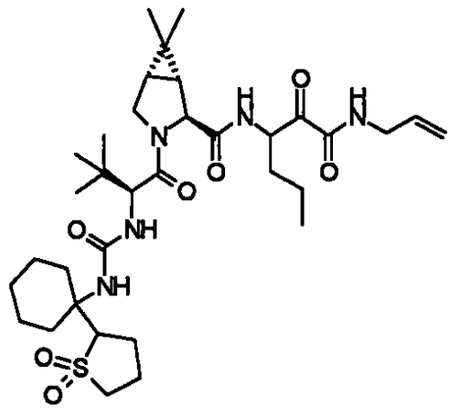
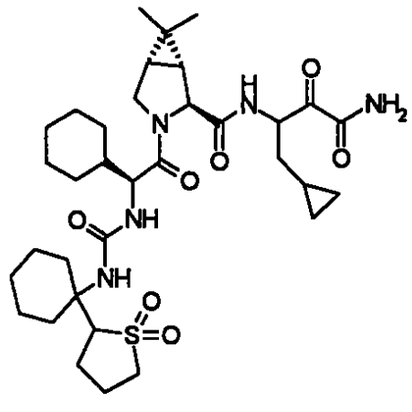
Ej. de Prep.	COMPUESTO	Datos de espec. de masa. selec	rango de Ki*
334			A
335			A
336			A

1020

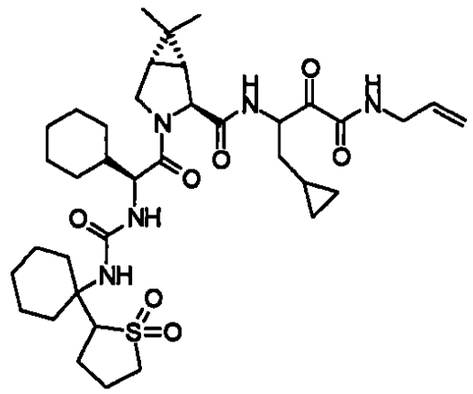
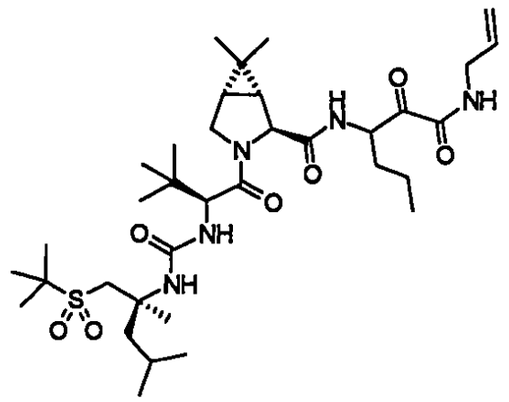
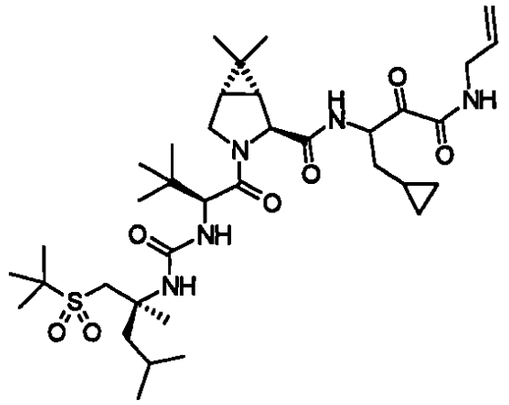
1013

Ej. de Prep.	COMPUESTO	Datos de espec de masa. selec.	rango de Ki*
337			A
338			A
339			A

1014

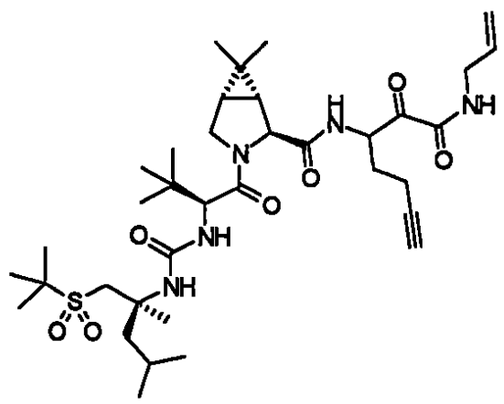
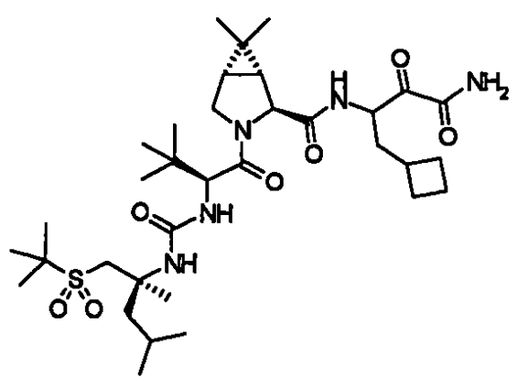
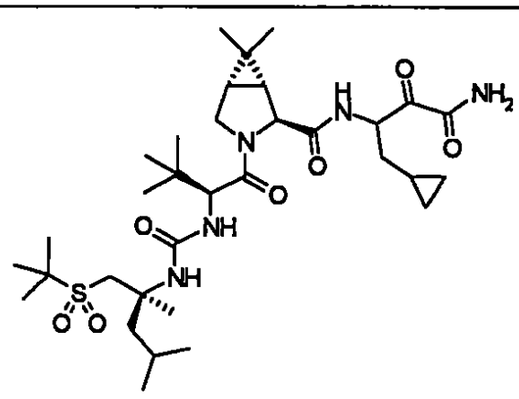
Ej de Prep.	COMPUESTO	Datos de espec. de masa selec.	rango de Ki*
340			A
341			A
342			A

1015

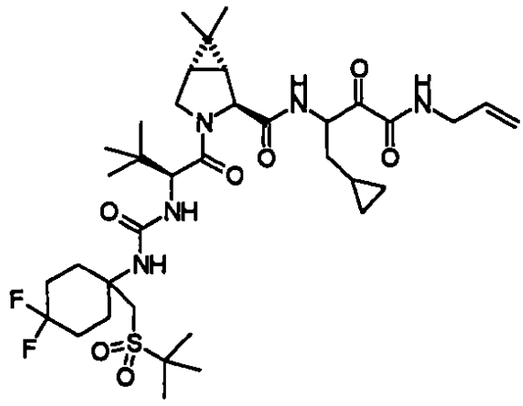
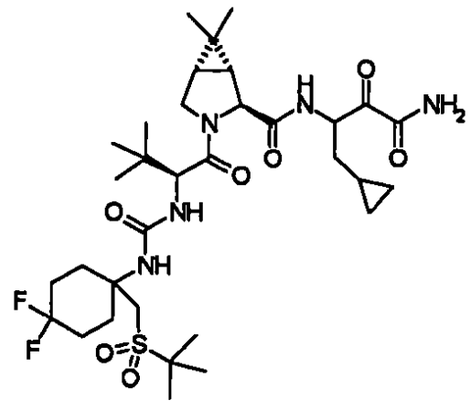
Ej. de Prep.	COMPUESTO	Datos de espec. de masa selec.	rango de Ki*
343			A
344			C
345			C

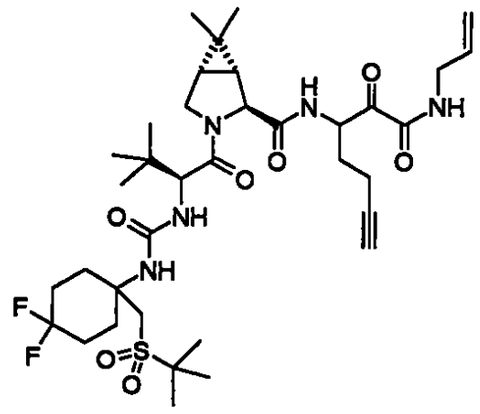
1033

1016

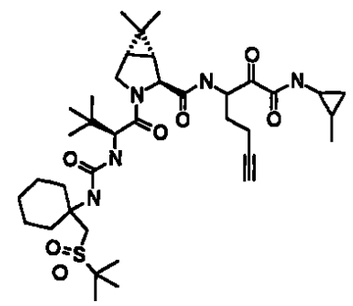
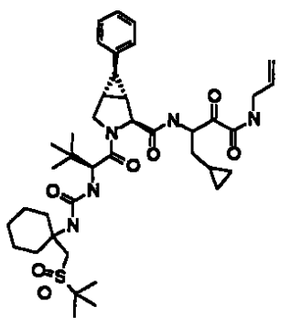
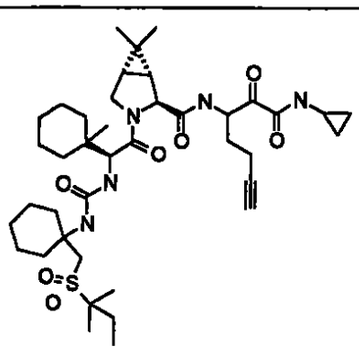
Ej. de Prep	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
346			B
347			B
348			B

1017

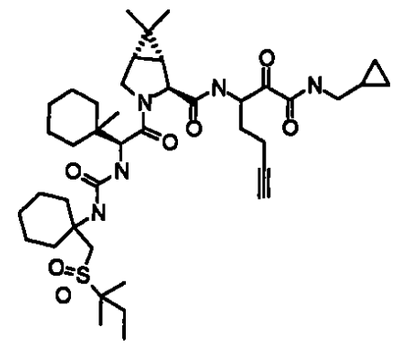
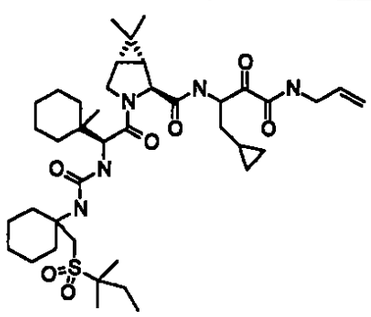
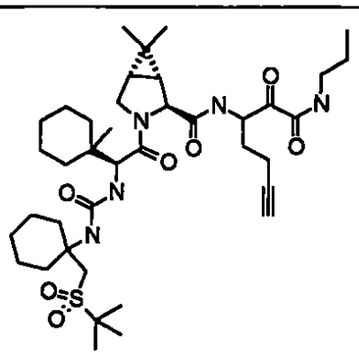
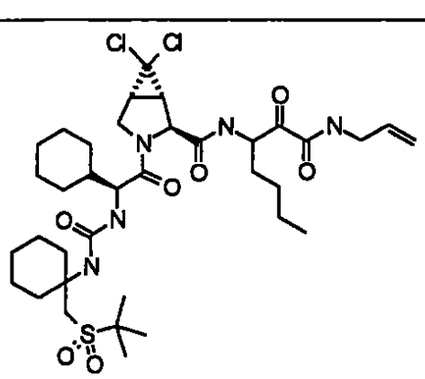
Ej. de Prep	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
349			A
350			A

Ej. de Prep	COMPUESTO	Datos de espec. de masa. selec.	rango de Ki*
351			A

1079

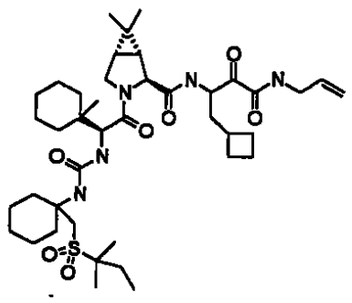
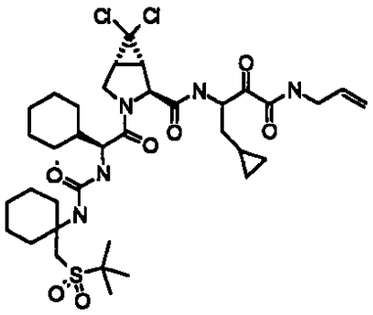
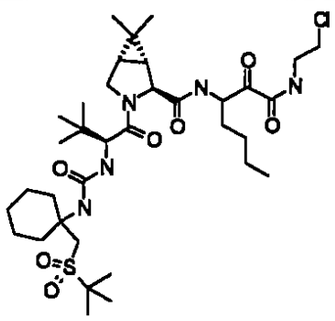
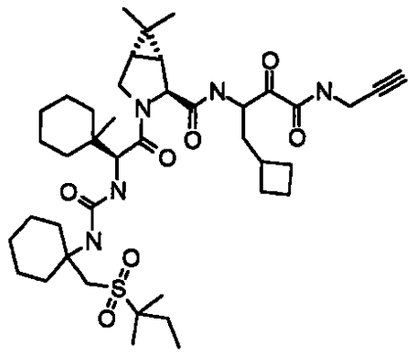
	18	717,9761
	C	754,0095
	7	758,0414

1020

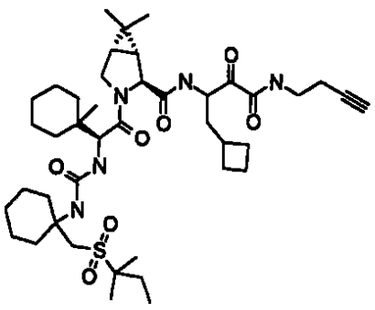
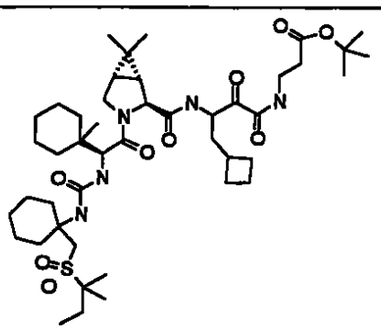
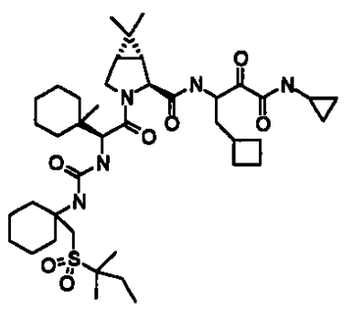
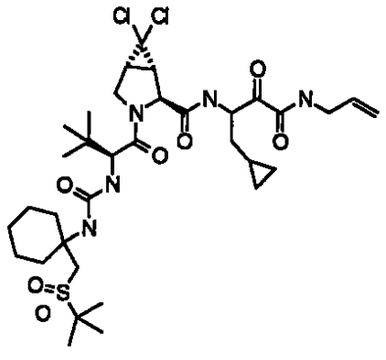
	10	772,0685
	14	760,0574
	4	746,0303
	5	774,855

1038

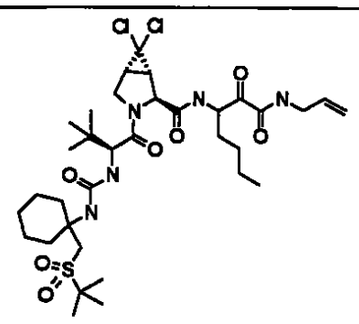
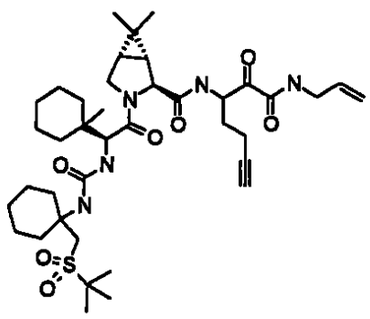
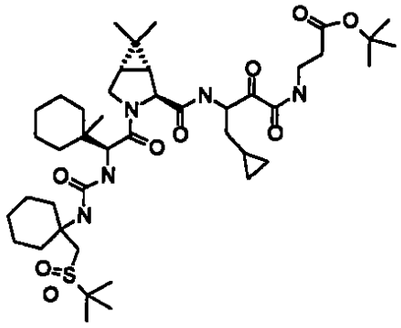
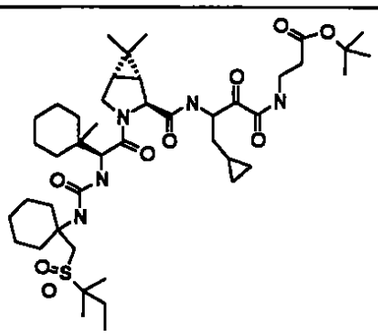
1021

	37	774,0844
	18	772,8391
	27	730,4148
	34	772,0685

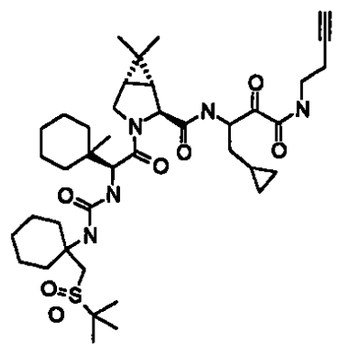
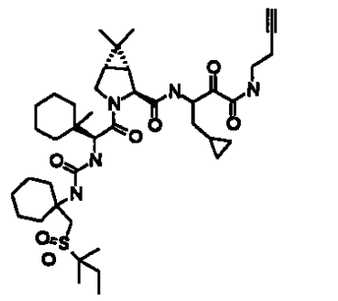
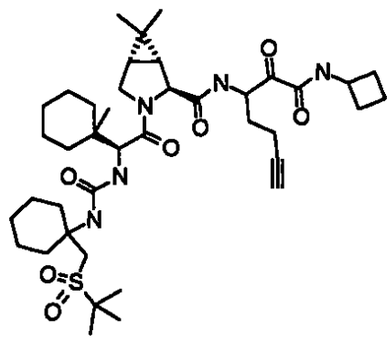
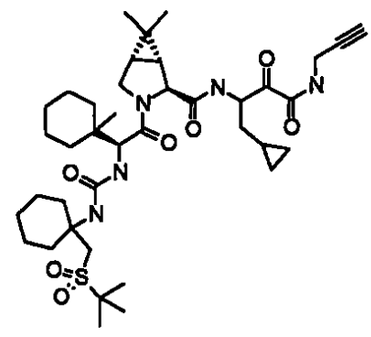
1022

	48	786,0956
	52	862,1916
	54	774,0844
	9	746,8008

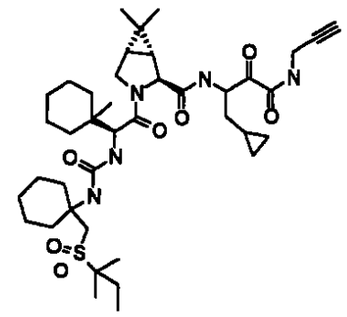
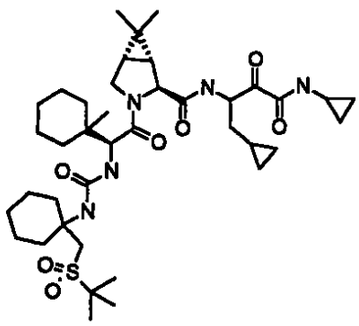
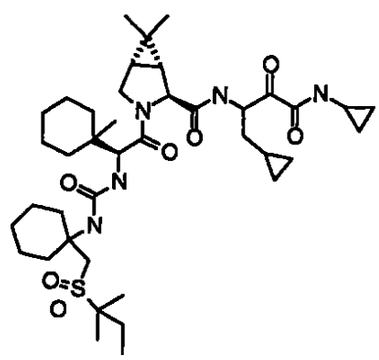
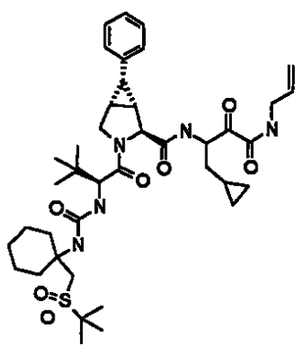
1023

	8	748,8168
	5	744,0143
	17	834,1374
	19	848,1645

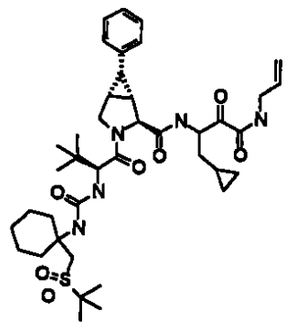
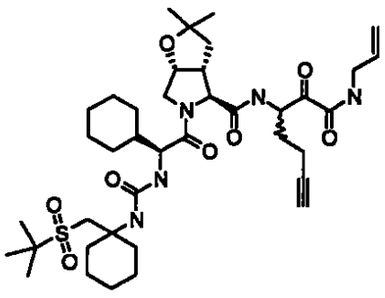
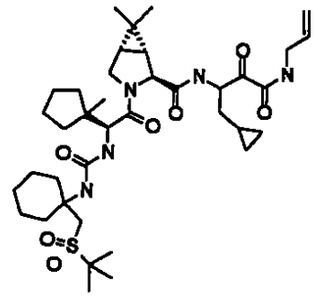
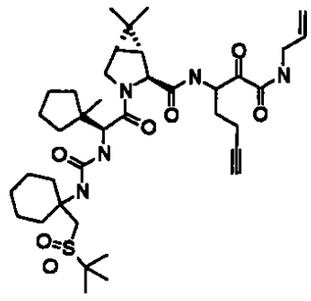
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	17	758,0414
	20	772,0685
	10	758,0414
	8	744,0143

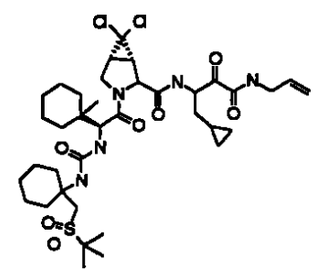
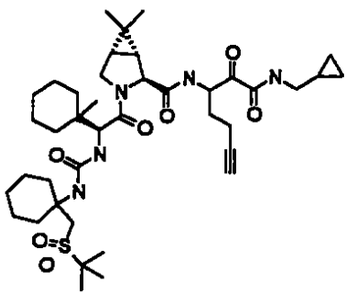
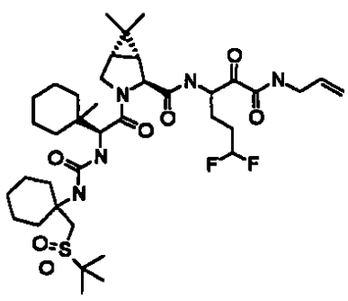
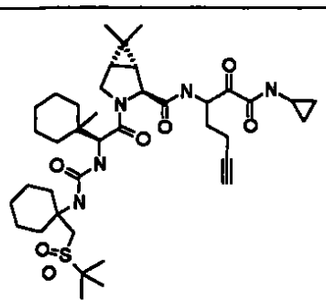
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	17	758,0414
	12	746,0303
	13	760,0574
	C	754,0095

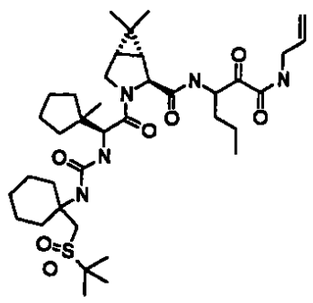
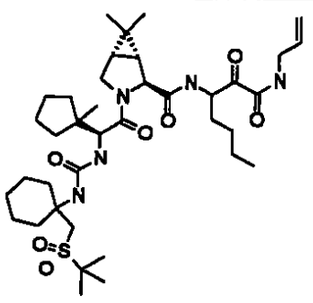
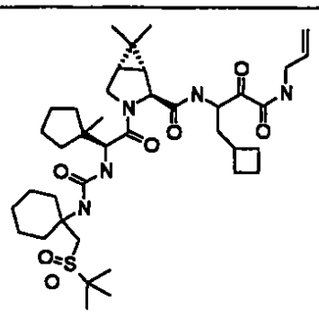
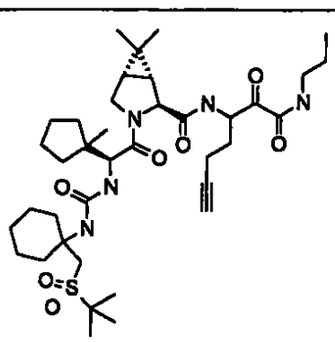
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	C	754,0095
	23	760,0137
	12	732,0032
	2,4	729,9872

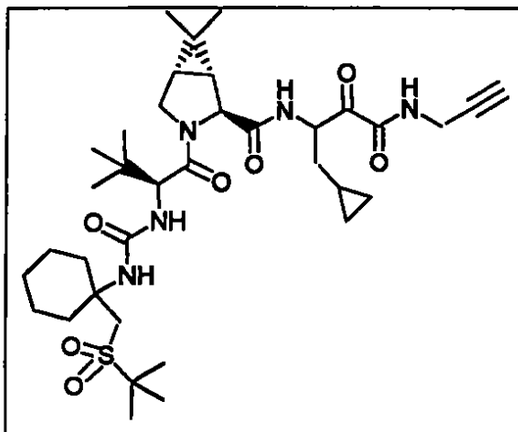
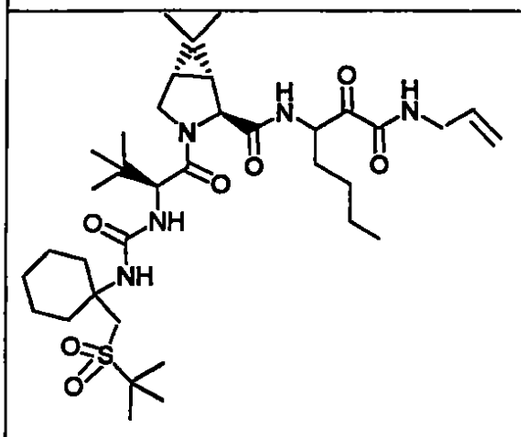
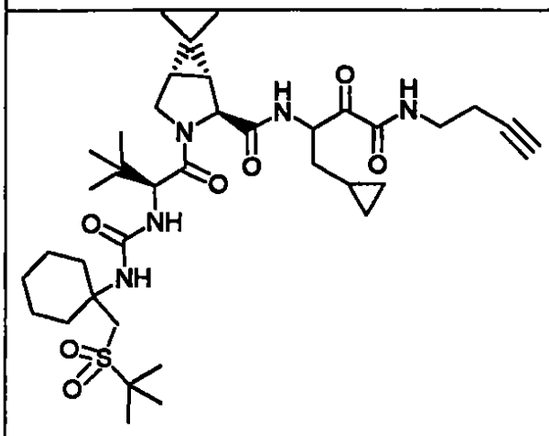
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	B	786,8661
	4	758,0414
	6	770
	6	744,0143

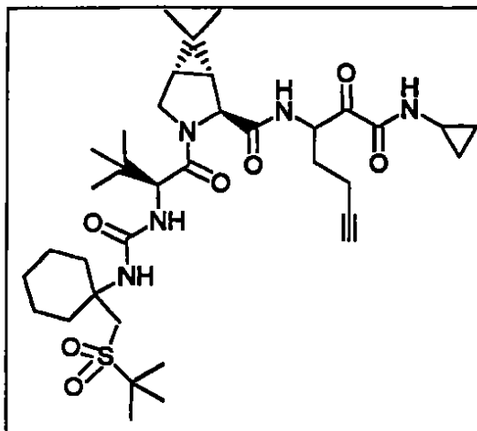
1028

	22	719,992
	22	734,0191
	34	746,0303
	13	732,0032

1029

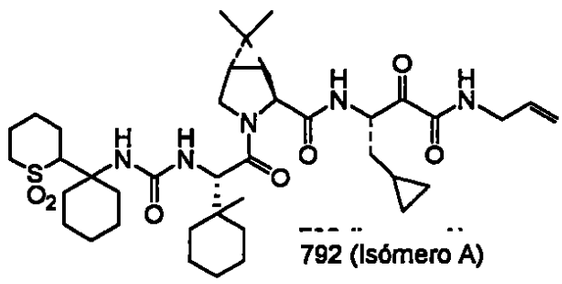
		
		
		

1030



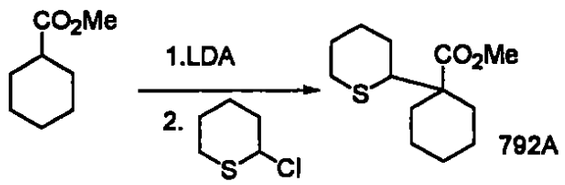
La **Tabla 3A** enumera compuestos adicionales preparados de acuerdo con la presente invención. Los siguientes procedimientos experimentales describen la preparación de los compuestos que se muestran en la **Tabla 3A** que continúa a las descripciones experimentales.

Ejemplo 792



792 (Isómero A)

Paso1



792A

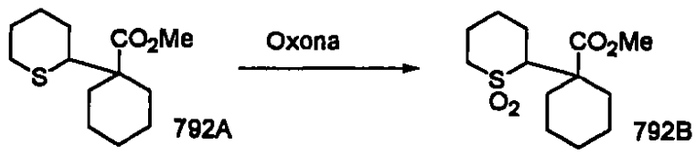
A una solución de sulfuro de pentametileno (10 09 g) en benceno seco (120 ml) se agregó, por porciones (en un período de 40 mín.), N-clorosuccinimida (13,02g) mientras se mantenía la temperatura interna por debajo de los 9°C. La mezcla de reacción resultante se agitó por debajo de los 15°C durante 45 min. El

1031

precipitado se filtró y el sobrenadante se concentró a presión reducida El residuo se diluyó con hexano frío, se filtró y el sobrenadante se concentró a presión reducida para dar el cloruro como un aceite amarillo (11,88g).

A diisopropilamina (12,5 ml) en THF anhidro (15 ml) se agregó n-BuLi (53ml de una solución 1,6M en hexanos) a –78°C, bajo una atmósfera de nitrógeno, y la mezcla resultante se mantuvo a esta temperatura durante un período de 15 min., antes del agregado de ácido metil ciclohexanocarboxílico (12,47 ml) y la reacción se mantuvo a –78°C por 40 min. adicionales. El cloruro en THF anhidro (50 ml) se agregó a la mezcla de reacción y el matraz se retiró del baño refrigerante y se dejó entibiar lentamente hasta la temperatura ambiente. La reacción se desactivó con KH_2PO_4 ac. 5% (100 ml) que contenía HCl conc. acuoso (2,7 ml) Los componentes orgánicos se extrajeron en Et_2O/EtOAc, se secaron ($MgSO_4$) y se concentraron a presión reducida para producir un residuo que se purificó por cromatografía en columna de gel de sílice usando 0-2% EtOAc en hexanos como eluyente. Se obtuvo el compuesto bicíclico (792A; 8,12g) como un aceite amarillo.

Paso 2



792A 792B

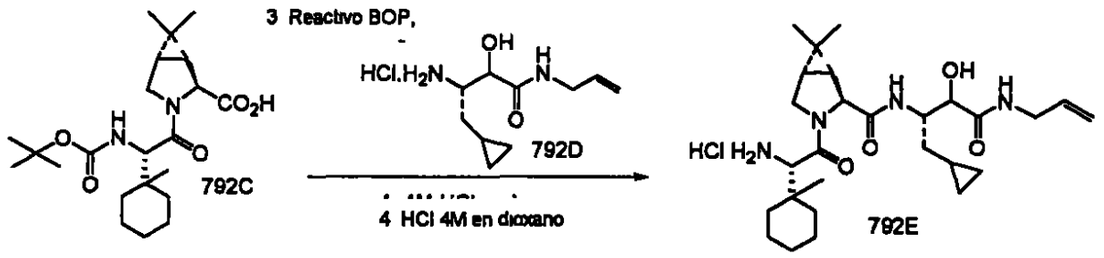
Una solución del sulfuro (792A; 0,780 g) en MeOH ac 50% (8ml) se enfrió hasta 0°C y se agregó a una suspensión fría (0°C) de oxona (5,97g) en MeOH ac 50% (8ml) y la reacción se dejó entibiar hasta la temperatura ambiente hasta la mañana siguiente ntes de repartirse entre cloruro de metileno y agua. La fase acuosa se extrajo adicionalmente con cloruro de metileno y las fases orgánicas combinadas se secaron ($MgSO_4$) y se concentraron a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice usando EtOAc (25-35%) en hexanos para dar la sulfona (792B, 0,1598g). La reacción se repitió usando el

1032

sulfuro (792A; 8,12g), oxona (62,06g), metanol (30 ml), agua (30 ml) para dar la sulfona (792B; 4,73g).

La mezcla racémica (792B; 0,4925 g) se purificó adicionalmente por HPLC quiral usando una columna Chiralpak AS preparativa, usando i-PrOH 40% en hexanos (45ml/min; monitoreado a 218nm Se obtuvo (792B-enantiómero A; 0,247 g; tiempo de retención 37 min), seguido de (792B-enantiómero B; 0,249 g; tiempo de retención 63min).

Pasos 3 y 4:



Paso 3

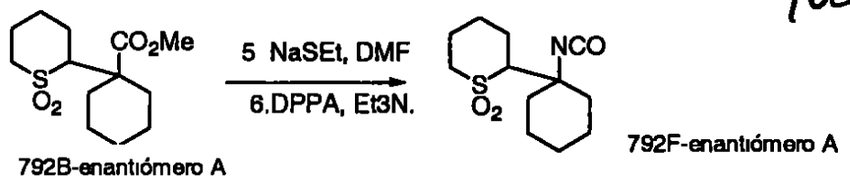
A una solución del ácido carboxílico (792C; 0,172g) y el clorhidrato (792D) en diclorometano (5 ml) se agregó reactivo BOP (0,246g) seguido de trietilamina (0,232 ml) y la mezcla de reacción resultante se agitó hasta la mañana siguiente a temperatura ambiente. La mezcla de reacción se repartió entre EtOAc y HCl acuoso al 10%. Se separó la fase orgánica, se lavó con NaHCO3 ac. sat., agua, se secó ($MgSO_4$) y los volátiles se eliminaron a presión reducida para producir un residuo que se usó en el Paso 4 sin purificación.

Paso 4

Al residuo del paso 3 se agregó HCl 4M en dioxano (10 ml) y la solución se dejó reposar a temperatura ambiente durante un período de 2h. Los volátiles se eliminaron a presión reducida para producir el clorhidrato (792E), usado sin purificación.

Pasos 5 y 6

1033



792B-enantiómero A

792F-enantiómero A

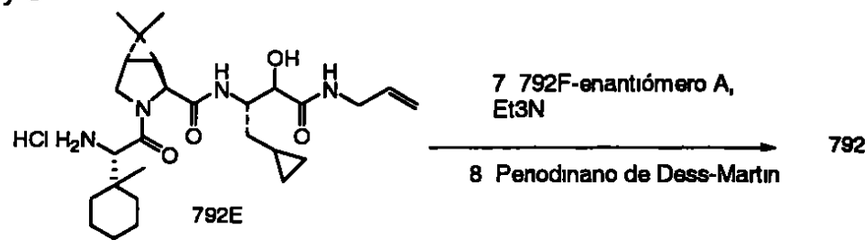
Paso 5

A una solución del metil éster (792B-enantiómero A; 0,100 g) se disolvió en DMF anhidra (1ml) y se agregó etanotiolato de sodio (0,122g) y la mezcla de reacción se dejó agitar a temperatura ambiente durante aprox. 72h. La reacción se repartió entre EtOAc y HCl acuoso al 10%. Se separó la fase orgánica, se lavó con agua (X4), se secó ($MgSO_4$) y los volátiles se eliminaron a presión reducida.

Paso 6

El residuo del paso 5 se disolvió en tolueno anhidro (2 ml) y se agregaron DPPA (0,083ml) y Et_3N (0,054 ml) y la reacción se calentó hasta 120°C, bajo una atmósfera de nitrógeno durante 1h. Luego de enfriar, la reacción se repartió entre EtOAc y NaHCO3 ac. sat. Se separó la fase orgánica, se secó ($MgSO_4$) y los volátiles se eliminaron a presión reducida para dar el isocianato (792F-enantiómero A), usado sin purificación.

Pasos 7 y 8



792E

Paso 7

Al clorhidrato (792E; 0,050 g) en diclorometano (3ml) se agregó trietilamina (0,100 ml) seguido del isocianato (792F; aprox. 0,040 g) en tolueno (1ml) y la mezcla de reacción se agitó a temperatura ambiente hasta la mañana siguiente. La mezcla de reacción se repartió entre EtOAc y HCl acuoso al 10%. Se separó la fase orgánica, se lavó con bicarbonato de sodio ac. sat., agua, se secó ($MgSO_4$).

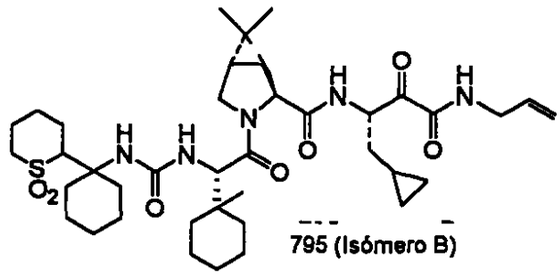
1034

Los volátiles se eliminaron a presión reducida para producir un residuo que se usó sin purificación en el Paso 8.

Paso 8

El residuo del paso 7 se disolvió en diclorometano (3ml) y se agregó periodinano de Dess-Martin (0,100 g) y la reacción se agitó a temperatura ambiente durante 1h. La reacción se repartió entre EtOAc y tiosulfato de sodio 10% ac. Se separó la fase orgánica, se lavó con bicarbonato de sodio ac sat., se secó ($MgSO_4$) y los volátiles se eliminaron a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice usando EtOAc-Hexanos (1:1) como eluyente para dar la cetoamida (792; 0,0436g) como un sólido blanco.

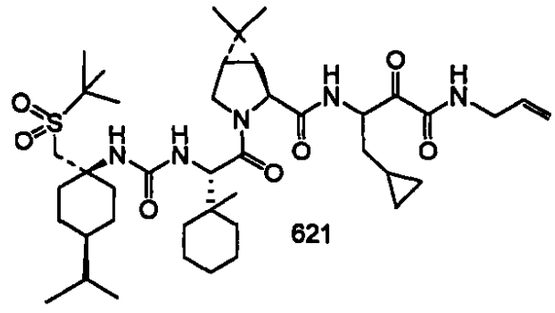
Ejemplo 795



795 (Isómero B)

Usando los procedimientos descriptos para la preparación de 792, 792B-enantiómero B se transformó en el correspondiente isocianato como se describió en los pasos 5 y 6. Luego utilizando 792E y los pasos 7 y 8 y el isocianato derivado de 792B-enantiómero B, se produjo 795.

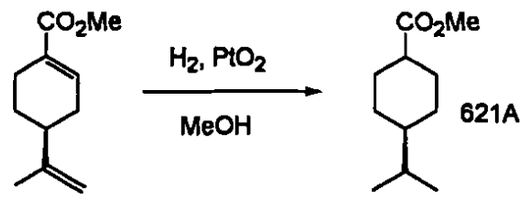
Ejemplo 621:



621

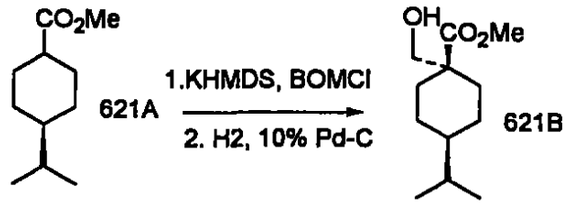
Paso 1

1035



A Perilato de Metilo (3g) en metanol (20ml) se agregó PtO_2 (0,3g) y la suspensión resultante se colocó bajo atmósfera de hidrógeno (globo) hasta la mañana siguiente La suspensión se filtró a través de un taco de celite y el sólido se lavó minuciosamente con metanol El filtrado se concentró a presión reducida para producir el ciclohexano (621A; 2,93g), una mezcla de diastereómeros, como un aceite incoloro.

Pasos 2 y 3



Paso 2

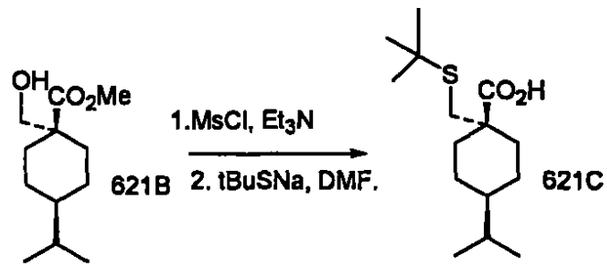
Los ésteres carboxílicos (621A;3,75 g) se disolvieron en dietil éter anhidro (50 ml) y se enfrió hasta –78°C, bajo una atmósfera de nitrógeno. Se agregó gota a gota KHMDS (69ml de una solución 0,5M en tolueno) y la mezcla resultante se agitó durante un adicional de 15 min., antes del agregado de BOMCl (1,7eq.) y el matraz de reacción se retiró del recipiente refrigerante y se dejó entibiar lentamente hasta la temperatura ambiente. Se agregó agua (aprox. 10 ml) y la mezcla se repartió entre EtOAc y HCl acuoso al 10%. Se separó la fase orgánica, se lavó con bicarbonato de sodio ac. sat., agua, se secó ($MgSO_4$), y los volátiles se eliminaron a presión reducida El residuo se purificó por cromatografía en columna de gel de sílice usando EtOAc·Hexanos (1:20) como eluyente, dando el bencil éter intermediario (3,01g), un aceite incoloro

Paso 3

1036

Al bencil éter del paso 2 (2g) se agregó metanol (10 ml), seguido de Pd-C 10% (1g) y la suspensión negra se colocó bajo una atmósfera de hidrógeno (globo) hasta la mañana siguiente. La reacción se filtró a través de un taco de celite y el sólido se lavó minuciosamente con metanol. El filtrado se concentró para dar el alcohol deseado (621B;1,362g) como un aceite incoloro.

Pasos 4 y 5



Paso 4

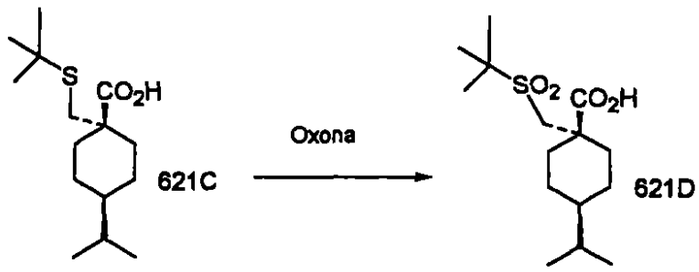
El alcohol (621B; 0,32g) se disolvió en diclorometano (5 ml) y se agregaron cloruro de metansulfonilo (0,166 ml) seguido de trietilamina (0,37 ml) y la reacción resultante se agitó durante 0,5 h antes de repartirse entre EtOAc y HCl acuoso al 10%. Se separó la fase orgánica, se lavó con bicarbonato de sodio ac. sat., agua, se secó (MgSO4) y los volátiles se eliminaron a presión reducida para producir un residuo que se usó en el Paso 5 sin purificación.

Paso 5

El residuo del paso 4 se disolvió en DMF (10 ml) y se agregó ter-butil tiolato de sodio y la mezcla de reacción resultante se agitó a temperatura ambiente bajo una atmósfera de nitrógeno hasta la mañana siguiente. La mezcla de reacción se repartió entre EtOAc y HCl ac. 10%. Se separó la fase orgánica, se lavó con agua (X4), se secó ($MgSO_4$) y los volátiles se eliminaron a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice usando EtOAc-Hexanos (3:7) como eluyente para dar el ácido carboxílico (621C;0,214g)

Paso 6

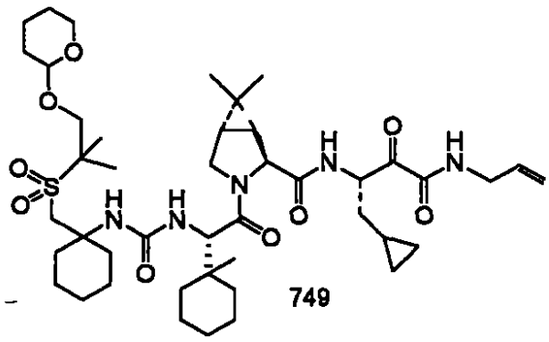
1037



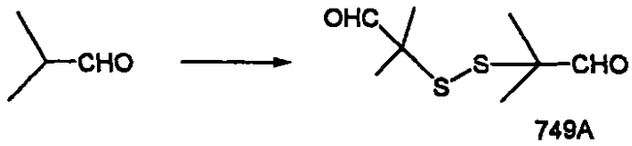
Usando el sulfuro (621C; 0,090 g), oxona (0,61g), metanol (2 ml), agua (2 ml) y el procedimiento establecido en el ejemplo 792 (Paso 2), se obtuvo la sulfona (621D; 0,091g) como un sólido blanco.

Como se describió con anterioridad (Ejemplo 792; Pasos 6 hasta 8), el ácido sulfona-carboxílico se convirtió en el compuesto 621

Ejemplo 749:



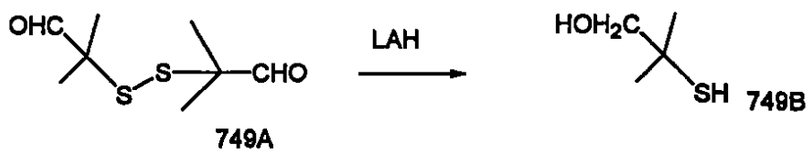
Paso 1



Procedimiento: A isobutiraldehído (59g, 0,69mol) en CCl4 se agregó monocloruro de azufre (27,6ml, 0,345mol, 0,5eq.) gota a gota a 50°C. Luego de un breve lapso (10min), comenzó la evolución de HCl gaseoso. Luego de cesar la evolución de HCl, la mezcla se agitó a 55°C durante 2,5hrs, tras las cuales la TLC indicó que la reacción estaba casi completada. Luego se enfrió hasta la temperatura ambiente El producto bruto se concentró hasta sequedad El residuo oleoso, el disulfuro (749A), fue usado sin purificación.

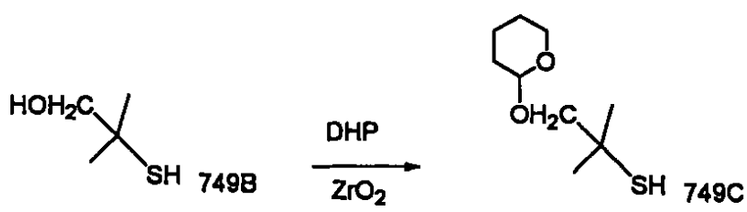
1038

Paso 2



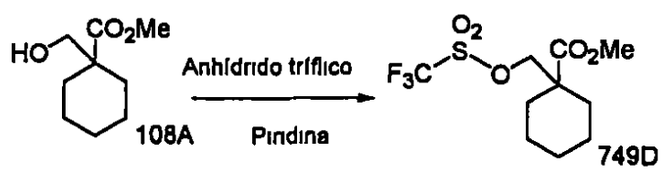
Al disulfuro (749A; 7,5g, 36 mmol) en THF se agregó $LiAlH_4$ (2,76g, 72,7 mmol, 2eq.) a 0°C muy lentamente. La mezcla se agitó a temperatura ambiente durante 3hrs, luego se agregó gota a gota Na2SO4 sat. hasta aparición de un sólido blanco grisáceo. Se agitó a temperatura ambiente durante 10min. Se diluyó con CH_2Cl_2. Se secó sobre $MgSO_4$. Se filtró y se concentró hasta sequedad. Se purifiacó por HPFC con EtOAc 2~20% en Hexano para dar el alcohol (749B, 6,81g). Rendimiento 89%

Paso 3



Al alcohol (749B; 10g, 94,2 mmol) se agregó 3,4-dihidro-2H-pirano (8,8ml, 94,2 mmol, 1equiv) y ZrO_2. (2,0g, 20% p/p) La mezcla se agitó a 80°C durante 2hrs. La reacción se diluyó con CH_2Cl_2 y se filtró El filtrado se concentró hasta sequedad y se purificó por HPFC con EtOAc 2~10% en hexano para dar 14,3g del producto (749C). Rendimiento 80%

Paso 4

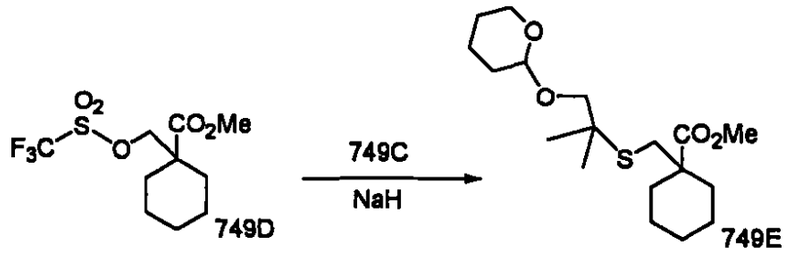


Al alcohol (108A; 3,0g, 17,4 mmol, 1equiv) en CH_2Cl_2 se agregó piridina (2,4 ml, 29,6 mmol, 1,7equiv) y anhídrido tríflico (3,8ml, 22,6 mmol, 1,3equiv) a

1039

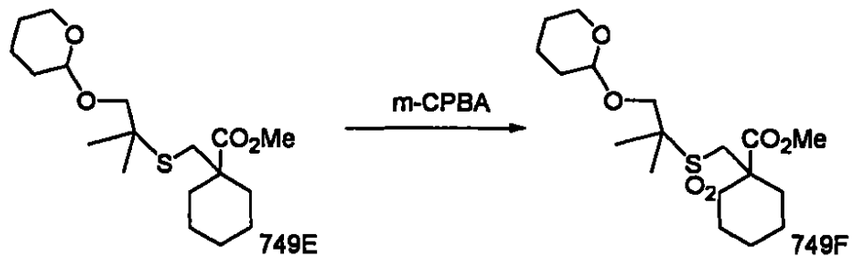
-20°C. La reacción se agitó entre -20~10°C durante 2hr, tras las cuales la EM y la TLC indicaron que la reacción se había completado. Se diluyó con EtOAc, se lavó con NH_4Cl sat.y salmuera. Se secó sobre MgSO4 Se concentró hasta sequedad para dar el sulfonato (749D; 5,21g). Rendimiento 98%.

Paso 5



A THF a 0°C se agregó NaH(1,02g, 25,6 mmol, 1,5eq.), luego (749C; 4,88g, 25,6 mmol, 1,5eq.). La mezcla se agitó a 0°C durante 10min, luego se agregó (749D; 5,21g, 17,1 mmol) a 0°C. La reacción se agitó a temperatura ambiente durante 1hr, tras lo cual la TLC indicó que no restaban más materiales de partida. Se diluyó con EtOAc y agua Se extrajo la fase acuosa con EtOAc La fase orgánica combinada se lavó con H_2O y salmuera. La fase orgánica se secó sobre $MgSO_4$ Se concentró hasta sequedad Se purificó por HPFC con EtOAc 2~8% en hexano para dar (749E;5,89 g) de producto. Rendimiento 100%.

Paso 6



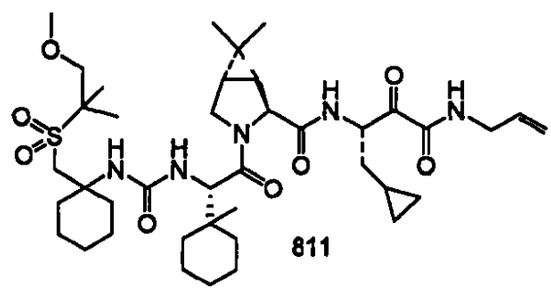
Al sulfuro (749E; 0,17g, 0,49mmol) en CH_2Cl_2 se agregó $NaHCO_3$ (0,205g, 2,45 mmol, 5equiv), mCPBA(0,304g, 1,23mmol, 2,5eq) a 0°C. La reacción se agitó a temperatura ambiente durante 2hrs, tras las cuales la TLC y EM mostraron

1040

que la reacción se había completado. Se diluyó con CH2Cl2. Se lavó con NaHCO3 sat. y salmuera Se secó sobre MgSO4. Se purificó por HPFC con EtOAc 5~20% en hexano para dar 0,14g de la sulfona (749F). Rendimiento 76%.

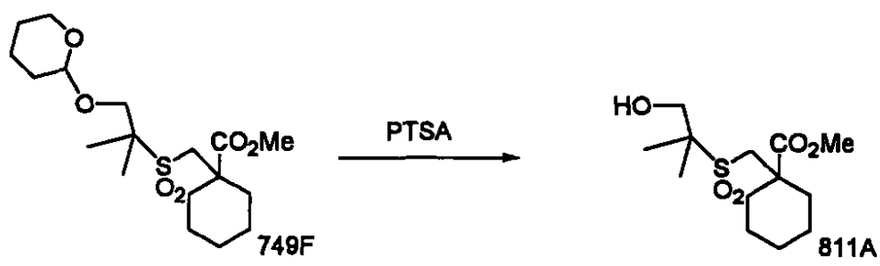
El metil éster (749F) puede convertirse al correspondiente ácido carboxílico y posteriormente al isocianato (Ejemplo 108; Pasos 5 y 6) y convertirse a 749 (Ejemplo 792; Pasos 7 y 8).

Ejemplo 811:

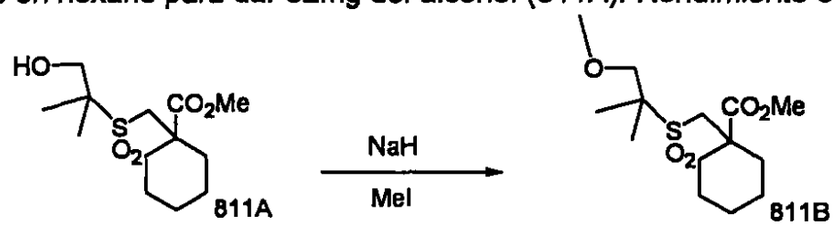


811

Paso 1



Al 749F (70mg,0,18 mmol) en MeOH se agregó pTsOH. La reacción se agitó a temperatura ambiente hasta la mañana siguiente. La EM demostró que la reacción casi se había completado. Se concentró hasta sequedad. Se diluyó con EtOAc. Se lavó con $NaHCO_3$ sat., salmuera. Se purificó por HPFC con EtOAc 10~40% en hexano para dar 52mg del alcohol (811A). Rendimiento 99%.

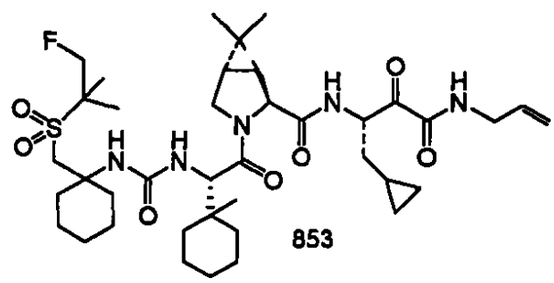


1041

A NaH (88mg, 2,21 mmol, 1,3equiv) en DMF a 0°C se agregó el alcohol (811A; 0,5g, 1,7 mmol) y MeI (0,16ml, 2,56 mmol, 1,5equiv) . La reacción se agitó a temperatura ambiente durante 2hrs, tras las cuales la TLC indicó que la reacción no se había completado. Se agregó nuevamente 1 equiv. de MeI. La reacción se agitó a temperatura ambiente hasta la mañana siguiente. Se diluyó con EtOAc. Se lavó con agua, salmuera Se secó sobre MgSO4. Se purificó por HPFC con EtOAc 2~10~40% en hexano para dar el éter (811B; 0,283g). Rendimiento 54%.

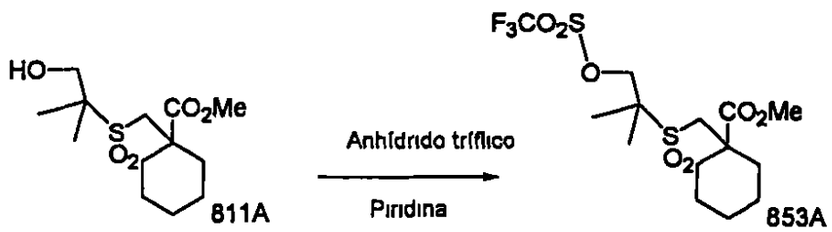
El metil éster (811B) puede convertirse al correspondiente ácido carboxílico y posteriormente al isocianato (Ejemplo 108, Pasos 5 y 6) y convertirse a 749 (Ejemplo 792; Pasos 7 y 8).

Ejemplo 853:



853

Paso 1



Al alcohol (811A; 56mg, 0,19mmol, 1equiv) en CH_2Cl_2 se agregó piridina (0,026ml, 0,32 mmol, 1,7equiv) y anhídrido tríflico (0,042ml, 0,25 mmol, 1,3equiv)

1042

a -20°C. La reacción se agitó a -20~10°C durante 2hr, tras las cuales la EM y TLC indicaron que la reacción se había completado. Se diluyó con EtOAc, se lavó con NH4Cl sat. y salmuera Se secó sobre MgSO4. Se concentró hasta sequedad para dar 75,9 mg del producto bruto (853A).

Paso2

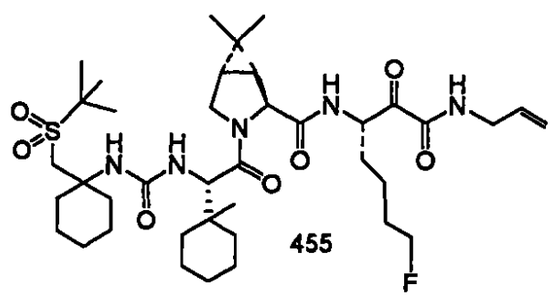


853A 853B

A 853A (75,9mg, 0,18 mmol, 1equiv) en éter se agregó fluoruro de tetra-n-butil amonio (0,23ml, 0,23mmol, 1,3equiv) gota a gota a -15°C. La reacción se agitó a temperatura ambiente hasta el día siguiente. Se diluyó con éter, se lavó con NH4Cl sat. y salmuera. Se secó sobre $MgSO_4$. Se purificó con EtOAc 2~10% en hexano para dar 32mg del fluoruro (853B). Rendimiento 60%.

El metil éster (853B) puede convertirse al correspondiente ácido carboxílico y posteriormente al isocianato (Ejemplo 108; Pasos 5 y 6) y convertirse a 749 (Ejemplo 792, Pasos 7 y 8)

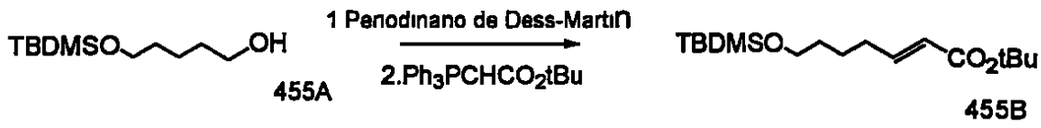
Ejemplo 455:



455

Pasos 1 y 2

1043

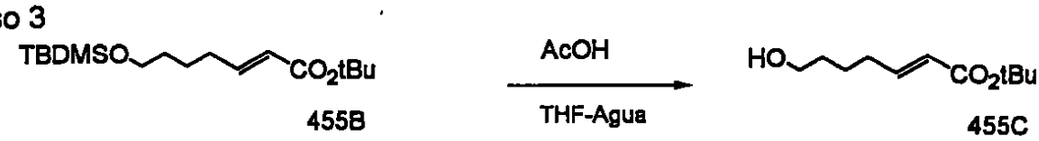


455A 455B

Pasos 1 y 2 ('en un recipiente')

Se agregó Periodinano de Dess-Martin (21,35 g) a una solución del alcohol (455A; 10.00 g) en diclorometano (100 ml) y se agitó durante 45 min antes del agregado del fosforano (17,42g) y se agitó hasta la mañana siguiente. La mezcla de reacción se repartió entre tiosulfato de sodio ac. 5% y EtOAc y se separó la fase orgánica, se lavó con bicarbonato de sodio ac. sat., agua, se secó ($MgSO_4$) y se concentró a presión reducida. Se agregaron hexanos al residuo y la suspensión resultante se agitó vigorosamente durante 2h y se filtró. El filtrado se concentró a presión reducida y se purificó por cromatografía en columna de gel de sílice usando EtOAc-Hexanos (1:99) como eluyente para dar el alqueno deseado (455B; 7,33g) como un aceite amarillo.

Paso 3



455B 455C

Se agregó ácido acético (26 ml) a una solución del silil éter en THF (6 ml) y agua (14 ml) y la mezcla resultante se agitó a temperatura ambiente hasta la mañana siguiente. La reacción se repartió entre EtOAc y bicarbonato de sodio ac. sat. Se separó la fase orgánica, se lavó con agua, se secó ($MgSO_4$) y los volátiles se eliminaron a presión reducida El residuo se purificó por cromatografía en columna de gel de sílice usando EtOAc-Hexanos (1:5) como eluyente para dar el alcohol (455C; 4,46g) como un aceite incoloro

Paso 4

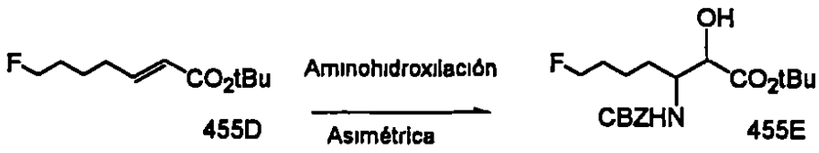


455C 455D

1044

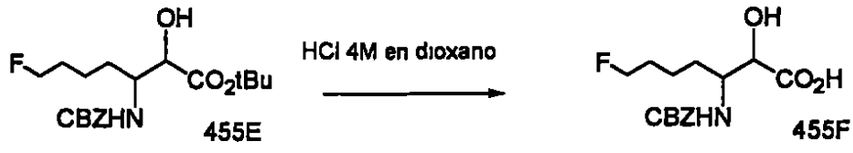
Se agregó DAST (1,32 ml) a una solución agitada del alcohol (455C; 2,00 g) en diclorometano (50 ml) a -78°C, bajo una atmósfera de nitrógeno. Cuando el agregado estuvo completo se retiró el baño refrigerante y la reacción se dejó agitar a temperatura ambiente durante 2h , antes de repartirla entre EtOAc y agua. Se separó la fase orgánica, se secó ($MgSO_4$) y los volátiles se eliminaron a presión reducida antes de la purificación por cromatografía en columna Se obtuvo el fluoruro (455D; 0,758g).

Paso 5



Usando bencilcarbamato (2,06g) en n-PrOH (18ml), el alqueno (455D; 0,881g), NaOH (0,537g), tBuOCl recién preparado (1,54 ml), $(DHQ)_2PHAL$ (0,176g) en nPrOH (16 ml), osmiato de potasio (0,065 g) y el procedimiento expuesto en Angewandte Int. Ed. (Engl), 1996, 35, 2813, se formó un producto en bruto que se purificó por cromatografía en columna de gel de sílice usando EtOAc-Hexanos (1:5) como eluyente para dar la hidroxiamida deseada (455E; 0,892g).

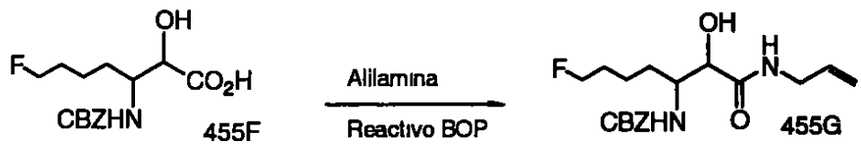
Paso 6



Se agregó HCl 4M en dioxano (25 ml) (ex. Aldrich) al t-Bu éster (455E; 0,69 g) y la solución resultante se dejó reposar a temperatura ambiente durante 2h. Los volátiles se eliminaron a presión reducida para producir el ácido carboxílico (455F; 0,613g), usado en posteriores reacciones sin purificación

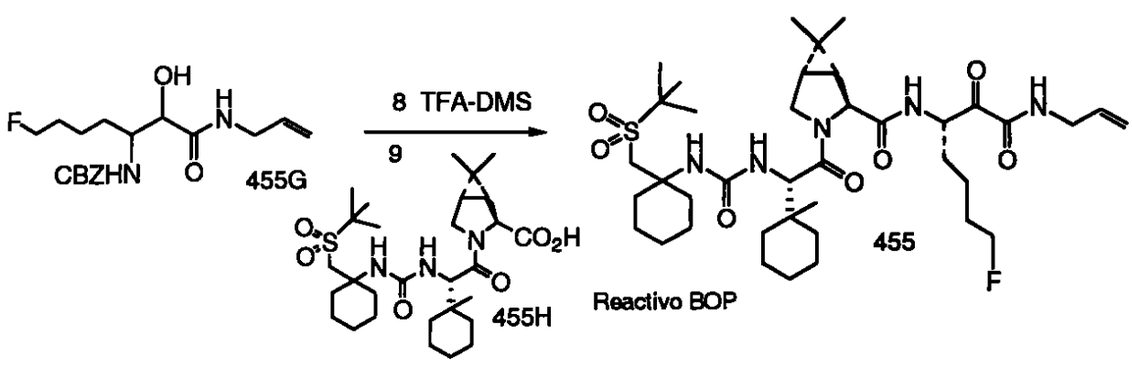
1045

Paso 7



Se agregó reactivo BOP (0,254g), seguido de trietilamina (0,240 ml) a una mezcla del ácido carboxílico (455F; 0,15 g) y alilamina (0,043ml) en diclorometano (5 ml) y la mezcla de reacción resultante se agitó a temperatura ambiente hasta la mañana siguiente. La reacción se repartió entre EtOAc y HCl acuoso al 10%. Se separó la fase orgánica, se lavó con bicarbonato de sodio ac. sat., agua, se secó ($MgSO_4$) y los volátiles se eliminaron a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice on silica gel usando EtOAc:Hexanos (7:3) como eluyente para dar la amida (455 g; 0,151g) como un sólido blanco.

Pasos 8, 9 y 10



10 Periodinano de Dess-Martin

Paso 8

Al bencilcarbamato (455 g; 0,037g) se agregó TFA (2 ml) seguido de sulfuro de metilo (0,5 ml) y la solución resultante se dejó reposar a temperatura ambiente durante 3h., antes de la eliminación de los volátiles. El producto de la reacción en bruto se usó en el Paso 9, a continuación, sin purificación.

Paso 9

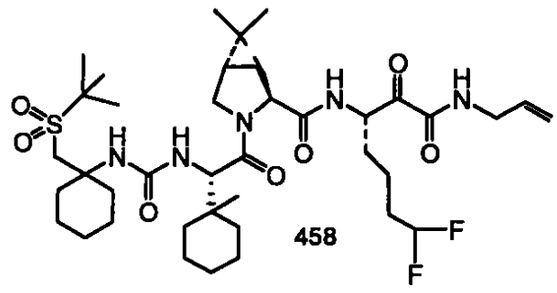
1046

Al residuo del paso 8 se agregó diclorometano (3ml), el ácido carboxílico (455H; 0,050 g), reactivo BOP (0,047g) y finalmente trietilamina (0,044 ml) y la mezcla resultante se agitó a temperatura ambiente hasta la mañana siguiente. La reacción se repartió entre EtOAc y HCl acuoso al 10%. Se separó la fase orgánica, se lavó con bicarbonato de sodio ac. sat., se secó ($MgSO_4$) y los volátiles se eliminaron a presión reducida para producir un residuo que se usó, en el Paso 10, a continuación, sin purificación.

Paso 10

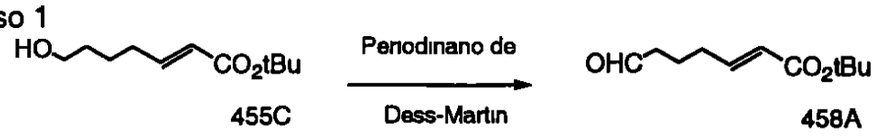
Al residuo del paso 9, se agregó diclorometano (3ml) seguido de Periodinano de Dess-Martin (0,075 g) y la suspensión se agitó a temperatura ambiente durante 2h., antes de repartirla entre between EtOAc y tiosulfato de sodio ac. 5%. Se separó la fase orgánica, se lavó con bicarbonato de sodio ac. sat., agua, se secó ($MgSO_4$) y los volátiles se eliminaron a presión reducida. El producto de la reacción en bruto se purificó por cromatografía en columna de gel de sílice para dar la ceto-amida deseada (455; 0,0467g) como un sólido blanco.

Ejemplo 458:



458

Paso 1



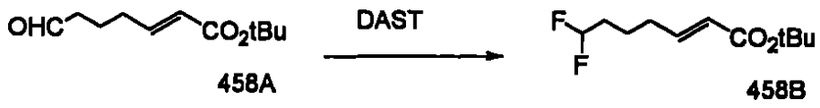
455C 458A

A una solución del alcohol (455C; 1,66g) en diclorometano (20 ml) se agregó Periodinano de Dess-Martin (4,22g) y la mezcla resultante se agitó a temperatura ambiente durante un período de 1h., antes de repartirla entre EtOAc

1047

y tiosulfato de sodio 5% ac. Se separó la fase orgánica, se lavó con bicarbonato de sodio ac. sat., agua, se secó ($MgSO_4$) y los volátiles se eliminaron a presión reducida para producir el aldehído (458A; 0,775 g), usado con purificación.

Paso 2

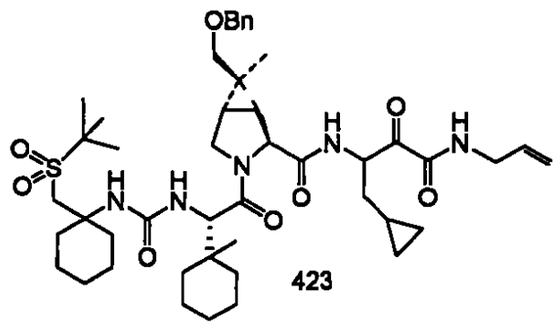


458A 458B

Se agregó DAST (1,11ml) gota a gota a una solución agitada del aldehído (458A; 0,755 g) en diclorometano (50 ml) mientras se enfriaba en un baño de hielo, bajo una atmósfera de nitrógeno. Luego de completarse el agregado, la mezcla resultante se agitó a temperatura ambiente durante un período de 2h., antes de repartirse entre EtOAc y agua. Se separó la fase orgánica, se secó ($MgSO_4$) y los volátiles se eliminaron a presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice para dar el difluoruro deseado (458B; 0,758g).

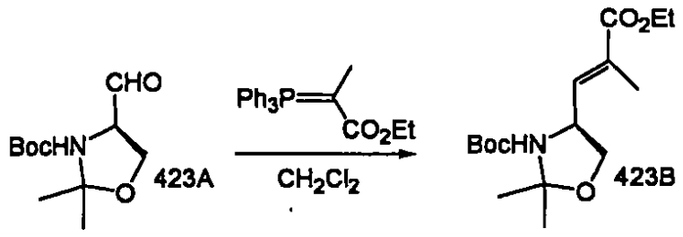
Usando 458B y los procedimientos señalados en el ejemplo 455 (Pasos 5 hasta 10) se obtuvo el producto 458 buscado.

Ejemplo 423.



423

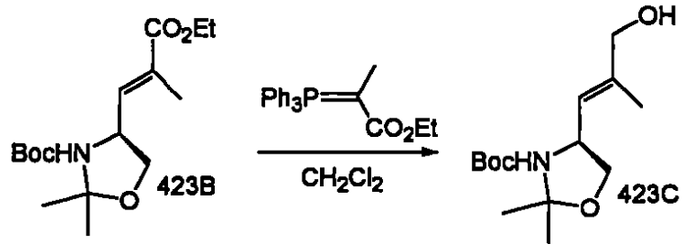
Paso 1



1048

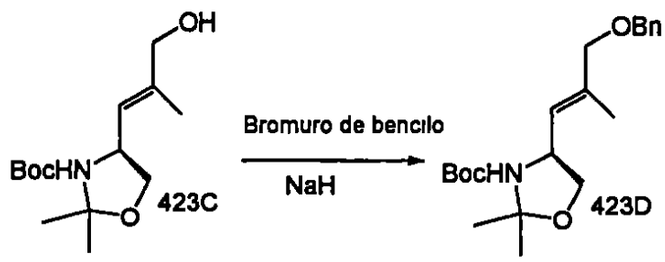
A una solución del aldehído de Garner (423A; 10,7g) en diclorometano (110 ml) se agregó (carbetoxietiliden)trifenilfosforano (28,75 g), la solución resultante se agitó a temperatura ambiente hasta la mañana siguiente. Los volátiles se eliminaron a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice usando EtOAc 4-10% en hexanos para dar el alqueno deseado (423B, 12,7g), como un aceite incoloro.

Paso 2



A una solución del etil éster (423B;12,72g) en diclorometano (20 ml) se agregó DIBAL-H (90ml de una solución 1M en diclorometano) a -78°C, bajo una atmósfera de nitrógeno. Cuando el agregado estuvo completo la reacción se mantuvo a esta temperatura durante un adicional de 30 min a temperatura ambiente durante 1h., antes del agregado de MeOH (3ml) y tartrato de sodio y potasio ac sat. (3ml) y EtOAc. Se separó la fase orgánica, se lavó con HCl acuoso 1M, salmuera y se secó ($MgSO_4$). Los volátiles se eliminaron a presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice usando EtOAc 6-35% en hexanos para dar el alcohol (9,06g), como un aceite incoloro.

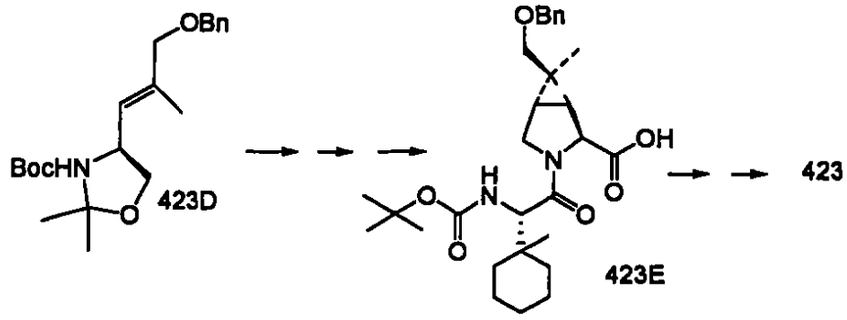
Paso 3



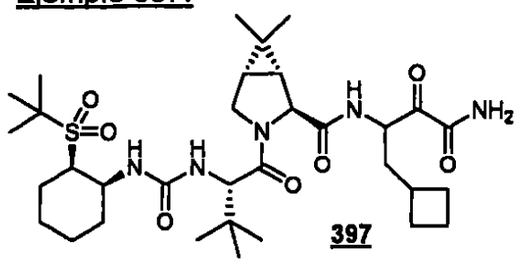
1049

A una solución del alcohol (423C; 8,66g) en DMF anhidra (30 ml), mientras se enfriaba en un baño de hielo, se agregó NaH (1,38g) y la mezcla resultante se mantuvo a esa temperatura durante 45 min., antes del agregado de bromuro de bencilo (5 ml). La reacción se dejó entibiar hasta la temperatura ambiente hasta la mañana siguiente antes del agregado de éter, seguido de HCl acuoso al 10%. Se separó la fase orgánica, se lavó con bicarbonato de sodio sat. ac., salmuera y se secó (Na_2SO_4). Los volátiles se eliminaron a presión reducida para producir un residuo que se purificó por cromatografía en columna de gel de sílice usando EtOAc 8% en hexanos para producir el bencil éter (8,10 g) como un aceite amarillo.

Usando procedimientos análogos descriptos anteriormente para la conversión de 22.03 a 22.01, 423D se transformó en 423E.

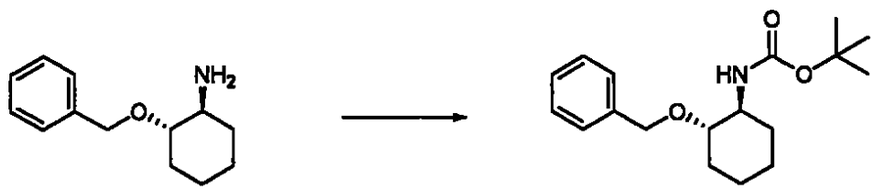


Ejemplo 397:



397

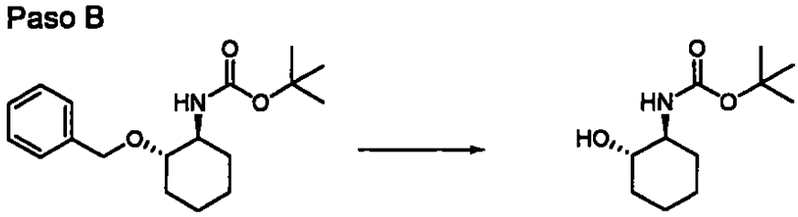
Paso A



397a **397b**

Una solución de benciloxiciclohexil amina **397a** (10,6 g, Lancaster) y N-metilmorfolina (8,5 ml, d 0,920) en 200 ml de diclorometano seco se enfrió hasta -78°C Se agregó anhídrido de Boc en 100 ml de diclorometano seco en un lapso de 15 min usando un embudo de incorporación. Luego de completado el agregado, se retiró el baño refrigerante y la mezcla se agitó por otros 30 min. La mezcla de reacción se repartió entre 300 ml de éter y 100 ml de HCl 1N acuoso La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida para obtener el producto **397b** (15,7 g; 99 %) como un sólido blanco que se usó sin purificación adicional.

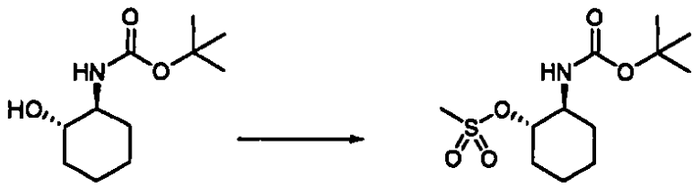
Paso B



397b **397c**

Se agregó dihidróxido de paladio 20% en carbón (30 moles%, 10,8 g) a una solución del bencil éter **397b** (15,7 g) en 300 ml de metanol. La mezcla heterogénea se sometió a hidrogenación a 2,76 x 10^5 Pa (40 psi) hasta que no se detectó más material de partida por TLC (acetato de etilo/hexanos; 2:8). Se filtró la mezcla a través de celite y el filtrado se concentró a presión reducida. No se llevó a cabo una ulterior purificación para el producto **397c** (11,1 g; 99%)

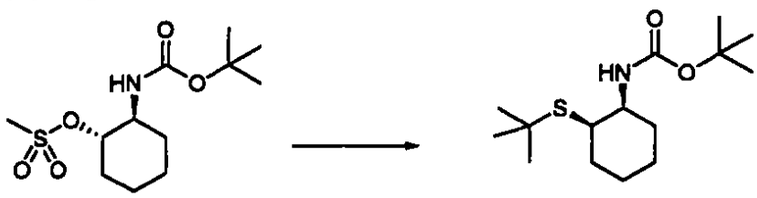
Paso C



397c **397d**

Se agregó piridina (25,0 ml) a una solución del ciclohexanol **397c** en 300 ml de diclorometano seco a 0°C. Se agregó cloruro de metansulfonilo (8,0 ml) en 100 ml de diclorometano seco en un lapso de 15 min. La mezcla de reacción se convirtió en una solución homogénea amarilla. La mezcla de reacción se agitó a 0°C durante 15 min y luego se retiró el baño refrigerante. La reacción se agitó a temperatura ambiente durante aproximadamente 3 h La mezcla se repartió entre éter (500 ml) y HCl acuoso 1N (100 ml). La fase orgánica se lavó con bicarbonato de sodio acuoso saturado (100 ml), salmuera (100 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se cromatografió sobre gel de sílice (gradiente· acetato de etilo/(Hexanos-diclorometano, 1:1); 0:10 hasta 2:8) para obtener el producto **397d** (9,7 g; 64 %) como un sólido blanco.

Paso D



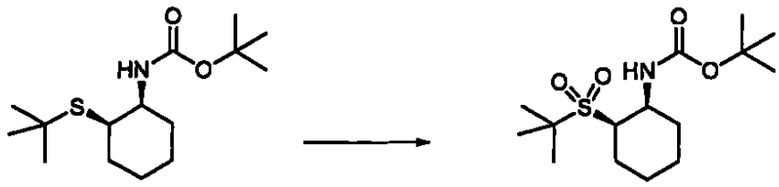
397d **397e**

Un matraz de 250 ml se cargó con el mesilato **397d** (3,0 g) y sal sódica del t-butiltiol (3,44 g) Al matraz se le inyectó nitrógeno y se agregaron 100 ml de DMF seca. La solución resultante se desgasificó (vacío/corriente de nitrógeno) y se calentó a 70°C. El curso de la reacción se monitoreó mediante TLC (acetato de etilo/hexanos; 2:8). Todo el material de partida se consumió en aproximadamente 3 h La mezcla de reacción se disolvió en 300 ml de acetato de etilo y se lavó con agua (3 x 50 ml) y salmuera (1 x 50 ml). La fase orgánica se secó sobre sulfato de

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magnesio, se filtró y se concentró. No se efectuó ninguna otra purificación para el producto **397e** (2,78 g; 95 %)

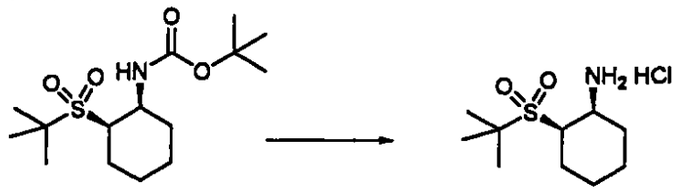
Paso E



397e **397f**

Una solución del sulfuro **397e** (10,22 mmol) en diclorometano seco (60 ml) se trató con m-CPBA (5,28 g; 60%) La mezcla homogénea mixture se calentó a 45°C durante alrededor de 3 h. El análisis por TLC (acetato de etilo/hexanos; 1:9) demostró que todo el material de partida se había consumido. La mezcla se concentró a presión reducida y el residuo se disolvió en 20 ml de éter y se trató con solución acuosa de tiosulfato de sodio a 0°C. La mezcla se diluyó con éter (350 ml) y se lavó con bicarbonato de sodio acuoso saturado (5 x 30 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se cromatografió sobre gel de sílice (gradiente. acetona/hexano; 3:97 hasta 2:8) para obtener el producto **397f** (2,45 g; 75 %) como un sólido blanco.

Paso F

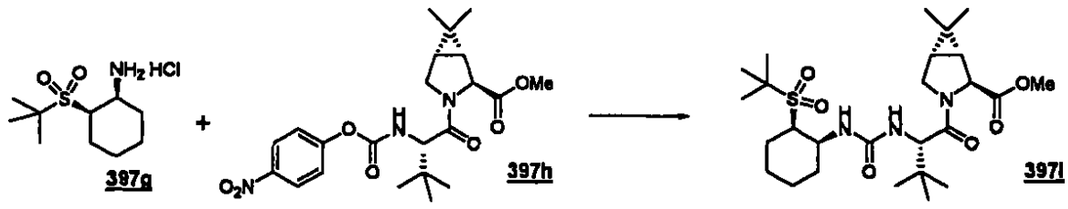


397f **397g**

La amina N-Boc protegida **397f** (2,43 g) se disolvió en 20 ml de HCl 4M en dioxanos. La mezcla se agitó a temperatura ambiente hasta que todo el material de partida se había consumido, según se determinó por análisis por TLC (acetato de etilo/hexanos; 2:8). Luego de 3 h, todos los volátiles se eliminaron a presión reducida para obtener el producto **397g** (1,90 g; 98 %) como un sólido blanco.

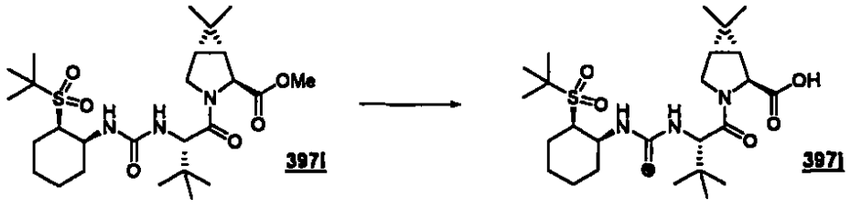
Paso G

1053



Una solución del p-nitrofenilcarbamato **397h** (640 mg) en 10 ml de acetonitrilo se trató con el clorhidrato de amina **397g** (350 mg). Se agregó N-metilmorfolina (0,37 ml, d 0,920) a la mezcla heterogénea y la mezcla de reacción se agitó a temperatura ambiente. La reacción se completó después de 7 h, según se determinó por análisis por TLC (acetona/hexanos; 2:8). La mezcla de reacción se concentró a presión reducida El residuo se disolvió en 150 ml de diclorometano y se lavó con HCl 1N acuoso (1 x 30 ml), y bicarbonato de sodio acuoso saturado (2 x 30 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto se purificó sobre gel de sílice (gradiente: acetona/hexanos; 1:9 hasta 4.6) para obtener el producto **397i** (625 mg; 87 %) como un sólido blanco.

Paso H

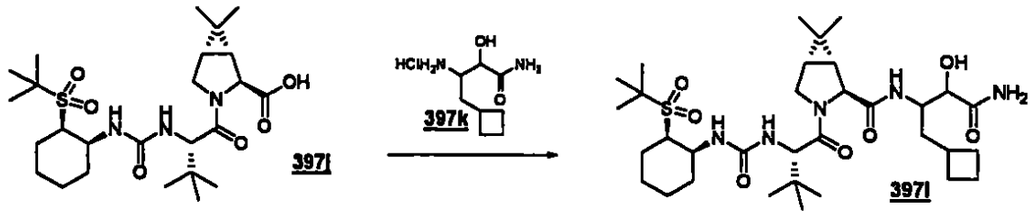


Una solución del metil éster **397i** (610 mg) en 15 ml de una mezcla de THF/MeOH/agua (1.1:1) se trató con hidróxido de litio monohidrato (121 mg). La reacción se agitó a temperatura ambiente y se monitoreó por TLC (acetona/hexanos; 3:7). Luego de 3 h, todos los volátiles se eliminaron a presión reducida. El residuo se repartió entre 30 ml de HCl 1N acuoso y 100 ml de diclorometano. La fase acuosa se volvió a extraer con diclorometano (2 x 30 ml). Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se

1054

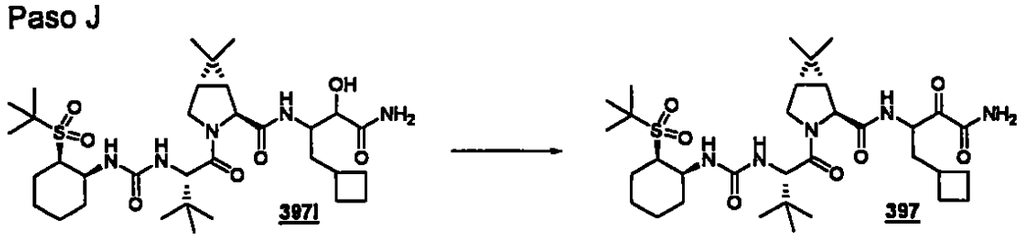
filtraron y se concentraron a presión reducida para obtener el producto **397j** (570 mg; 96 %) como un sólido blanco.

Paso I



Una solución del ácido **397j** (120 mg) en 2 ml de diclorometano seco y 2 ml de DMF seca se agitó a 0°C y se trató con HATU (124 mg). Se agregó el clorhidrato de amina **397k** (63 mg) seguido del agregado de N-metil morfolina (0,10 ml, d 0,920). La mezcla de reacción se entibió gradualmente hasta la temperatura ambiente y se agitó hasta la mañana siguiente. Todos los volátiles se eliminaron al vacío y el residuo se absorbió en 100 ml de acetato de etilo. La fase orgánica se lavó con HCl 1N acuoso (15 ml), bicarbonato de sodio acuoso saturado (15 ml) y salmuera (15 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida para obtener el producto deseado **397l** (150 mg; 96 %), que se usó sin purificación adicional.

Paso J

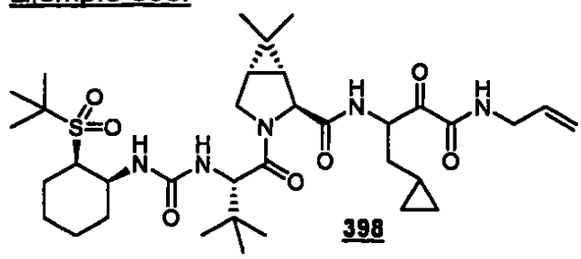


Una solución de **397l** (150 mg) en 6 ml de una mezcla 1:1 de tolueno/DMSO se trató con EDCI (430 mg) y ácido dicloroacético (0,09 ml, d 1,563). La mezcla de reacción se agitó a temperatura ambiente durante aproximadamente 2 h La mezcla de reacción se diluyó con diclorometano (100 ml) y se lavó con bicarbonato de sodio acuoso saturado (15 ml), HCl acuoso 1N (15 ml) y salmuera (15 ml). La fase orgánica se secó sobre sulfato de magnesio,

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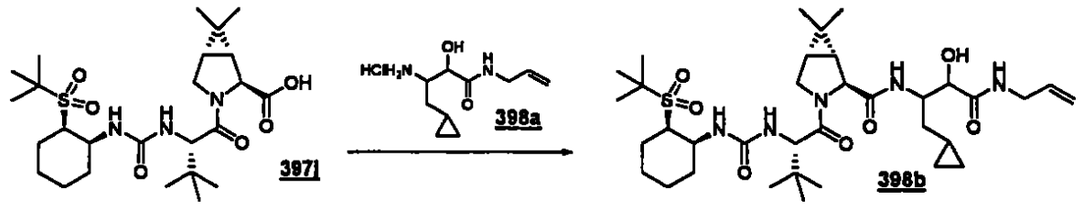
se filtró y se concentró a presión reducida El residuo se cromatografió sobre gel de sílice (gradiente acetona/hexanos; 2:8 hasta 5:5) para obtener el producto **397** (94 mg, 64%) como un sólido blanco. HRMS calculado for $C_{33}H_{58}N_5O_7S$ $[M+H]^+$ 666,3900, experimental 666,3883.

Ejemplo 398:



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Paso A

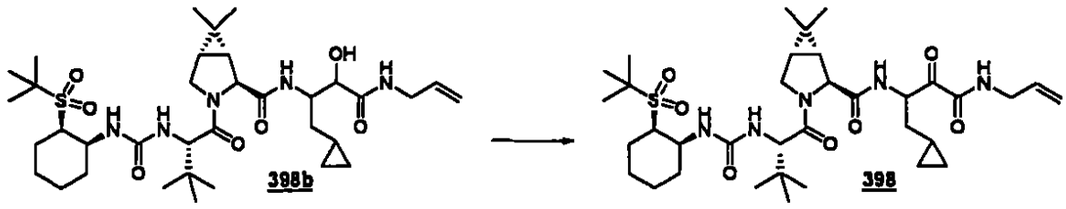


397j **398a** **398b**

Una solución del ácido **397j** (100 mg) en 2 ml de diclorometano seco y 2 ml de DMF seca se agitó a 0°C y se trató con HATU (103 mg). Se agregó el clorhidrato de amina **398a** (60 mg) seguido del agregado de N-metil morfolina (0,09 ml, d 0,920) La mezcla de reacción se entibió gradualmente hasta la temperatura ambiente y se agitó hasta la mañana siguiente. Todos los volátiles se eliminaron al vacío y el residuo se absorbió en 100 ml de acetato de etilo La fase orgánica se lavó con HCl acuoso 1N (15 ml), bicarbonato de sodio acuoso saturado (15 ml) y salmuera (15 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida para obtener el producto deseado **398b** (115 mg; 86 %)

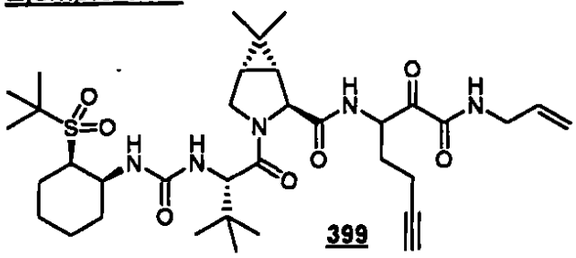
Paso B

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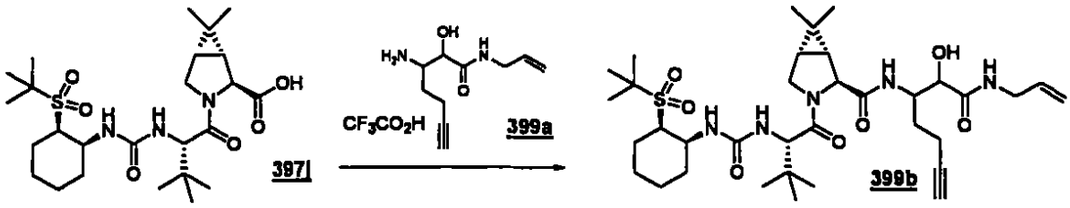


Una solución de la hidroxiamida **398b** (115 mg) en 10 ml de diclorometano seco se trató con Periodinano de Dess-Martin (210 mg) La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla se trató con solución acuosa de sulfito de sodio 1M (10 ml) y bicarbonato de sodio acuoso saturado (10 ml) y se agitó durante 15 min La mezcla se extrajo con diclorometano (3 x 30 ml). Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron, y se concentraron. El residuo se cromatografió sobre gel de sílice (gradiente: acetona/hexanos; 2:8 hasta 5:5) para obtener el producto **398** (60 mg; 53%) como un sólido blanco HRMS calculado para $C_{35}H_{58}N_5O_7S$ $[M+H]^+$: 692,4057, experimental 692,4081.

Ejemplo 399:



Paso A

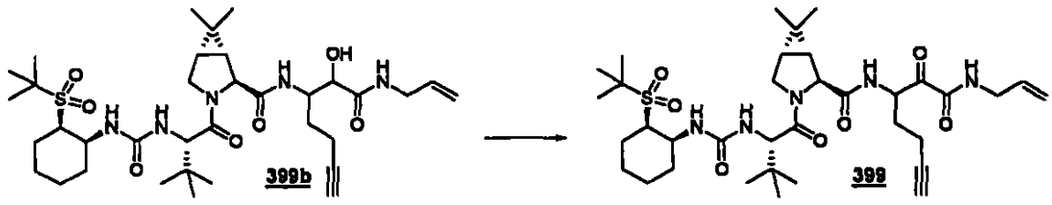


Una solución del ácido **397j** (100 mg) en 2 ml de diclorometano seco y 2 ml de dry DMF se agitó a 0°C y se trató con HATU (106 mg). Se agregó gota a gota una solución de la sal de amina **399a** (0,252 mmol) y N-metil morfolina (0,09 ml, d 0,920) en 1 ml de diclorometano. La mezcla de reacción se entibió gradualmente

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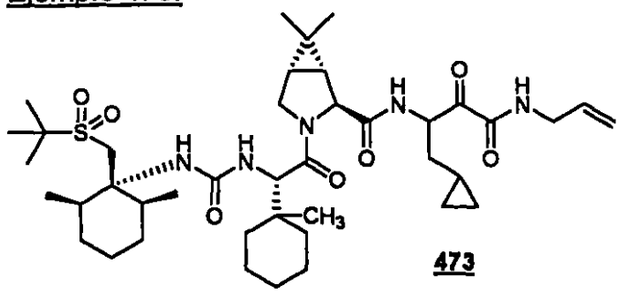
hasta la temperatura ambiente y se agitó hasta la mañana siguiente. Todos los volátiles se eliminaron al vacío y el residuo se absorbió en 100 ml de acetato de etilo. La fase orgánica se lavó con HCl acuoso 1N (15 ml), bicarbonato de sodio acuoso saturado (15 ml) y salmuera (15 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida para obtener el producto deseado **399b** (85 mg; 63 %).

Paso B



Una solución de la hidroxiamida **399b** *(85 mg) en 10 ml de diclorometano* seco se trató con Periodinano de Dess-Martin (157 mg). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla se trató con solución acuosa 1M de tiosulfato de sodio (10 ml) y bicarbonato de sodio acuoso saturado (10 ml) y se agitó durante 15 min. La mezcla se extrajo con diclorometano (3 x 30 ml). Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron, y se concentraron. El residuo se cromatografió sobre gel de sílice (gradiente: acetona/Hexanos; 2:8 hasta 4:6) para obtener el producto **399** (50 mg; 60%) como un sólido blanco. HRMS calculado para $C_{33}H_{55}N_6O_7S$ $[M+H]^+$. 679,3853, experimental 679,3834.

Ejemplo 473:



Paso A

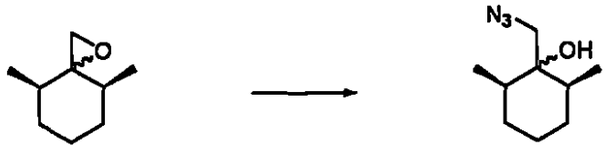
1058



473a **473b**

Se agregó cis-2,6-dimetil-1-metilenciclohexano (3,0 g, ChemSamp Co.) a una suspensión agitada de bicarbonato de sodio sólido (6 eq, 12,19 g) en 150 ml de diclorometano. La mezcla se enfrió hasta 0°C y se agregó en pequeñas porciones una suspensión de m-CPBA 70% (3 eq, 17,4 g) en 150 ml de diclorometano. Después de competado el agregado, se retiró el baño refrigerante y la mezcla se agitó durante aproximadamente 2h. El exceso de m-CPBA se desactivó a 0°C por agregado cuidadoso de solución acuosa saturada de tiosulfato de sodio. La mezcla se lavó con solución acuosa saturada de bicarbonato de sodio (100 ml). La fase orgánica se concentró en el rotavap (se usó un baño de hielo-agua). El residuo se disolvió en éter (80 ml) y hexanos (120 ml) y se lavó varias veces con solución acuosa saturada de bicarbonato de sodio. La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida (baño de hielo-agua). El residuo se cromatografió sobre gel de sílice (gradiente: éter/hexanos; 0:10 hasta 8:92) para obtener el producto **473b** (3,0 g; 90 %) como un aceite incoloro.

Paso B



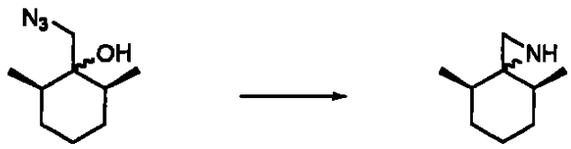
473b **473b**

Se trató una mezcla heterogénea del epóxido **473b** (3 g) y cloruro de amonio (5 eq, 5,72 g) en 80 ml de metanol con azida sódica (5 eq, 7,17 g) y se calentó a 65°C durante 3 h. El análisis por TLC demostró que quedaba algo de material de partida y se agregaron más cloruro de amonio (1,5 eq, 1,71 g) y azida sódica (1,5 eq, 2,15 g). La mezcla se calentó (65°C) hasta la mañana siguiente.

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La mezcla de reacción se diluyó con 30 ml de agua y se extrajo con éter (3 x 100 ml). Los extractos orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida. El residuo se cromatografió sobre gel de sílice (gradiente: éter/hexanos; 0.10 hasta 2:8) para obtener el correspondiente producto diastereomérico **473b** (2,73 g; 71 %) como un aceite incoloro.

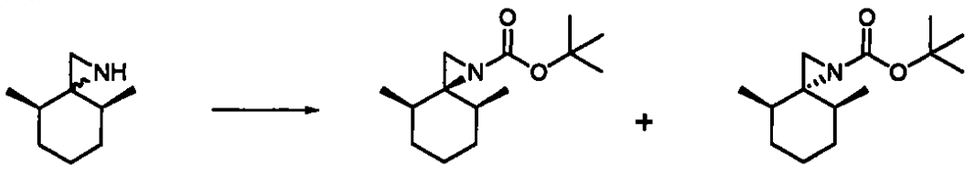
Paso C



473b **473c**

Una solución del azidoalcohol **473b** (1,73 g) en 50 ml de acetonitrilo se trató con trifenilfosfina (1,1 eq, 2,69 g) y se reflujó durante 1 h. La mezcla de reacción se concentró a presión reducida y el residuo se cromatografió sobre gel de sílice (gradiente: éter/hexanos; 5 5 hasta 9:1) para obtener la azirıdina deseada, el **473c** (2,0 g, 98 %).

Paso D



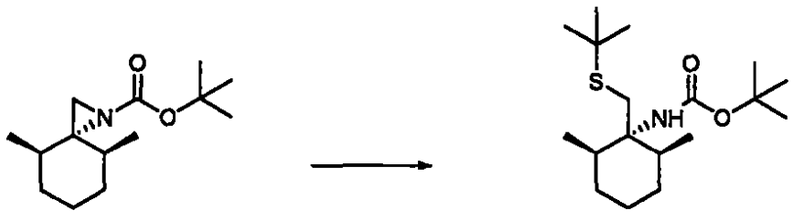
473c **473d** **473e**

Una solución de la aziridina **473c** (aprox. 1,5 g) en diclorometano seco (50 ml) se enfrió hasta 0°C y se trató con di-ter-butildicarbonato (1,3 eq, 3,0 g) en 50 ml de diclorometano seco. Se agregó N-metılmorfolina (2,5 eq, 2,9 ml, d 0,920) gota a gota y la mezcla se agıtó hasta la mañana sıguiente (temp: 0 a 25°C). La mezcla se diluyó con éter (300 ml) y se lavó con HCl 1M acuoso (100 ml), bicarbonato de sodio acuoso saturado (80 ml) y salmuera (80 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se cromatografió sobre gel de sílice (gradiente: éter/hexanos;

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0 10 hasta 1:9) para obtener los productos **473d** y **473e** como aceites transparentes (970 mg).

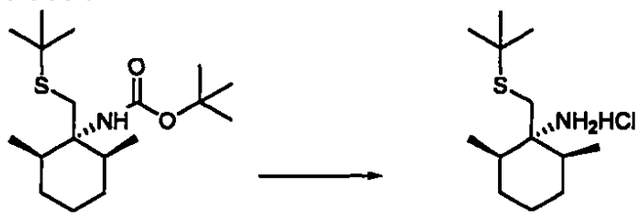
Paso E



473e **473f**

Se cargó un vial de 20 ml con una solución de la N-Boc-azirıdına **473e** (469 mg) en 20 ml de DMF seca y ter-butıltıolato de sodio (2 eq, 438 mg). La reacción se llevó a cabo en un horno de microondas a 130°C durante 30 min. La mezcla de reacción se dıluyó con 100 ml de éter y se lavó con agua (3 x 30 ml) y salmuera (20 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se cromatografió sobre gel de sílice (gradiente· Hexanos hasta éter/Hexanos 4:96) para obtener el producto **473e** (140 mg) como un sólido blanco y materıal de partida sın reaccionar (120 mg).

Paso F

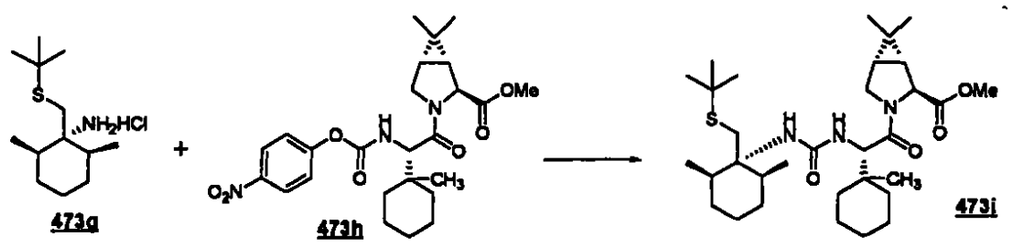


473f **473g**

La amina N-Boc protegida **473f** (140 mg) se disolvió en 10 ml de solución de HCl 4M en dıoxanos La solución resultante se agitó a temperatura ambiente durante 30 min hasta que todo el material de partida se había consumido, según lo determinado por análisis por TLC (éter/Hexanos; 5·95). Todos los volátiles se eliminaron a presión reducida y el residuo se sometió a alto vacío durante 3 h para obtener el producto **473g** (112 mg; 98%) como un sólido blanco.

Paso G

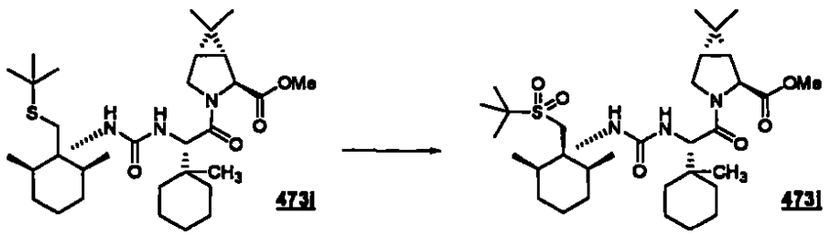
1061



473g 473h 473i

Una solución del p-nitrofenilcarbamato **473h** (1,05 eq, 212 mg) en 3 ml de acetonitrilo se trató con el clorhidrato de amina **473g** (110 mg) en 2 ml de acetonitrilo. Se agregó N-metilmorfolina (2,5 eq, 0,11 ml, d 0,920) y la solución amarilla resultante se agitó a temperatura ambiente durante 8 h. La mezcla de reacción se concentró a presión reducida y el residuo se disolvió en 100 ml de diclorometano y se lavó con HCl acuoso 1N (1 x 20 ml), y solución acuosa saturada de bicarbonato de sodio (2 x 20 ml) La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto se purificó sobre gel de sílice (gradiente· Hexanos hasta acetona/Hexanos, 2·8) para obtener el producto **473i** (150 mg; 63%).

Paso H



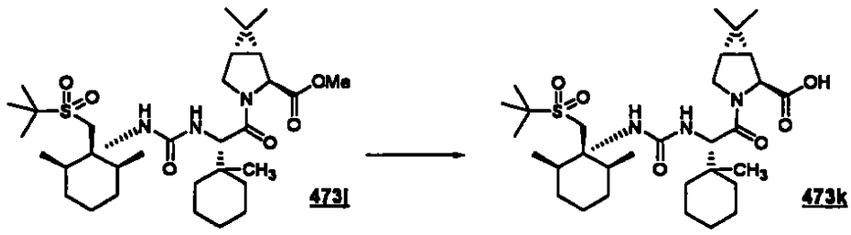
473i 473j

Una solución del sulfuro **473i** (150 mg) en diclorometano seco (15 ml) se trató con m-CPBA 60% (3 eq, 134 mg) La mezcla homogénea se calentó a 45°C por aproximadamente 1,5 h. El exceso de m-CPBA se desactivó por agregado de solución acuosa de tiosulfato de sodio (20 ml) y se continuó agitando por 10 min. Se agregó solución acuosa saturada de bicarbonato de sodio (20 ml) y el producto se absorbió en acetato de etilo (100 ml). La fase orgánica se concentró y el residuo se disolvió en acetato de etilo (80 ml). La fase orgánica se lavó con solución acuosa saturada de bicarbonato de sodio (3 x 10 ml) y salmuera (10 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. El

1062

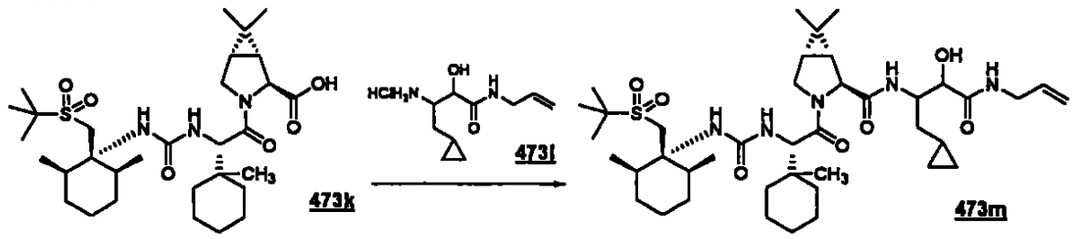
residuo se cromatografió sobre gel de sílice (gradiente: acetato de etilo/hexanos; 1:3 hasta 5:5) para obtener el producto **473j** (120 mg; 76%) como un aceite incoloro.

Paso I



Una solución del metil éster **473j** (110 mg) en 10 ml de una mezcla 1.1:1 de THF/agua/MeOH se enfrió hasta 0°C y se trató con hidróxido de litio monohidrato (2,5 eq, 19 mg). Se retiró el baño refrigerante después de 30 min y la mezcla se agitó a temperatura ambiente por otras 2 h hasta que todo el material de partida se había consumido, según se determinó por análisis por TLC (acetato de etilo/hexanos; 3:7). La mezcla de reacción se trató con 20 ml de HCl acuoso 1M (pH de la mezcla = 1) y los solventes orgánicos se eliminaron a presión reducida. El residuo acuoso se extrajo con diclorometano (3 x 50 ml). Los extractos orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida para obtener el producto **473k** (105 mg; 98%) como un aceite claro.

Paso J

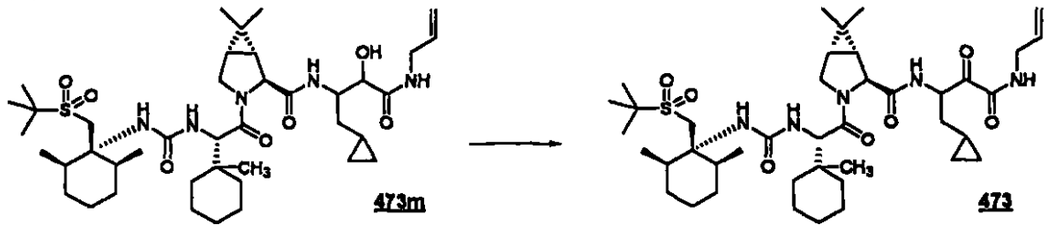


Una solución del ácido **473k** (50 mg) en 2 ml de diclorometano seco y 1 ml de DMF seca se agitó a 0°C y se trató con HATU (1,4 eq, 44 mg). Se agregó la sal de amina (1,3 eq, 25 mg) seguida de N-metilmorfolina (4 eq, 0,036 ml, d 0,920). La mezcla de reacción se agitó hasta la mañana siguiente (temp. 0 a 25°C).

1063

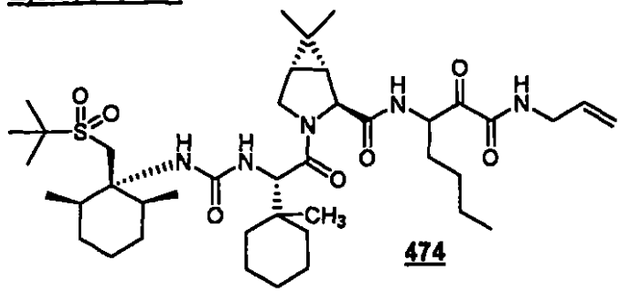
Todos los volátiles se eliminaron al vacío y el residuo se disolvió en 50 ml de acetato de etilo. La fase orgánica se lavó con agua (20 ml), HCl acuoso 1M (10 ml), solución acuosa saturada de bicarbonato de sodio (10 ml) y salmuera (10 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto **473m** (64 mg) se utilizó sin purificación adicional.

Paso K



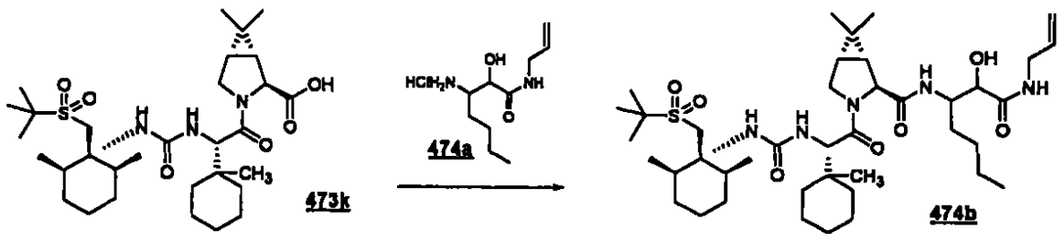
Una solución de la hidroxiamida **473m** (0,083 mmol) en 10 ml de diclorometano seco se trató con Periodinano de Dess-Martin (2,0 eq, 70 mg). La mezcla de reacción se agitó a temperatura ambiente durante 30 min. La mezcla se trató con solución acuosa 1M de tiosulfato de sodio (10 ml) y se agitó durante 5 min. También se agregó solución acuosa saturada de bicarbonato de sodio (20 ml) y se continuó agitando por otros 10 min La mezcla se extrajo con diclorometano (3 x 30 ml). Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron, y se concentraron. El residuo se cromatografió sobre gel de sílice (gradiente· acetona/hexanos; 1.9 hasta 4:6) para obtener el producto **473** (40 mg; 62% para dos pasos) como sólido blanco. HRMS calculado para $C_{41}H_{68}N_5O_7S$ $[M+H]^+$: 774,4839, experimental 774,4834.

Ejemplo 474:



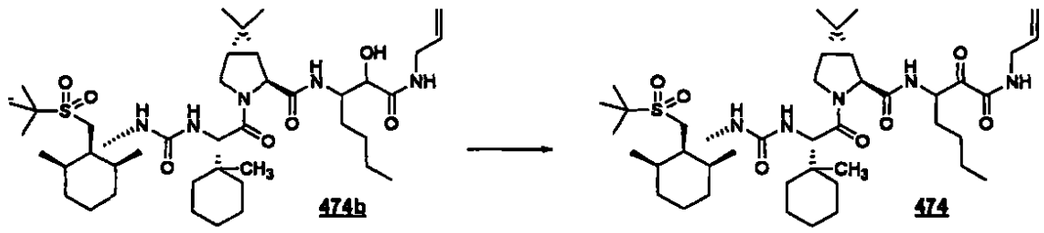
Paso A

1064



Una solución del ácido **473k** (50 mg) en 2 ml de diclorometano seco y 1 ml de DMF seca se agitó a 0°C y se trató con HATU (1,4 eq, 44 mg). Se agregó la sal de amina **474a** (1,3 eq, 25 mg) seguida de N-metilmorfolina (4 eq, 0,036 ml, d 0,920). La mezcla de reacción se agitó hasta la mañana siguiente (temp. 0 a 25°C). Todos los volátiles se eliminaron al vacío y el residuo se disolvió en 50 ml de acetato de etilo. La fase orgánica se lavó con agua (20 ml), HCl acuoso 1M (10 ml), solución acuosa saturada de bicarbonato de sodio (10 ml) y salmuera (10 ml) La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto **474b** (65 mg) se utilizó sin purificación adicional

Paso B

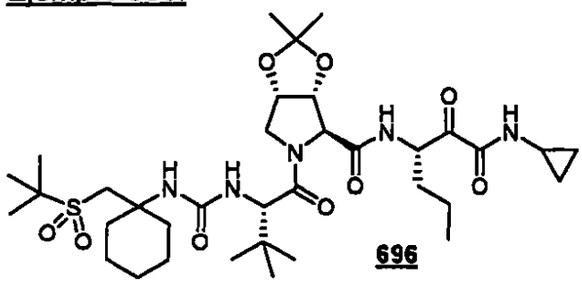


Una solución de la hidroxiamida **474b** (0,083 mmol) en 10 ml de diclorometano seco se trató con Periodinano de Dess-Martin (2,0 eq, 70 mg). La mezcla de reacción se agitó a temperatura ambiente durante 30 min. La mezcla se trató con solución acuosa 1M de tiosulfato de sodio (10 ml) y se agitó durante 5 min. También se agregó solución acuosa saturada de bicarbonato de sodio (20 ml) y se continuó agitando por otros 10 min. La mezcla se extrajo con diclorometano (3 x 30 ml). Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron, y se concentraron. El residuo se cromatografió sobre gel de sílice (gradiente acetona/hexanos; 1:9 hasta 4:6) para obtener el

1065

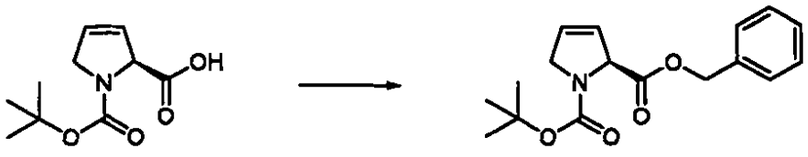
producto **474** (40 mg, 62% para dos pasos) como sólido blanco HRMS calculado para $C_{41}H_{70}N_5O_7S$ $[M+H]^+$: 776,4995, experimental 776,5005.

Ejemplo 696:



696

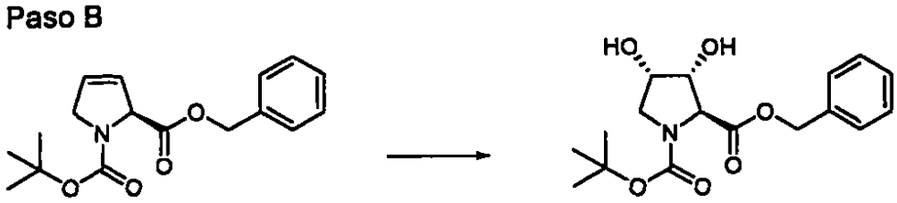
Paso A



696a **696b**

Una solución del ácido **696a** (3,0 g) en 140 ml de DMF seca se enfrió hasta 0°C y se trató con carbonato de cesio (1,1 eq, 5,04 g) seguido del agregado de bromuro de bencilo (1,2 eq, 2,00 ml, d 1,438). La mezcla de reacción se agitó durante 24 h (temp.: 0 a 25°C). La mezcla se diluyó con acetato de etilo (350 ml) y se lavó con agua (3 x 50 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se cromatografió sobre gel de sílice (gradiente: Hexanos hasta acetato de etilo/Hexanos 25:75) para obtener el producto **696b** (3,82 g; 90%) como un aceite claro.

Paso B



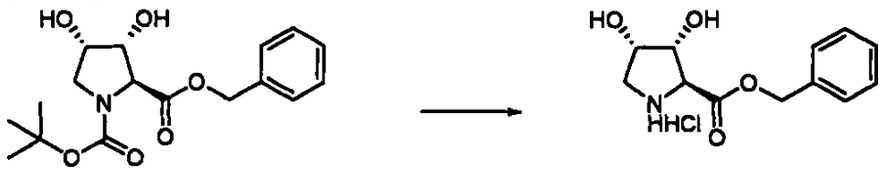
696b **696c**

Una solución de N-metilmorfolina-N-óxido (1,3 eq, 1,9 g) en ter-butanol (20 ml), THF (7 ml) y agua (3,5 ml) bajo atmósfera de argón se trató con tetróxido de osmio (0,1 eq, 318 mg) La solución de color amarillo pálido resultante se agitó

1066

durante 5 min., seguido del agregado gota a gota del bencilléster **696b** (3,8 g) en 30 ml de THF. La mezcla de reacción se agitó a temperatura ambiente durante 20 h. Se filtró la mezcla a través de un corto tramo de gel de sílice y los sólidos se lavaron con acetato de etilo (500 ml). La fase orgánica se lavó con salmuera (80 ml), se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se cromatografió sobre gel de sílice (gradiente. acetona/hexanos; 2:8 hasta 55:45) para dar el producto **696c** (3,5 g; 83%) como una pasta.

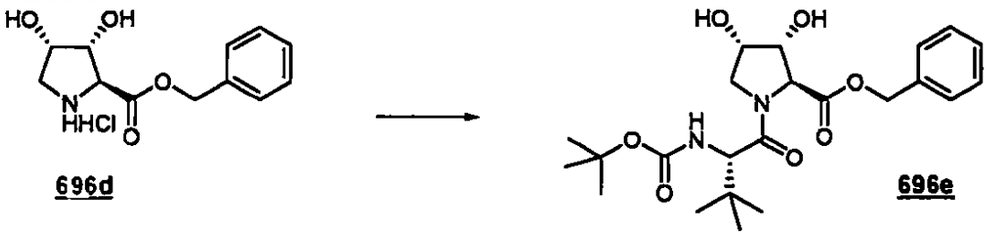
Paso C



696c **696d**

La N-Boc amina **696c** (3,5 g) se disolvió en 60 ml de HCl 4M en dioxano. La solución resultante se agitó a temperatura ambiente durante aproximadamente 2 h. Todos los volátiles se eliminaron a presión reducida para obtener el producto **696d** (2,8 g, 98%), que se usó sin purificación adicional.

Paso D



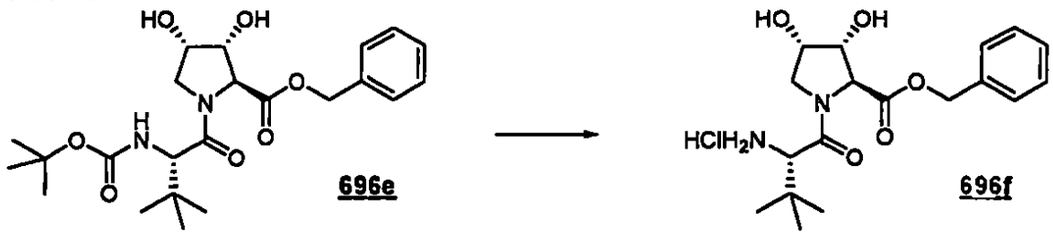
696d **696e**

Una solución de N-Boc-ter-butil glicina (2,15 g) en 100 ml de diclorometano seco y 20 ml de DMF seca se agitó a 0°C y se trató con HATU (1,4 eq, 4,96 g). Se agregó la sal de amina **696d** (1,1 eq, 2,8 g) en 30 ml de DMF, seguida del agregado de N-metilmorfolina (4 eq, 4,08 ml, d 0,920). La mezcla de reacción se agitó a 0°C hasta la mañana siguiente. Todos los volátiles se eliminaron al vacío y el residuo se disolvió en 300 ml de acetato de etilo. La fase

1067

orgánica se lavó con agua (1 x 100 ml), HCl acuoso 1M (100 ml), solución acuosa saturada de bicarbonato de sodio (100 ml) y salmuera (100 ml) La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se cromatografió sobre gel de sílice (acetato de etilo/hexanos; 6·4) para obtener el producto **696e** (3,29 g, 79%) como un aceite incoloro.

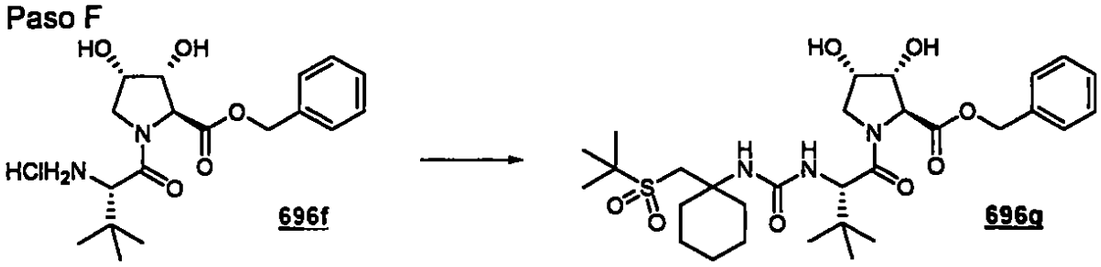
Paso E



696e **696f**

La N-Boc amina **696e** (1,24 g) se disolvió en 30 ml de HCl 4M en dioxano. La solución resultante se agitó a temperatura ambiente durante aproximadamente 2h. Todos los volátiles se eliminaron a presión reducida para obtener el producto **696f** (1,06 g; 98%) como un sólido blanco

Paso F



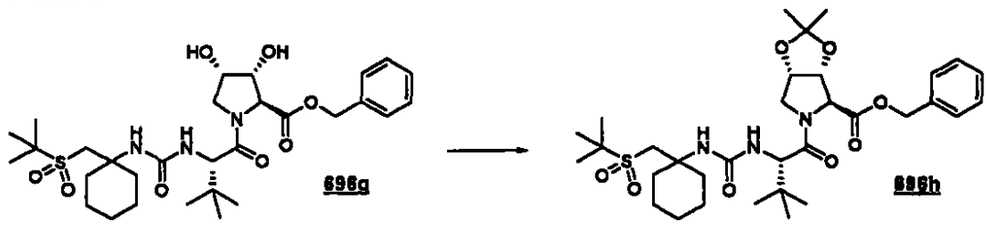
696f **696g**

Se agregó N-metil morfolina (1,3 eq, 0,39 ml, d 0,920) a una mezcla heterogénea del amino-diol **696f** (1,06 g) en 50 ml de diclorometano. Luego de 5 min, se agregó una solución de isocianato (1,05 eq, 9,63 ml de una solución 0,3M en tolueno). También se agregó DMF (5 ml) was also added y la suspensión se agitó a temperatura ambiente. La mezcla se convirtió gradualmente (en un lapso de 4 h) en una solución homogénea transparente. La mezcla se diluyó con acetato de etilo (300 ml) y se lavó con HCl acuoso 1M. La fase acuosa se volvió a extraer con 100 ml de acetato de etilo. Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron, y se concentraron a presión

1068

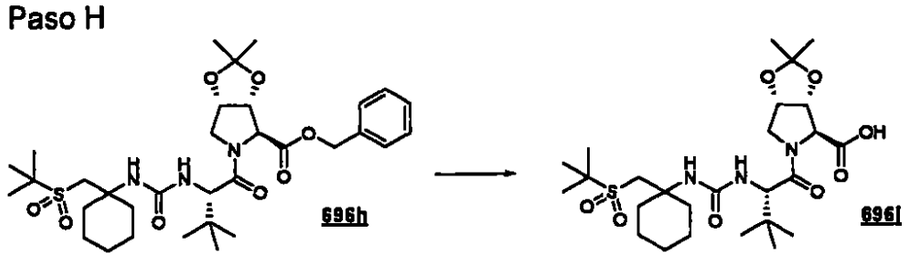
reducida. El residuo se cromatografió sobre gel de sílice (gradiente: acetona/Hexanos; 3:7 hasta 6:4) para dar el producto **696g** (1,6 g; 98%) como un aceite incoloro.

Paso G



Una solución del diol **696g** (1,5 g) se trató con 2,2-dimetoxipropano (2 eq, 0,6 ml, d 0,847) y una cantidad catalítica de p-toluensulfonato de piridinio (0,1 eq, 62 mg). La mezcla se agitó hasta la mañana siguiente a 50°C. La mezcla se diluyó con 200 ml de acetato de etilo y se lavó con 50 m de solución acuosa saturada de bicarbonato de sodio La fase acuosa se extrajo con acetato de etilo (100 ml). Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se cromatografió sobre gel de sílice (gradiente: acetona/Hexanos; 5·95 hasta 35:65) para obtener el producto **696h** (1,33 g; 83%) como un sólido blanco

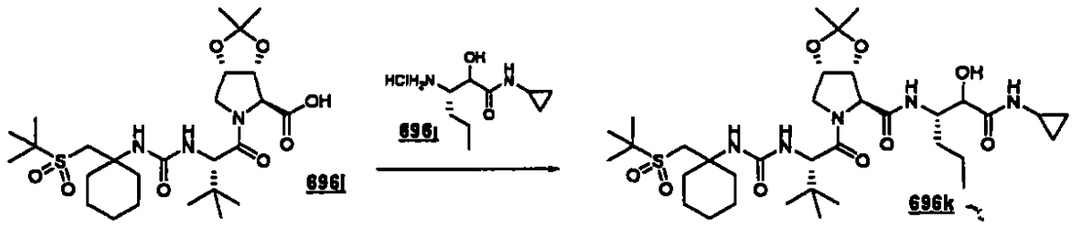
Paso H



El bencil éster **696h** (1,33 g) se disolvió en 70 ml de acetato de etilo y se trató con dihidróxido de paladio al 20% en carbón (0,1 mol%; 144 mg). La mezcla heterogénea se hidrogenó a 3,45 x 10^5 Pa (50 psi) durante 3 h La mezcla se diluyó con 200 ml de diclorometano y se filtró a través de un corto trecho de celite El filtrado se concentró a presión reducida para obtener el producto **696i** (1,14 g; 98%) como un sólido blanco

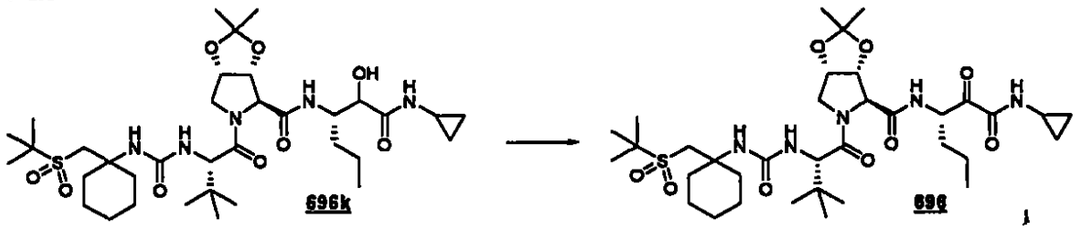
1069

Paso I



Una solución del ácido **696i** (100 mg) en 3 ml de diclorometano seco y 3 ml de DMF seca se agitó a 0°C y se trató con HATU (1,4 eq, 93 mg). Se agregó la sal de amina **696j** (1,2 eq, 47 mg) seguida de N-metilmorfolina (4 eq, 0,08 ml, d 0,920). La mezcla de reacción se agitó hasta la mañana siguiente (temp. 0 a 25°C). Todos los volátiles se eliminaron al vacío y el residuo se disolvió en 50 ml de acetato de etilo. La fase orgánica se lavó con agua (10 ml), HCl acuoso 1M (10 ml), solución acuosa saturada de bicarbonato de sodio (10 ml) y salmuera (10 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida El producto **696k** se utilizó sin purificación adicional.

Paso J

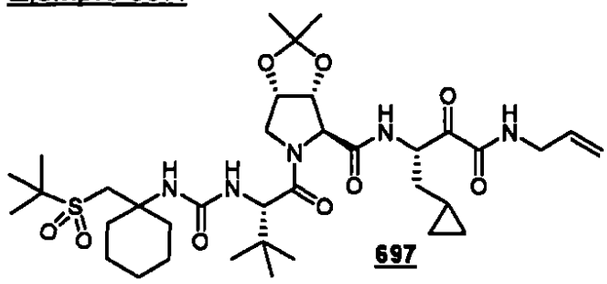


Una solución de la hidroxiamida **696k** (0,178 *mmol*) *en* 10 *ml de* diclorometano seco se trató con Periodinano de Dess-Martin (2,0 eq, 150 mg). La mezcla de reacción se agitó a temperatura ambiente durante 30 min. La mezcla se trató con solución acuosa 1M de tiosulfato de sodio (10 ml) y se agitó durante 5 min. También se agregó solución acuosa saturada de bicarbonato de sodio (10 ml) y se continuó agitando por otros 10 min La mezcla se extrajo con diclorometano (3 x 30 ml). Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron, y se concentraron El residuo se cromatografió sobre gel de sílice (gradiente: acetona/Hexanos; 15:85 hasta 1:1) para obtener el

1070

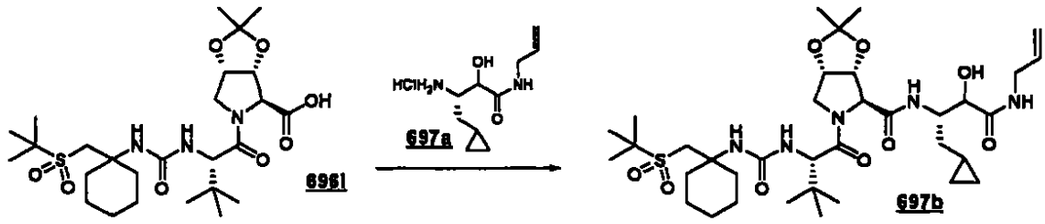
producto **696** (120 mg; 93%) como sólido blanco. HRMS calculado para $C_{35}H_{60}N_5O_9S$ $[M+H]^+$: 726,4112, experimental 726,4128.

Ejemplo 697:



697

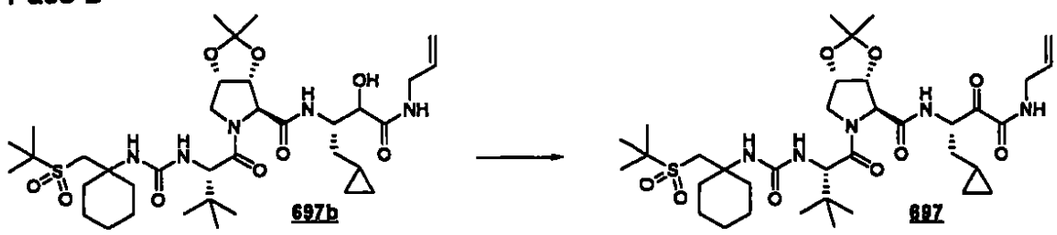
Paso A



696i 697a 697b

Una solución del ácido **696i** (100 mg) en 3 ml de diclorometano seco y 3 ml de DMF seca se agitó a 0°C y se trató con HATU (1,4 eq, 93 mg) Se agregó la sal de amina **697a** (1,2 eq, 50 mg) seguida de N-metilmorfolina (4 eq, 0,08 ml, d 0,920). La mezcla de reacción se agitó hasta la mañana siguiente (temp. 0 a 25°C). Todos los volátiles se eliminaron al vacío y el residuo se disolvió en 50 ml de acetato de etilo. La fase orgánica se lavó con agua (10 ml), HCl acuoso 1M (10 ml), solución acuosa saturada de bicarbonato de sodio (10 ml) y salmuera (10 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto **697b** se utilizó sin purificación adicional.

Paso B

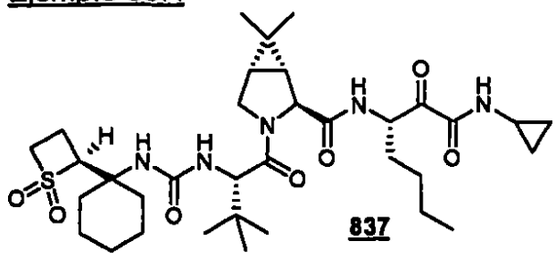


697b 697

1071

Una solución de la hidroxiamida **697b** (0,178 mmol) en 10 ml de diclorometano seco se trató con Periodinano de Dess-Martin (2,0 eq, 150 mg). La mezcla de reacción se agitó a temperatura ambiente durante 30 min. La mezcla se trató con solución acuosa 1M de tiosulfato de sodio (10 ml) y se agitó durante 5 min. También se agregó solución acuosa saturada de bicarbonato de sodio (10 ml) y se continuó agitando por otros 10 min La mezcla se extrajo con diclorometano (3 x 30 ml). Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron, y se concentraron. El residuo se cromatografió sobre gel de sílice (gradiente: acetona/hexanos; 15:85 hasta 1:1) para obtener el producto **697** (120 mg; 91%) como sólido blanco. HRMS calculado para $C_{36}H_{60}N_5O_9S$ $[M+H]^+$: 738,4112, experimental 738,4092.

Ejemplo 837:



837

Paso A



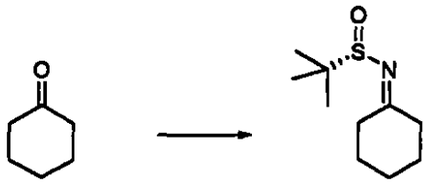
837a **837b**

Una solución de tietano (10 g, 9,727 ml, d 1,028, Aldrich) en 200 ml de diclorometano se trató con una suspensión de ácido m-cloroperoxibenzoico (2,3 eq, 76 g de m-CPBA 70%) en diclorometano (400 ml) a 0°C Se retiró el baño refrigerante y la mezcla se agitó durante 3 h. Los sólidos se eliminaron por filtración y el filtrado se concentró a presión reducida El residuo se disolvió en acetato de etilo (400 ml) y la solución se lavó extensivamente con solución acuosa saturada de bicarbonato de sodio La fase orgánica se secó sobre sulfato de

1072

magnesio, se filtró y se concentró. El residuo se purificó por cromatografía en columna para obtener el producto **837b** como un sólido blanco.

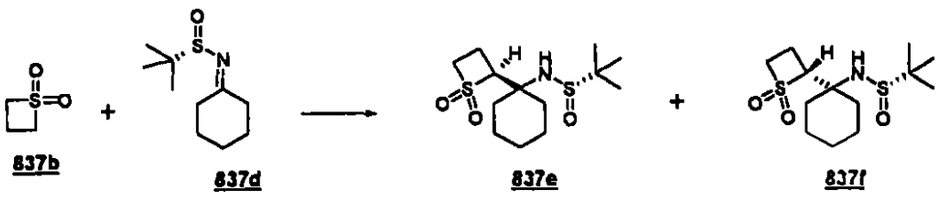
Paso B



837c **837d**

Se agregó tetraetóxido de titanio (2 eq, 24,2 ml, d 1,088) a una solución de ciclohexanona (1,2 eq, 7,18 ml, d 0,947) en 150 ml de THF seco bajo atmósfera de nitrógeno. Luego de 5 min, se agregó gota a gota t-butansulfinamida (7,0 g, Aldrich) en 50 ml de THF. La mezcla se calentó hasta 60°C hasta la mañana siguiente. La mezcla de reacción se vertió en igual volumen de solución acuosa saturada de bicarbonato de sodio con rápida agitación e inmediatamente se filtró a través de papel de filtro whatman #1. La torta del filtro se lavó con acetato de etilo (100 ml). Las capas del filtrado se separaron y la fase acuosa se extrajo con acetato de etilo (100 ml) Las fases orgánicas combinadas se lavaron con solución acuosa saturada de bicarbonato de sodio (100 ml), se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se cromatografió sobre gel de sílice (acetato de etilo/hexanos; 3:7) para obtener el producto **837d** (7,5 g; 55%) como un aceite incoloro El producto se conserva en atmósfera inerte a -20°C

Paso C



837b **837d** **837e** **837f**

Se agregó gota a gota n-Butil litio (1,1 eq, 7,6 ml de una solución 1,6M en ciclohexano) a una solución fría (-78°C) de la sulfona **837b** (1,15 eq, 1,35 g) en 100 ml de THF seco bajo atmósfera anhidra. La mezcla se agitó durante 1 h a esa

1073

temperatura y luego se transfirió via cánula a una solución pre-enfriada (-78°C) de la sulfinilimina **837d** (2,23 g) en 100 ml de THF seco. La mezcla resultante se agitó a -78°C y se monitoreó por TLC (acetona/hexanos; 3:7). Toda la sulfinilimina **837d** usada como material de partida se consumió en 2 h. La reacción se desactivó por agregado de solución acuosa saturada de cloruro de amonio (5 ml). La mezcla se dejó alcanzar la temperatura ambiente y se repartió entre acetato de etilo (200 ml) y bicarbonato de sodio acuoso saturado (80 ml). La fase acuosa se volvió a extraer con acetato de etilo (2 x 60 ml). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida. El residuo se cromatografió sobre gel de sílice (gradiente: diclorometano hasta acetona/diclorometano; 3:7) para obtener los correspondientes products diastereoméricos **837e** y **837f** como mezcla 1,4:1 (1,64 g; 50% rendimiento comb.).

Paso D

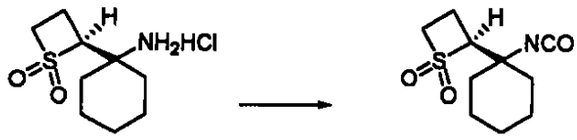


837e **837g**

La sulfinamida **837e** (910 mg) se disolvió en 50 ml de metanol y se trató con 20 ml de solución de HCl 4M en dioxano. La mezcla se agitó durante aproximadamente 1 h hasta que todo el material de partida se había consumido según se determinó por TLC (acetona/Hexanos; 1:9). La mezcla se concentró hasta sequedad. Se agregó diclorometano (10 ml) para obtener una solución homogénea; luego se agregó éter (80 ml) y se formó un precipitado blanco. El clorhidrato de amina, producto **837g** (700 mg; 98%), se recuperó por filtración como un sólido blanco.

Paso E

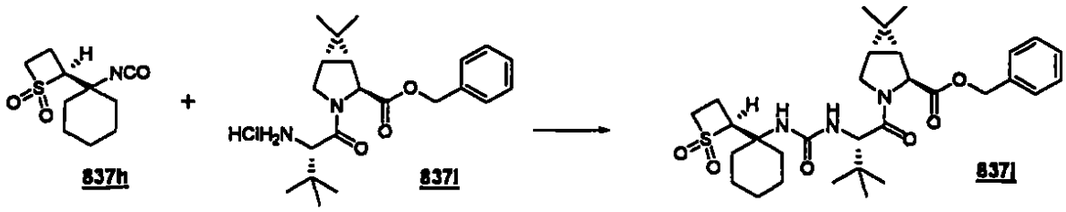
1074



837g 837h

Una solución del clorhidrato de amina **837g** (2,960 mmol) en 40 ml de diclorometano se trató con 20 ml de solución acuosa saturada de bicarbonato de sodio y se agitó vigorosamente durante 10 min a 0°C. Se detuvo la agitación y se permitió que las capas se separaran Se agregó fosgeno (10 ml de solución al 20% en tolueno) a través de una aguja a la fase orgánica (capa inferior) en una porción. La mezcla se agitó vigorosamente inmediatamente después del agregado durante 10 min a 0°C y se agitó adicionalmente a temperatura ambiente durante 3 h. La mezcla se diluyó con 100 ml de diclorometano y se separaron las capas. La fase orgánica se lavó con 50 ml de solución acuosa fría saturada de bicarbonato de sodio y se secaron sobre sulfato de magnesio La fase orgánica se filtró y se diluyó con 50 ml de tolueno. La solución resultante se concentró y se conservó como solución 0,118M en tolueno.

Paso F



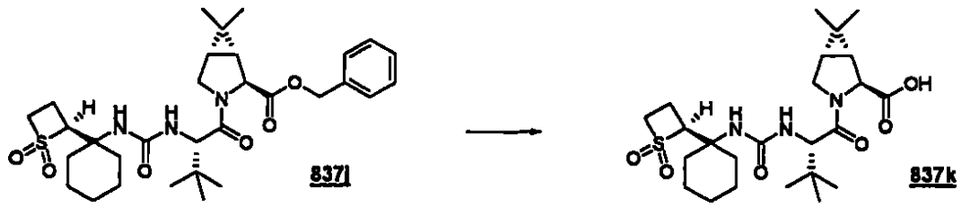
837h 837i 837j

Una solución del clorhidrato de amina **837i** (1,5 mmol) en 30 ml de diclorometano se trató con 5 ml de solución acuosa saturada de bicarbonato de sodio La mezcla se agitó durante 10 min seguido del agregado del isocianato **837h** (1,03 eq, 13,1 ml de una solución 0,118M en tolueno). La mezcla de reacción se agitó hasta la mañana siguiente La mezcla de reacción se diluyó con diclorometano (200 ml) y se lavó con solución acuosa saturada de bicarbonato de sodio (40 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se cromatografió sobre gel de sílice

1075

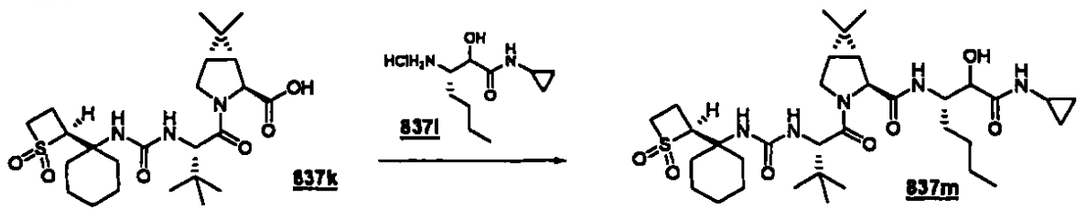
(gradiente: acetona/Hexanos; 1:9 hasta 1:1) para obtener el producto **837j** (740 mg; 84%) como un sólido blanco.

Paso G



El bencil éster **837j** (740 mg) se disolvió en 20 ml de metanol y se trató con dihidróxido de paladio al 20% en carbón (0,1 mol%, 90 mg). La mezcla heterogénea se hidrogenó a 3,45 x 10^5 Pa (50 psi) por 2 h. La TLC (acetona/Hexanos; 35:65) demostró que todo el material de partida se había consumido. La mezcla se diluyó con 100 ml de diclorometano y se filtró a través de un corto trecho de celite. El filtrado se concentró a presión reducida para obtener el producto **837k** (620 mg; 98%) como un sólido blanco.

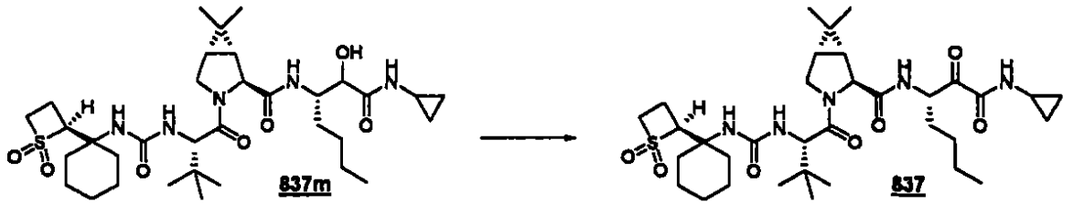
Paso H



Una solución del ácido **837k** (69 mg) en 2 ml de diclorometano seco y 2 ml de DMF seca se agitó a 0°C y se trató con HATU (1,4 eq, 74 mg). Se agregó la sal de amina **837l** (1,2 eq, 39 mg) seguida de N-metilmorfolina (4 eq, 0,06 ml, d 0,920). La mezcla de reacción se agitó hasta la mañana siguiente (temp. 0 a 25°C) Todos los volátiles se eliminaron al vacío y el residuo se disolvió en 50 ml de acetato de etilo. La fase orgánica se lavó con agua (10 ml), HCl acuoso 1M (10 ml), solución acuosa saturada de bicarbonato de sodio (10 ml) y salmuera (10 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto **837m** se utilizó sin purificación adicional.

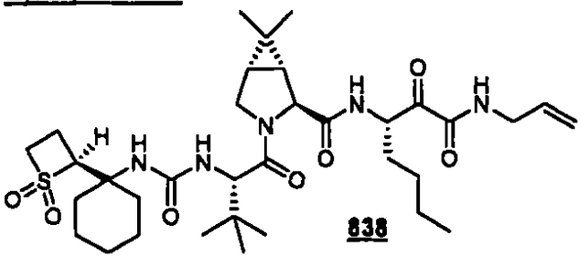
1076

Paso I

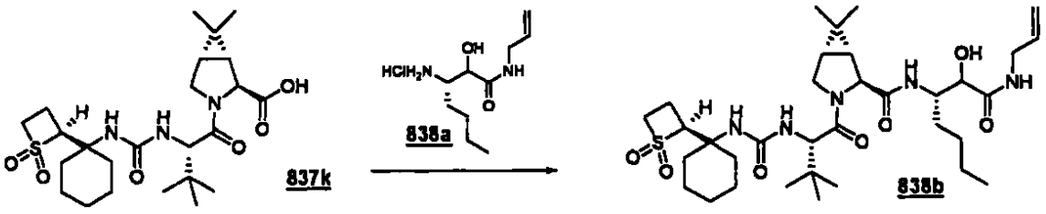


Una solución de la hidroxiamida **837m** (0,138 mmol) en 10 ml de diclorometano seco se trató con Periodinano de Dess-Martin (2,0 eq, 117 mg). La mezcla de reacción se agitó a temperatura ambiente durante 30 min. La mezcla se trató con solución acuosa 1M de tiosulfato de sodio (10 ml) y se agitó durante 5 min También se agregó solución acuosa saturada de bicarbonato de sodio (10 ml) y se continuó agitando por otros 10 min. La mezcla se extrajo con diclorometano (3 x 30 ml). Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se cromatografió sobre gel de sílice (gradiente: acetona/Hexanos; 2:8 hasta 1:1) para obtener el producto **837** (66 mg, 70%) como sólido blanco. HRMS calculado para $C_{34}H_{56}N_5O_7S$ $[M+H]^+$: 678,3900, experimental 678,3883.

Ejemplo 838:



Paso A

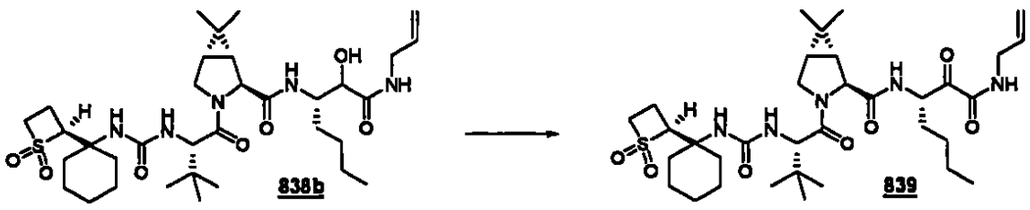


Una solución del ácido **837k** (69 mg) en 2 ml de diclorometano seco y 2 ml de DMF seca se agitó a 0°C y se trató con HATU (1,4 eq, 74 mg) Se agregó la sal

1077

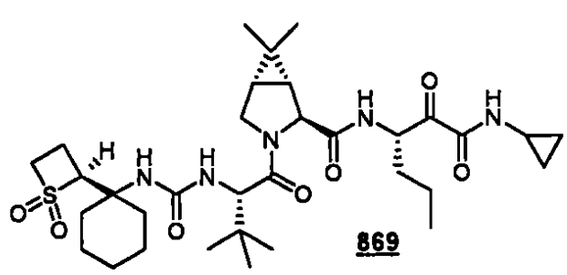
de amina **838a** (1,2 eq, 39 mg) seguida de N-metilmorfolina (4 eq, 0,06 ml, d 0,920). La mezcla de reacción se agitó hasta la mañana siguiente (temp. 0 a 25°C). Todos los volátiles se eliminaron al vacío y el residuo se disolvió en 50 ml de acetato de etilo. La fase orgánica se lavó con agua (10 ml), HCl acuoso 1M (10 ml), solución acuosa saturada de bicarbonato de sodio (10 ml) y salmuera (10 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto **838b** se utilizó sin purificación adicional.

Paso B



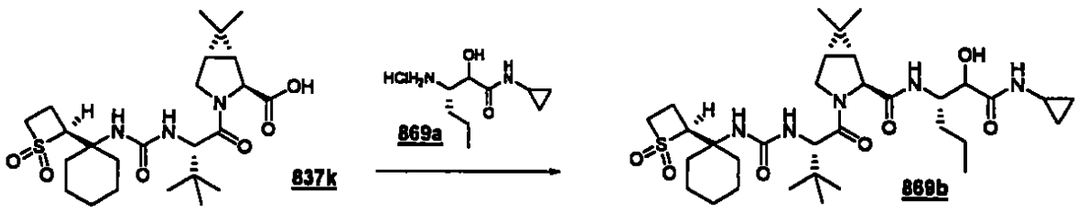
Una solución de la hidroxiamida **838b** (0,138 mmol) en 10 ml de diclorometano seco se trató con Periodinano de Dess-Martin (2,0 eq, 117 mg). La mezcla de reacción se agitó a temperatura ambiente durante 30 min. La mezcla se trató con solución acuosa 1M de tiosulfato de sodio (10 ml) y se agitó durante 5 min También se agregó solución acuosa saturada de bicarbonato de sodio (10 ml) y se continuó agitando por otros 10 min La mezcla se extrajo con diclorometano (3 x 30 ml). Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se cromatografió sobre gel de sílice (gradiente: acetona/Hexanos; 1:9 hasta 4:6) para obtener el producto **838** (71 mg, 76%) como sólido blanco. HRMS calculado para $C_{34}H_{56}N_5O_7S$ $[M+H]^+$: 678,3900, experimental 678,3883.

Ejemplo 869:



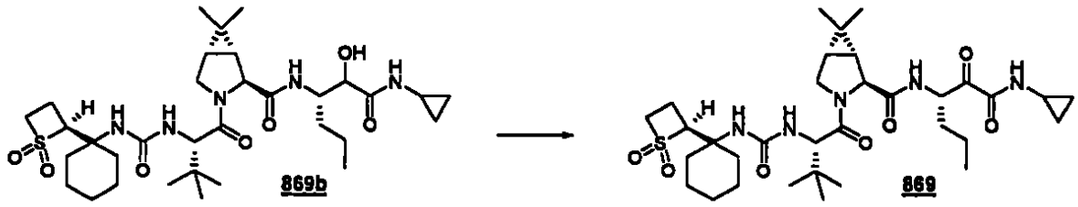
1078

Paso A



Una solución del ácido **837k** (69 mg) en 2 ml de diclorometano seco y 2 ml de DMF seca se agitó a 0°C y se trató con HATU (1,4 eq, 74 mg). Se agregó la sal de amina **869a** (1,2 eq, 37 mg) seguida de N-metilmorfolina (4 eq, 0,06 ml, d 0,920). La mezcla de reacción se agitó hasta la mañana siguiente (temperatura 0 a 25°C). Todos los volátiles se eliminaron al vacío y el residuo se disolvió en 50 ml de acetato de etilo. La fase orgánica se lavó con agua (10 ml), HCl acuoso 1M (10 ml), solución acuosa saturada de bicarbonato de sodio (10 ml) y salmuera (10 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El producto **869b** se utilizó sin purificación adicional.

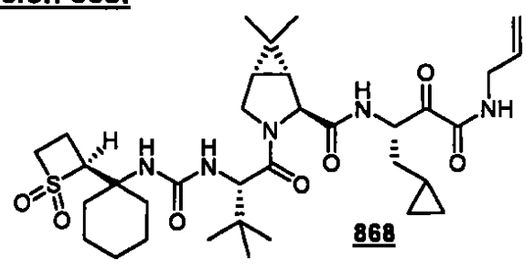
Paso B



Una solución de la hidroxiamida **869b** (0,138 mmol) en 10 ml de diclorometano seco se trató con Periodinano de Dess-Martin (2,0 eq, 117 mg). La mezcla de reacción se agitó a temperatura ambiente durante 30 min. La mezcla se trató con solución acuosa 1M de tiosulfato de sodio (10 ml) y se agitó durante 5 min. También se agregó solución acuosa saturada de bicarbonato de sodio (10 ml) y se continuó agitando por otros 10 min. La mezcla se extrajo con diclorometano (3 x 30 ml). Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se cromatografió sobre gel de sílice (gradiente acetona/Hexanos, 18:85 to 45:55) para obtener el producto **869** (69 mg; 75%) como sólido blanco.

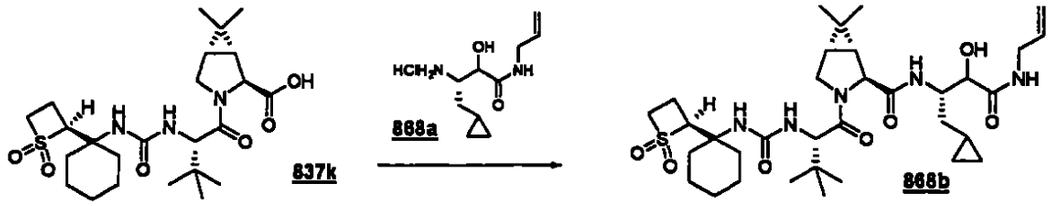
1079

Ejemplo de Preparación 868:



868

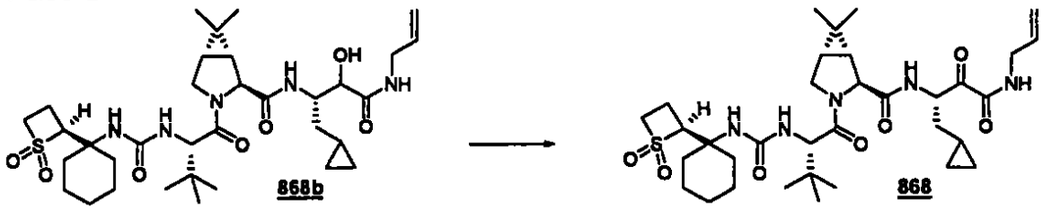
Paso A



837k **868a** **868b**

Una solución del ácido **837k** (69 mg) en 2 ml de diclorometano seco y 2 ml de DMF seco se agitó a 0°C y se trató con HATU (1,4 eq, 74 mg). Se agregó la sal de amina **868a** (1,2 eq, 39 mg) seguida de N-metilmorfolina (4 eq, 0,06 ml, d 0,920). La mezcla de reacción se agitó hasta la mañana siguiente (temperatura 0 a 25°C). Todos los volátiles se eliminaron al vacío y el residuo se disolvió en 50 ml de acetato de etilo. La fase orgánica se lavó con agua (10 ml), HCl acuoso 1M (10 ml), solución acuosa saturada de bicarbonato de sodio (10 ml) y salmuera (10 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida El producto **868b** se utilizó sin purificación adicional.

Paso B



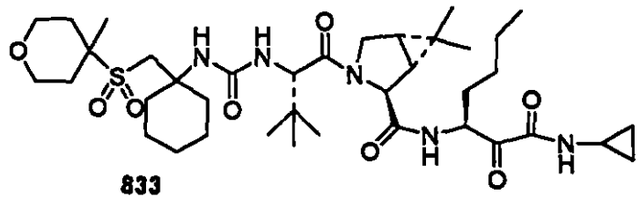
868b **868**

Una solución de la hidroxiamida **868b** (0,138 mmol) en 10 ml de diclorometano seco se trató con Periodinano de Dess-Martin (2,0 eq, 117 mg) La mezcla de reacción se agitó a temperatura ambiente durante 30 min La mezcla se trató con solución acuosa 1M de tiosulfato de sodio (10 ml) y se agitó durante 5

1080

min. También se agregó solución acuosa saturada de bicarbonato de sodio (10 ml) y se continuó agitando por otros 10 min. La mezcla se extrajo con diclorometano (3 x 30 ml). Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se cromatografió sobre gel de sílice (gradiente: acetona/Hexanos; 1:9 hasta 4:6) para obtener el producto **868** (73 mg; 78%) como sólido blanco

Ejemplo **833**:



833

Paso 1



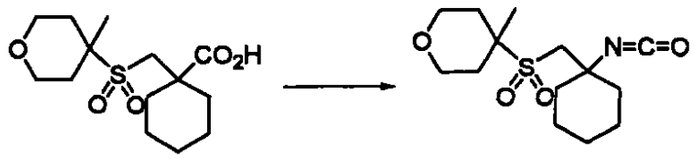
833a **833b**

A una solución del etilsulfona ácido **833a** (2,06 g, 8,79 mmol) en THF anhidro a -78°C bajo N_2 se agregó solución de LiHMDS (19,3 ml, 1,0 M en THF). La mezcla se agitó a -78°C durante 30 min antes de dejar entibiar hasta 0°C junto con un baño frío de acetona. Luego se re-enfrió hasta -78°C y se le agregó 2-bromoetil éter (1,8 ml, 13,2 mmol). Luego de agitarse a -78°C durante 30 min, la mezcla se entibió hasta t.a. y se agitó durante 2 h Nuevamente se re-enfrió hasta -78°C y se le agregó solución de LiHMDS (10,6 ml, 10,6 mmol). Luego de agitarse a -78°C durante 30 min, la mezcla se entibió hasta t.a. y se agitó durante 3 h antes de desactivar con solución acuosa 1 N de HCl hasta que el pH fue de alrededor de 1-2 La solución se extrajo con CH_2Cl_2 (2x450 ml). La solución orgánica combinada se secó ($MgSO_4$), se filtró y se concentró. El producto en bruto se disolvió en solución 1 N de NaOH (300 ml) y se extrajo con EtOAc (100 ml). Luego de separarse las capas, la solución orgánica se lavó con NaOH 1 N

1081

(2x150 ml). La solución acuosa combinada se acidificó hasta un pH~1 usando solución 6 N de HCl. Se extrajo con EtOAc (3 x 300 ml). Se combinaron las soluciones orgánicas, se secaron ($MgSO_4$), se filtraron y se concentraron para dar 2,3 g de producto (**833b**, 7,56 mmol, 89%).

Paso 2



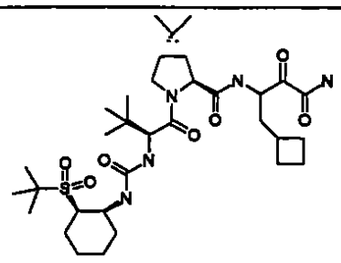
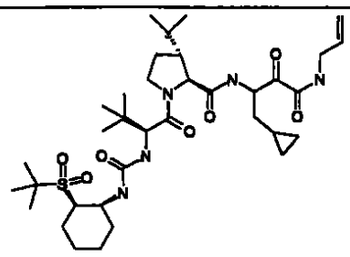
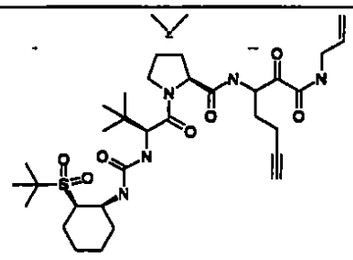
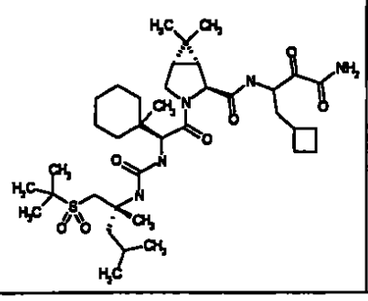
833b **833c**

Al ácido **833b** (2,30 g, 7,56 mmol) en tolueno a temperatura ambiente bajo N_2 se agregó trietilamina (1,15 ml, 8,32 mmol) y difenilfosforil azida (1,79 ml, 8,32 mmol). La mezcla resultante se agitó a temperatura ambiente durante 30 min y se calentó a reflujo durante 5,5 h. Después de enfriar a t.a., se agregó más tolueno para preparar una solución 0,19 M del isocianato **833c**, que se usó sin purificación adicional

Usando los procedimientos arriba mencionados, **833c** se transformó en **833**

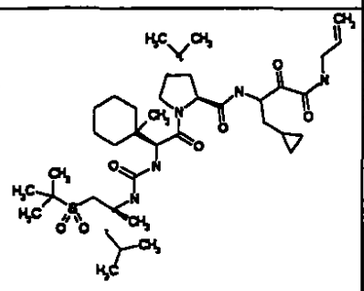
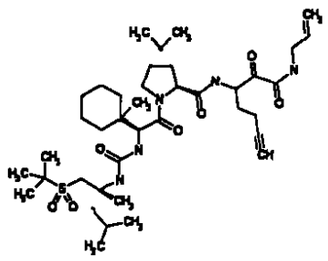
1082

Tabla 3A

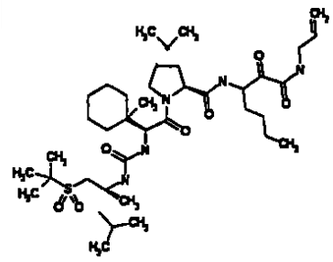
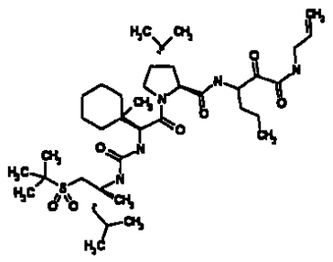
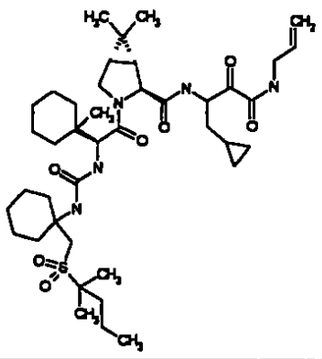
Comp.. #	estructura	peso molec de estruct	Datos de CL-EM Selec (M+H)	Rango de Ki*
397		665,887	666,3	B
398		691,925	692,4	C
399		689,909	690,3	B
400		722 008	722,4	A

1083

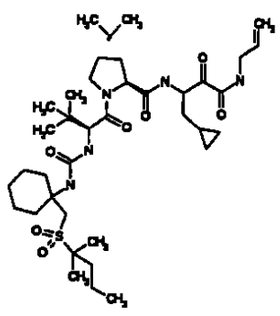
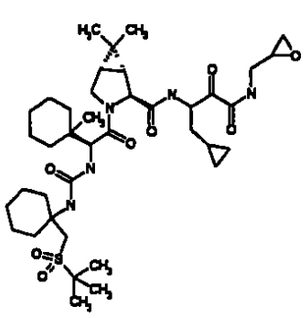
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401		748,0462	748,4	A
402		746,0303	746,2	A

1084 1107

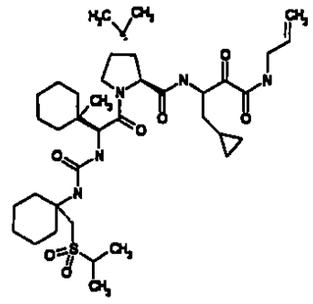
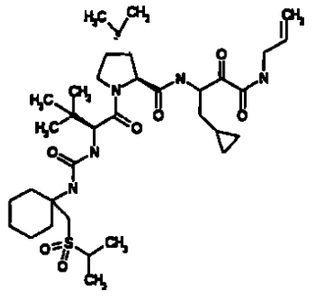
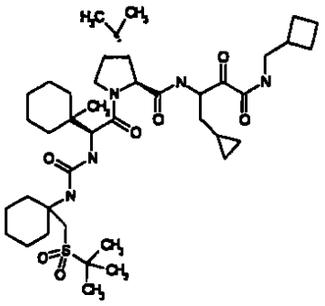
403		750 0621	750,4	A
404		736,0351	736,4	A
405		774,0844		A

1085

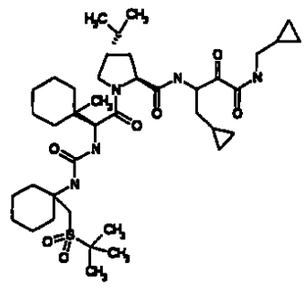
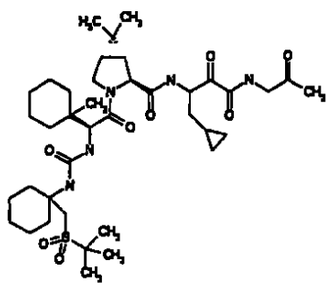
406		734,0191		A
407		762,0297		A

1086

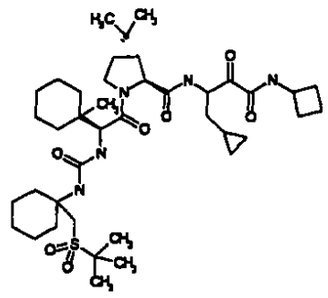
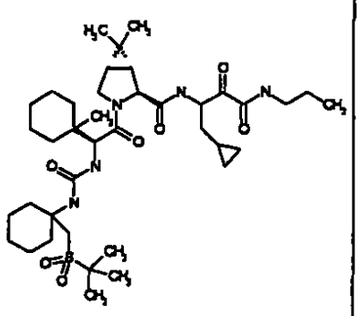
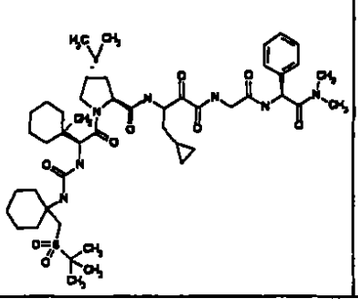
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408		732,0032		A
409		691,9378		A
410		774,0844		A

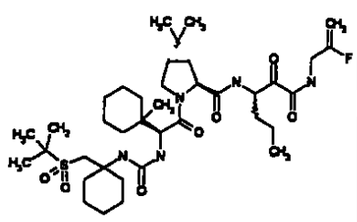
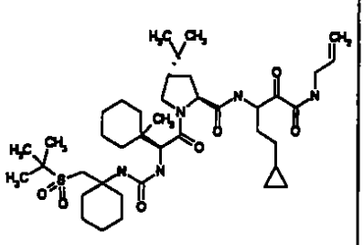
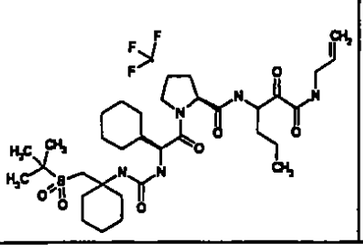
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411		760,0574		A
412		762,0297		A

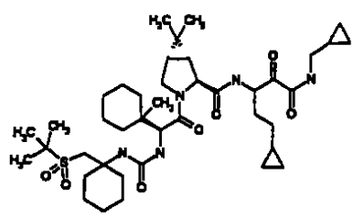
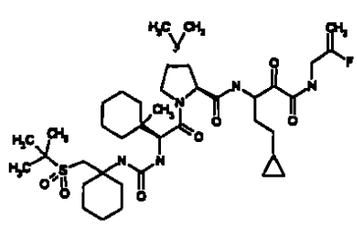
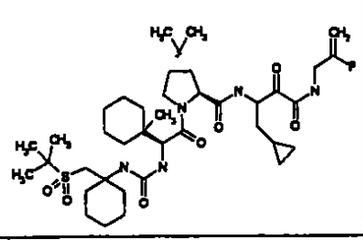
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413		760,0574		A
414		748,0462		A
415		924,2225		B

1089

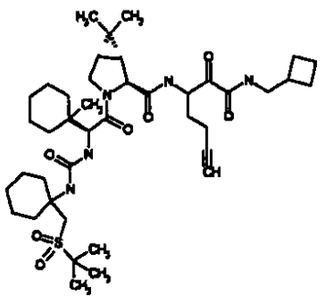
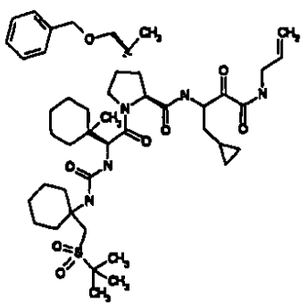
416		752,0095		A
417		760,0574		A
418		747,9251		A

1090

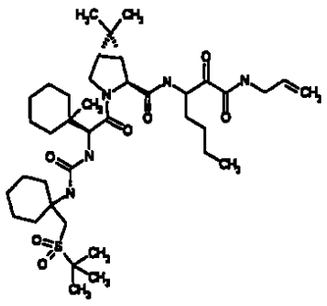
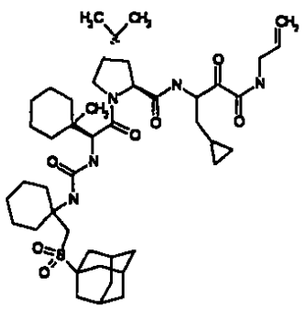
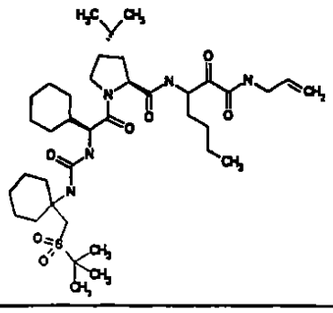
419		774,0844		A
420		778,0478		A
421		764,0207		A

A108

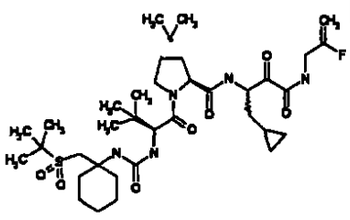
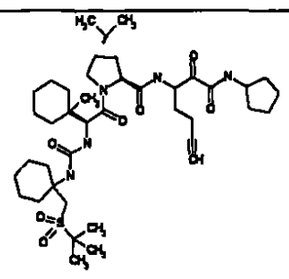
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422		772,0685		A
423		852,1555	852,5	A

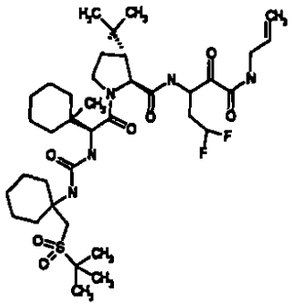
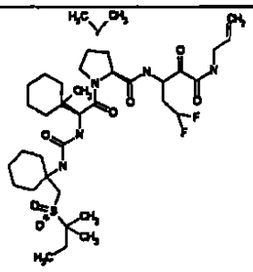
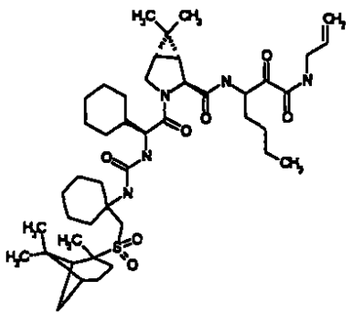
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424		748,0462		A
425		824,145		A
426		734,0191		A

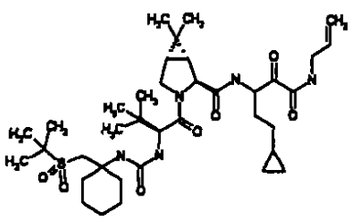
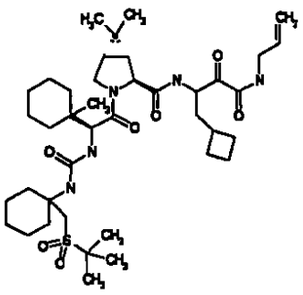
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427		723,9554		A
428		772,0685		A

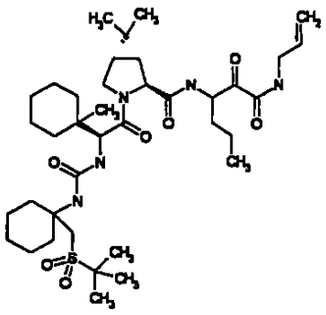
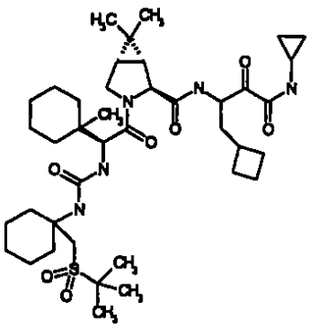
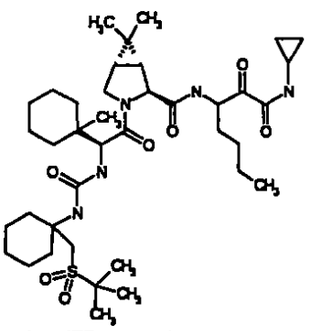
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429		755,9729		A
430		770		A
431		814,1498		A

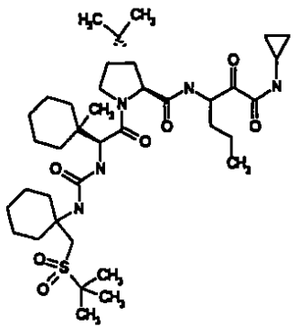
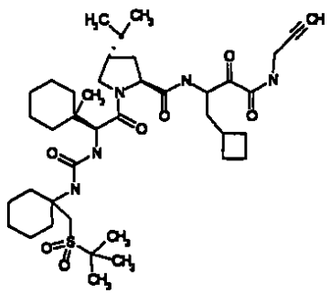
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432		719,992		A
433		760,0574		A

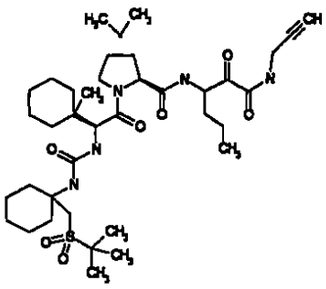
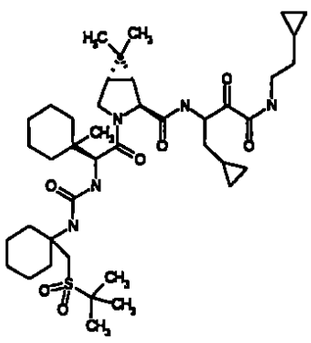
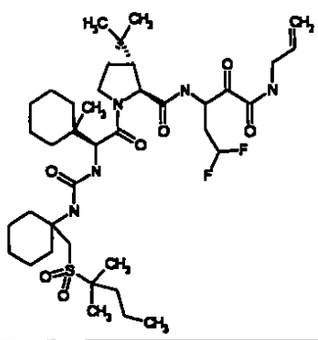
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434		734,0191		A
435		760,0574		A
436		748,0462		A

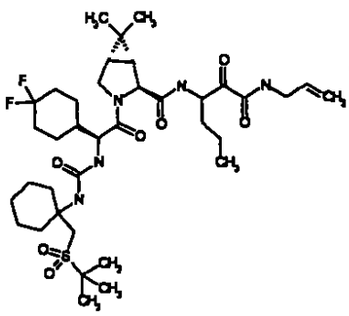
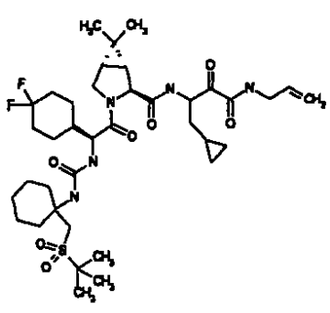
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437		734,0191		A
438		758,0414		A

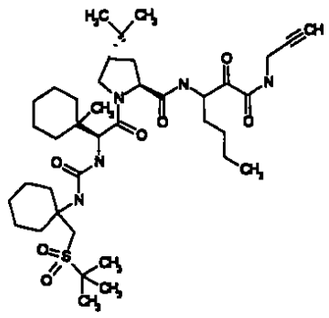
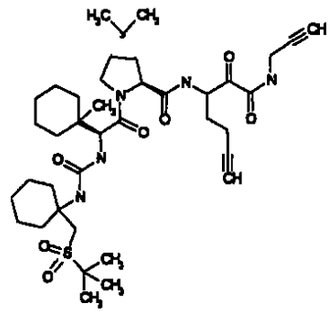
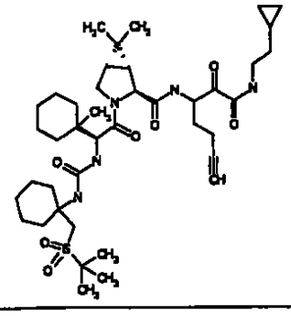
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439		732,0032		A
440		774,0844	774,2	A
441		784,0271	784,2	A

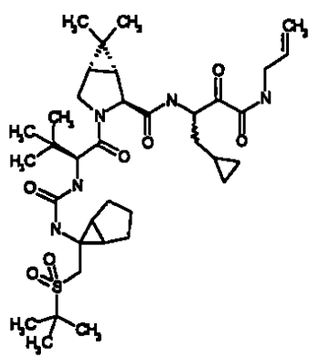
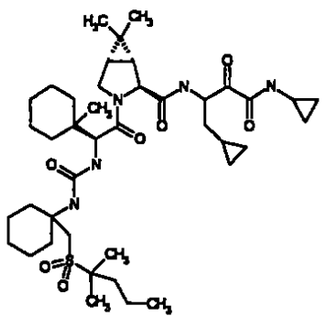
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442		755,9729	756,2	A
443		767,984	768,4	A

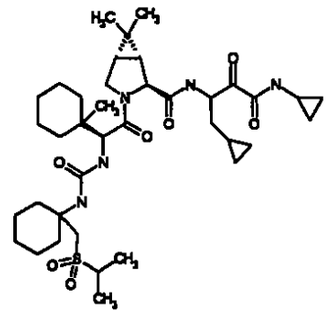
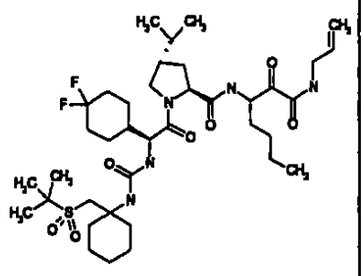
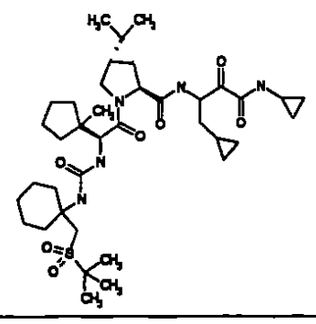
1100

444		746,0303		A
445		741,9984		A
446		772,0685		A

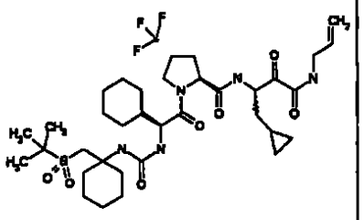
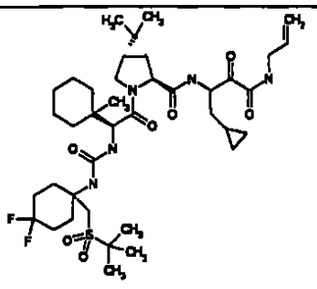
1101 A448

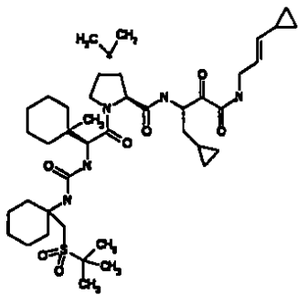
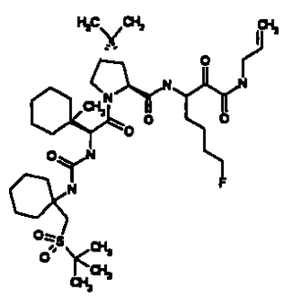
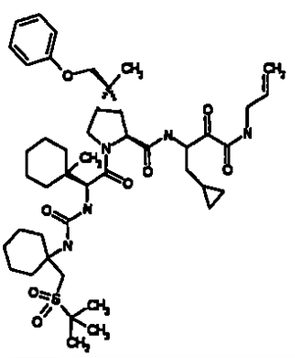
447		703,949	704,4	A
448		774,0844		A

1102

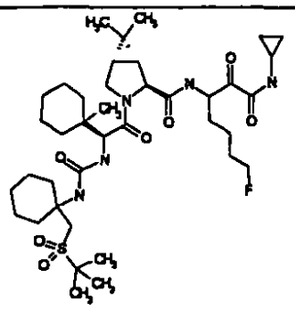
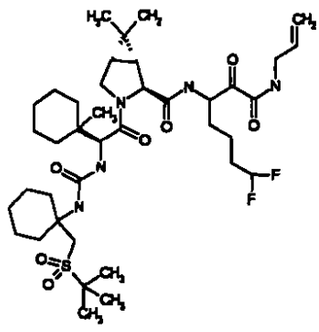
449		732,0032		A
450		770	770,2	A
451		732,0032	732,2	A

1103 1120

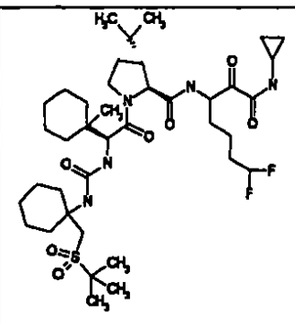
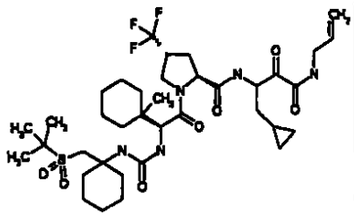
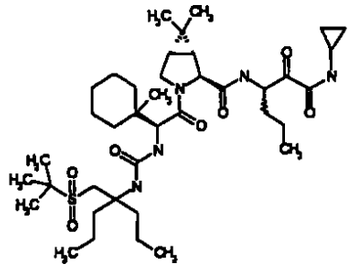
452		759,9362		A
453		782,0111		A

454		786,0956		A
455		766,0366		A
456		838,1284		B

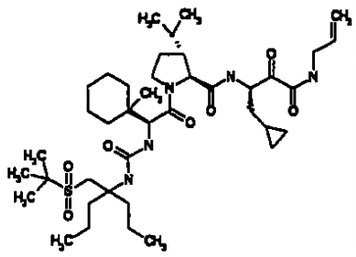
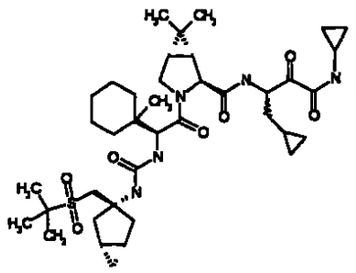
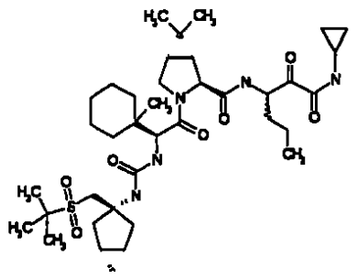
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457		766,0366	766,4	A
458		784,0271	784,4	A

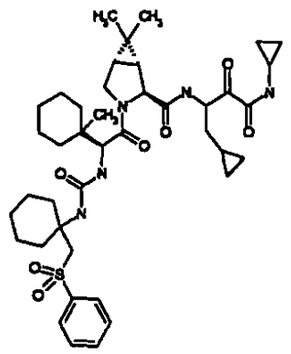
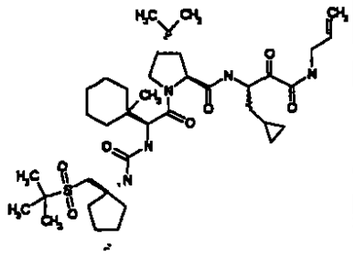
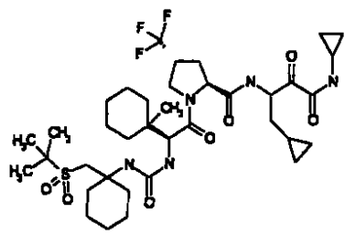
1106

459		784,0271	784,2	A
460		773,9633		A
461		750.0621	750,9	B

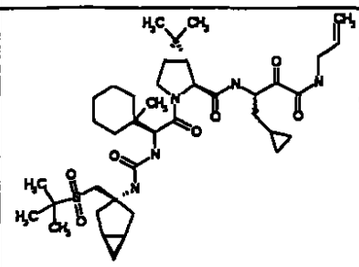
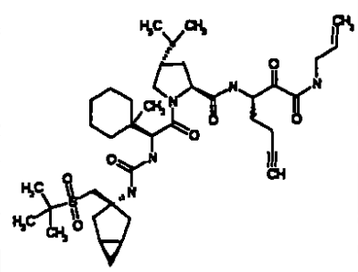
1107

462		762,0733	762,41	C
463		744,0143	744,2	B
464		732,0032	732,4	A

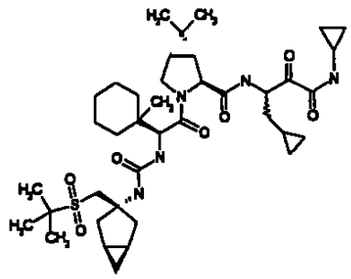
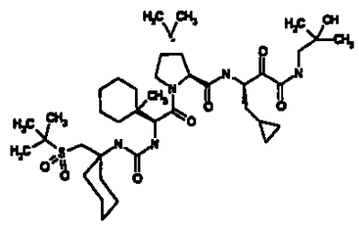
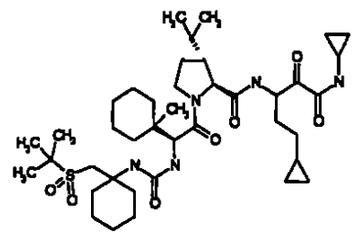
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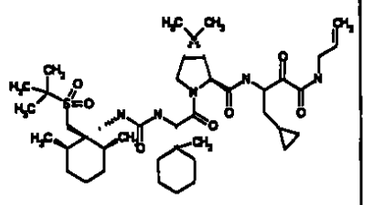
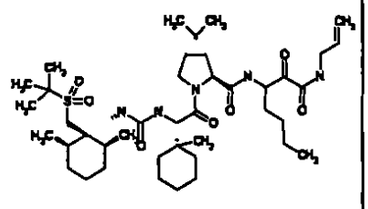
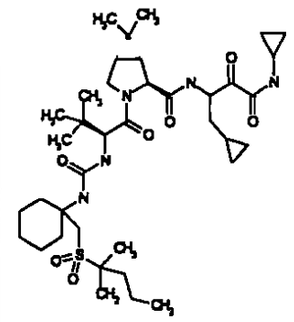
465		766,0207		B
466		744,0143	744,4	A
467		773,9633		B

1109

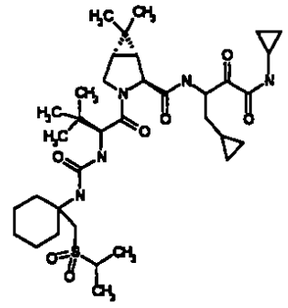
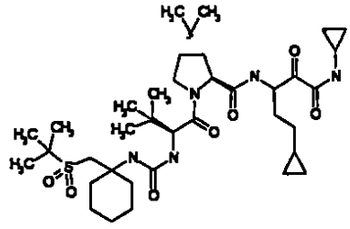
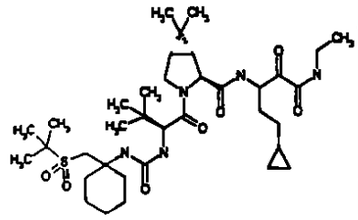
468		744,0143	744,70	B
469		741,9984	742,40	A

1110

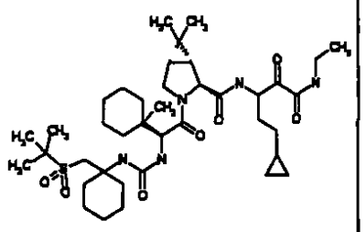
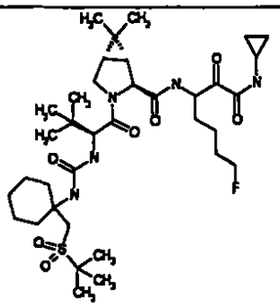
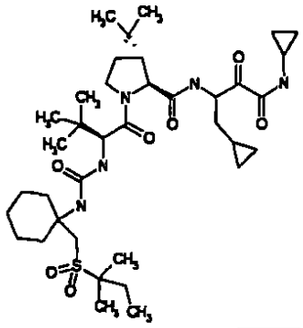
470		744,0143	744,38	B
471		778,0727	778,7	B
472		760,0574		A

473		774,0844	774,4	A
474		776,1004	776,5	A
475		734,0191		A

1112

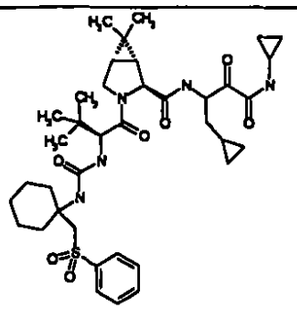
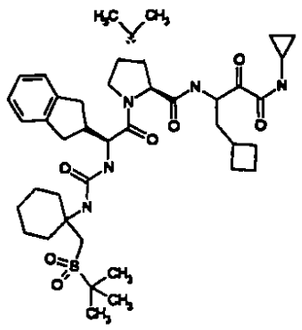
476		691,9378		B
477		719,992		A
478		707,9809		A

1113

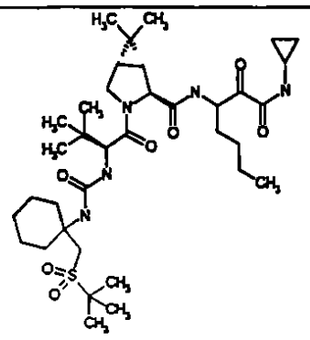
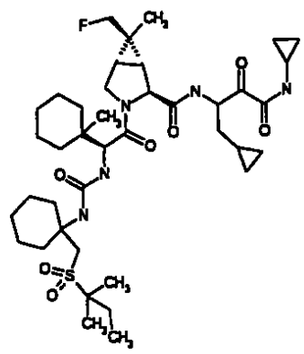
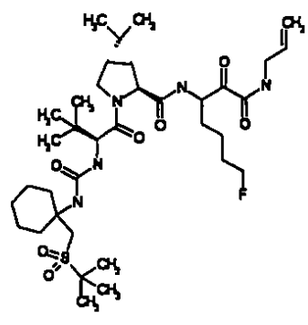
479		748,0462	
480		725,9713	726,4
481		719,992	

1114

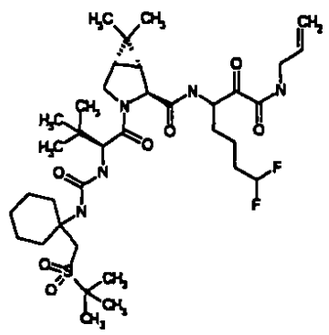
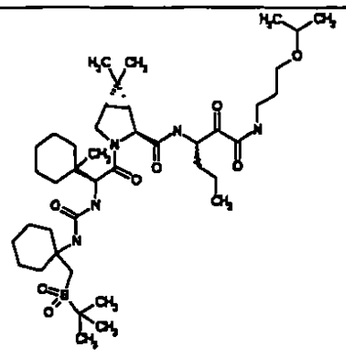
A-154

482		725,9554	
483		780,0478	

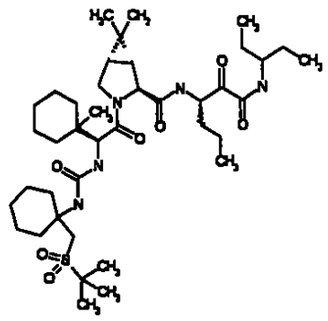
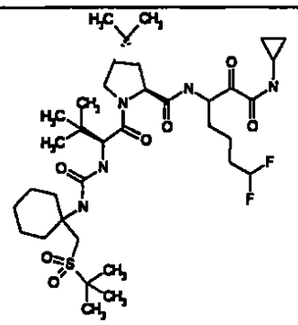
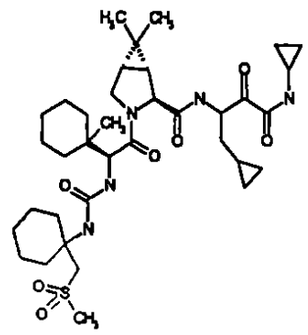
1115

484		707,9809	
485		778,0478	
486		725,9713	

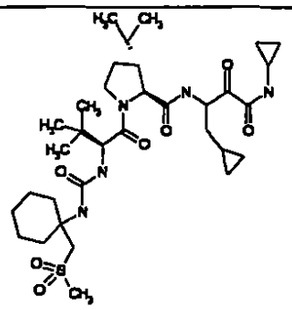
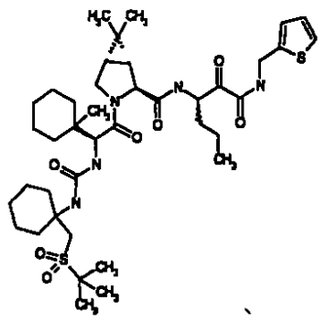
1116

487		743,9617	
488		794,1157	794,2

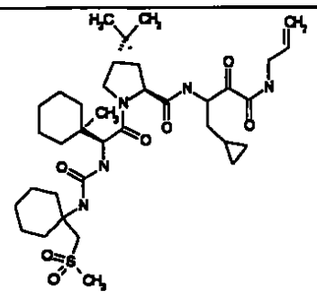
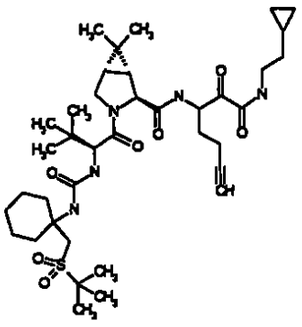
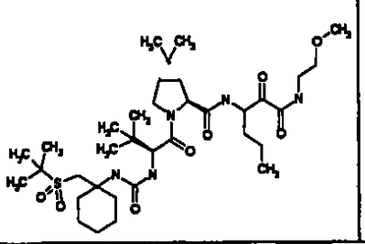
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489		764,0892	764,1
490		743,9617	744,4
491		703,949	

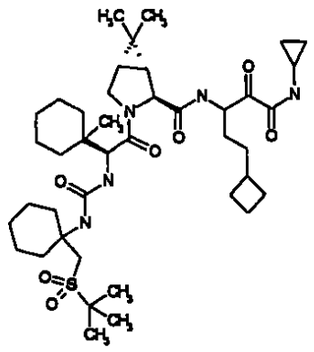
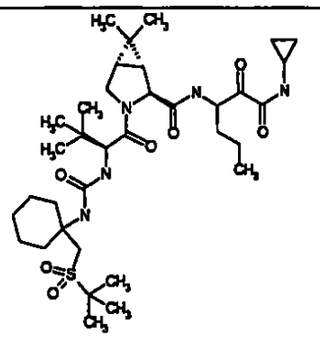
1118

492		663,8837	
493		790,1054	791,4

1119

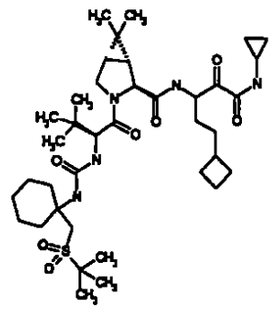
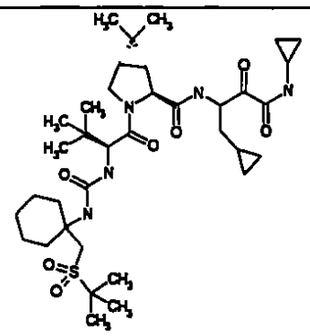
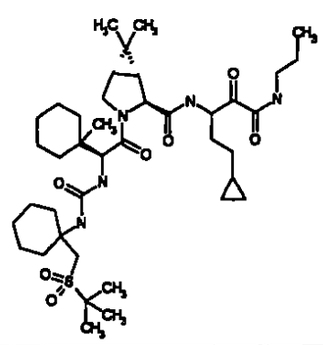
494		703,949	
495		732,0032	
496		712	

1120

497		774	774,2
498		693,9538	

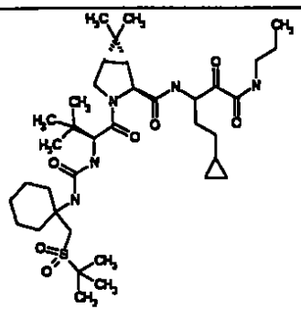
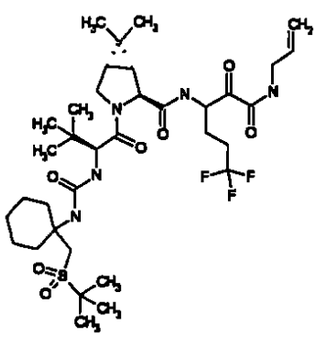
1121

A434

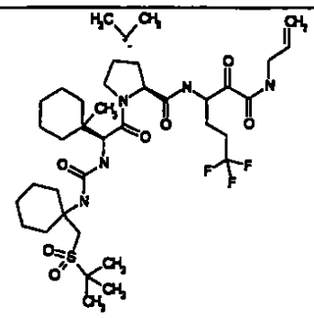
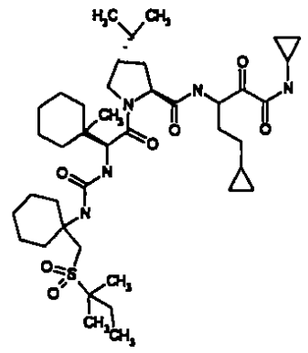
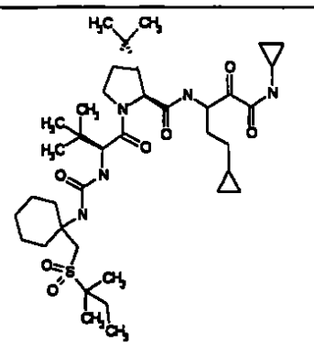
499		734	735,2
500		706	
501		762	

1122

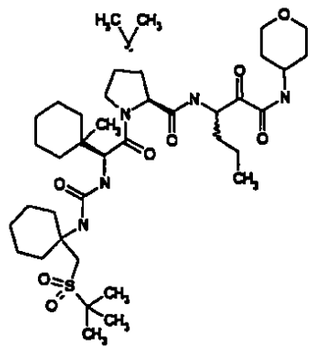
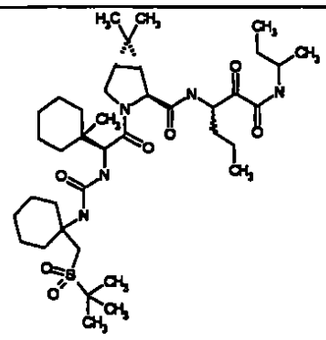
A439

502		722	
503		748	

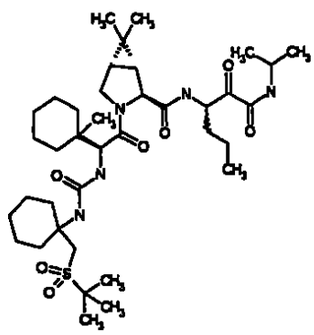
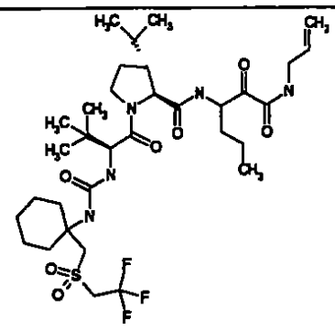
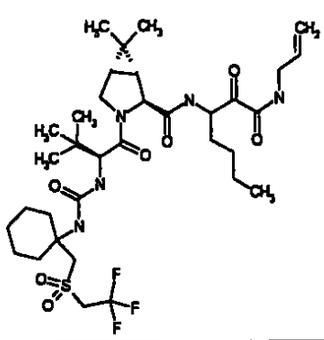
1123

504		788	
505		774	
506		734	

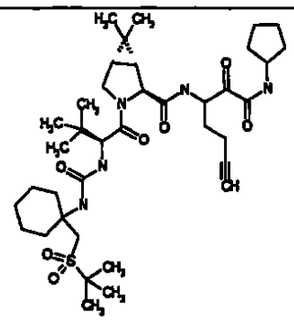
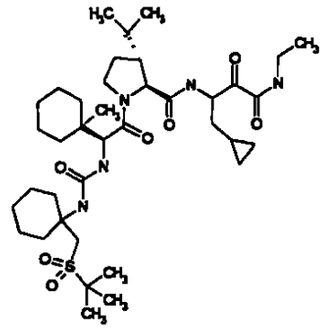
1124

507		778	778,2
508		750	750,5

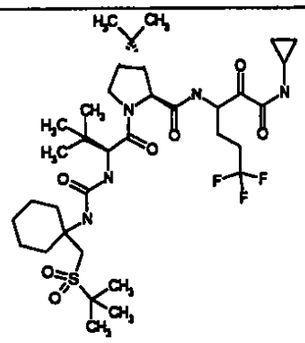
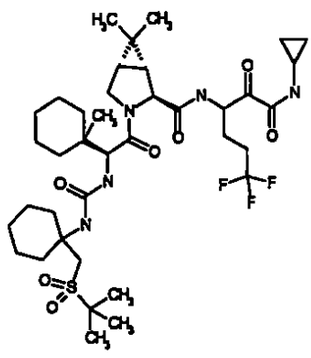
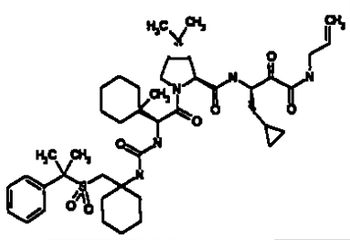
1125

509		736	736,2
510		720	
511		734	

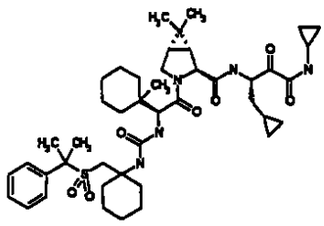
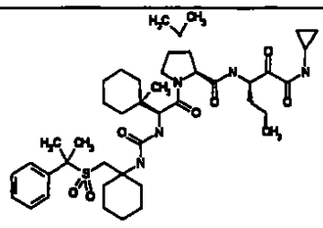
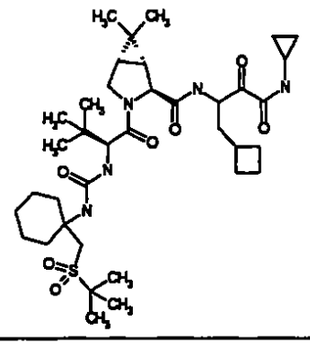
1126

512		732	733,4
513		734	734,4

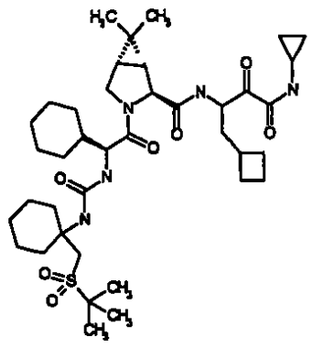
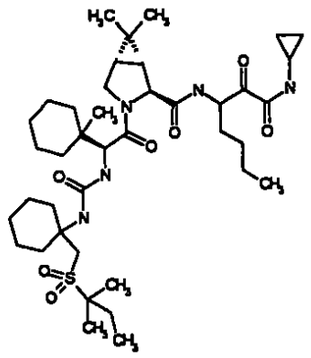
1127

514		748	
515		788	
516		808,102	809,1

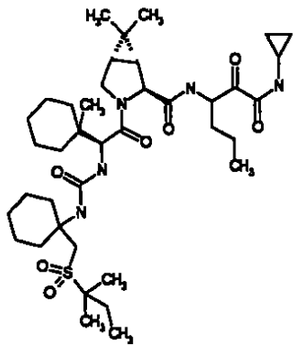
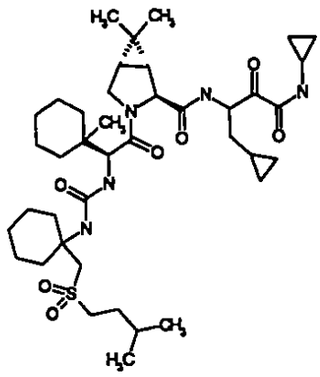
1128

517		808,102	809,1
518		796,0908	797,1
519		719,992	

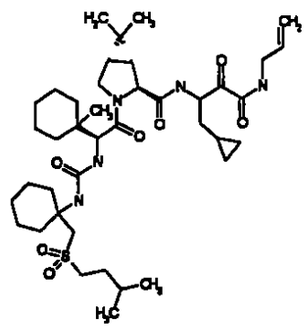
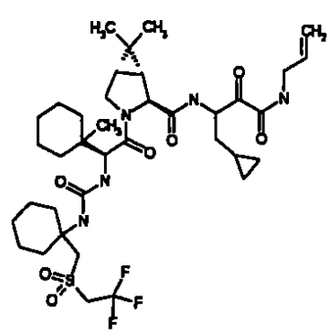
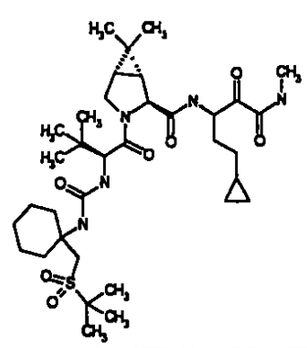
1129

520		746,0303	
521		762,0733	

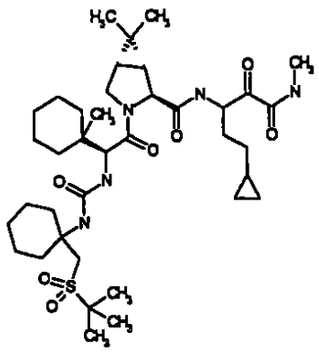
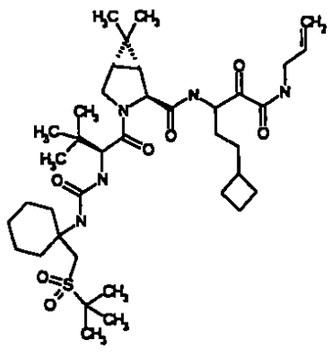
1130

522		748,0462	
523		760,0574	

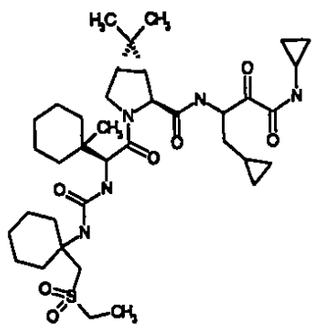
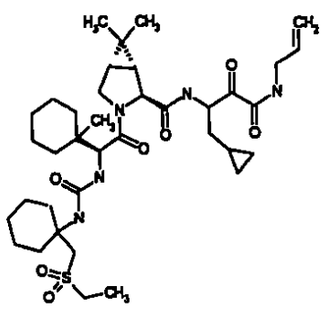
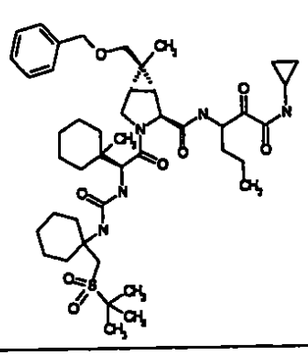
1131

524		760,0574	
525		771,9474	
526		693,9538	

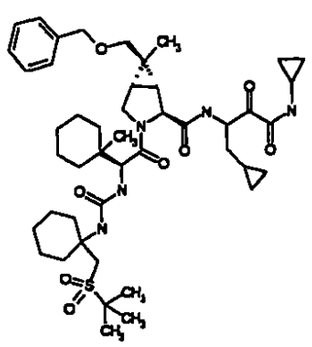
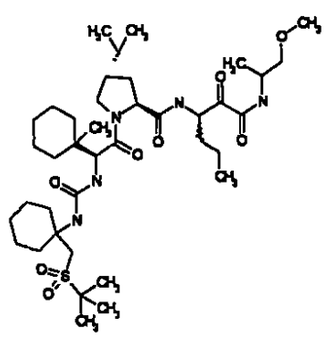
1132

527		734,0191	
528		734,0191	

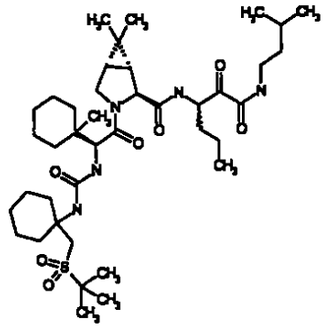
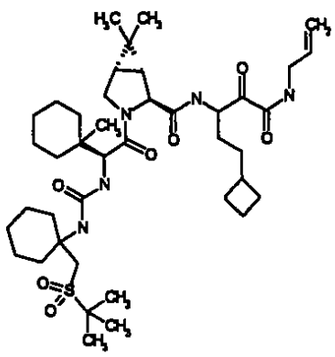
1133

529		717,9761	
530		717,9761	
531		840,1444	

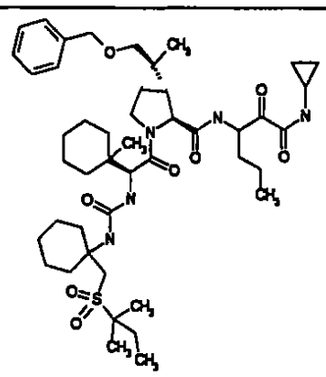
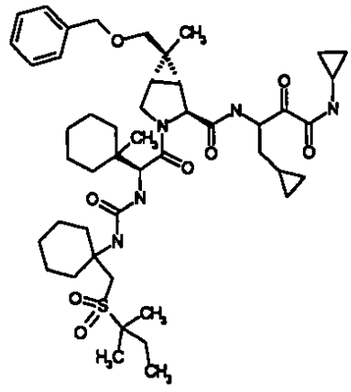
1134 · 451

532		852,1555	
533		766,0615	766,4

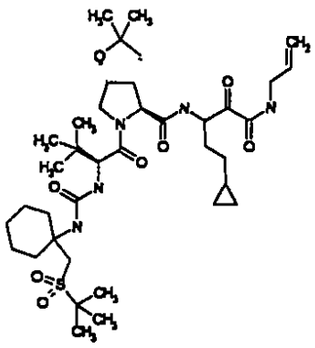
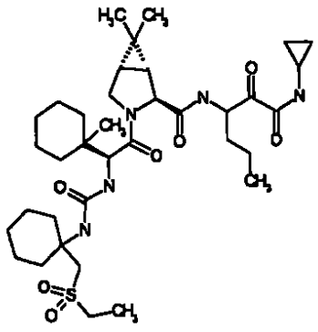
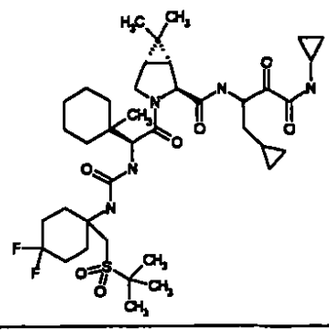
1135

534		764,0892	764,4
535		774,0844	
536		854,1715	

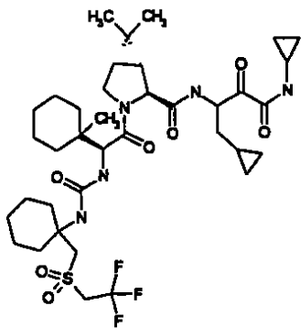
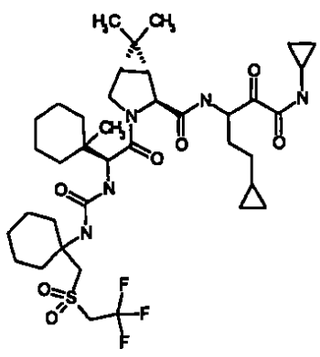
1136

			
537		866,1826	

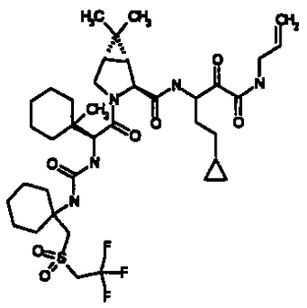
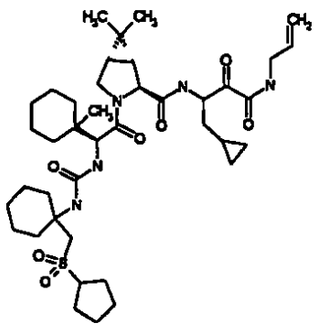
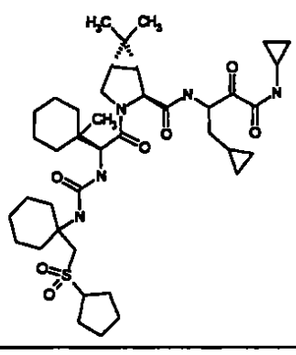
1137

538		750 0185	750,4
539		705,9649	
540		782,0111	

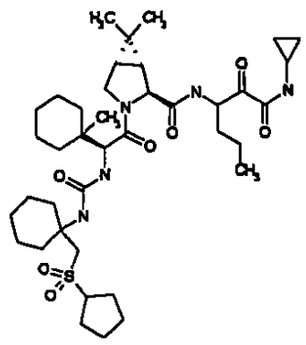
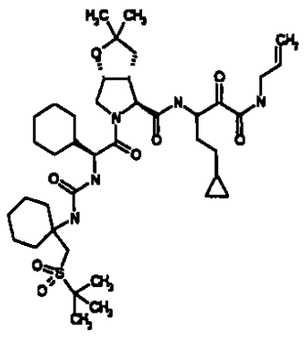
1138

541		771,9474	
542		785,9745	

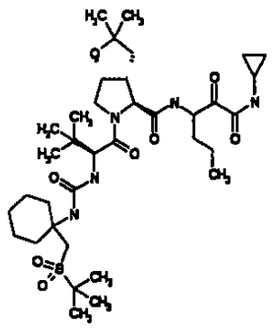
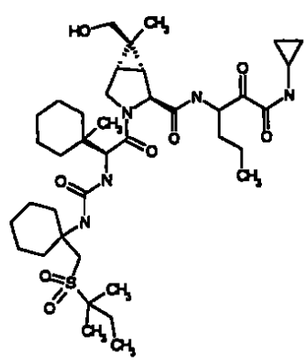
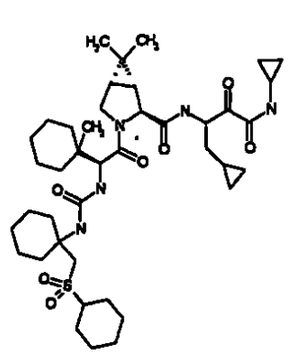
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543		785,9745	
544		758,0414	
545		758,0414	

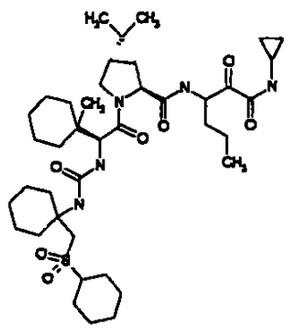
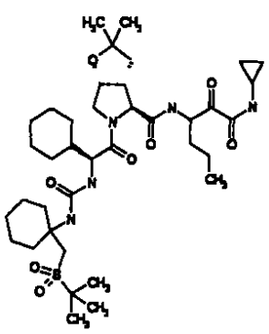
1140

546		746,0303	
547		776,0568	776,4

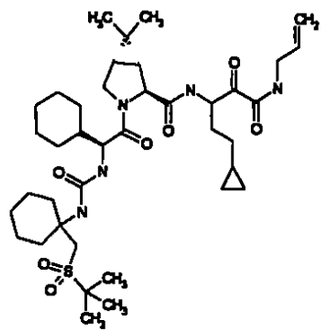
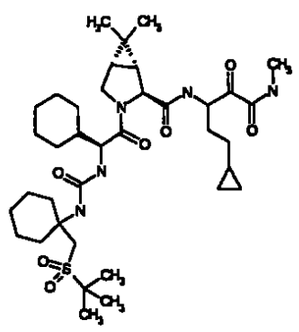
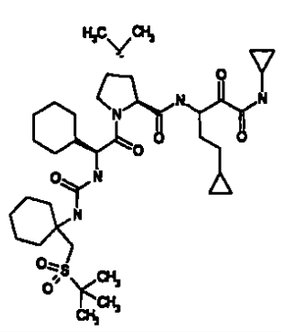
1147

548		723,9803	724,4
549		764,0456	
550		772,0685	

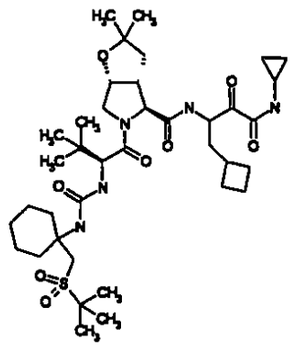
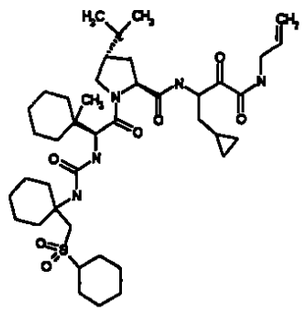
1142

551		760,0574	
552		750 0185	750,1

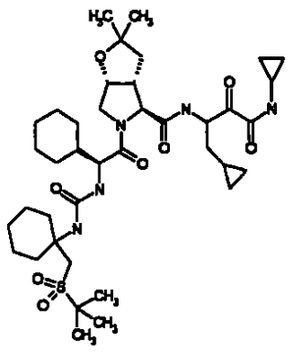
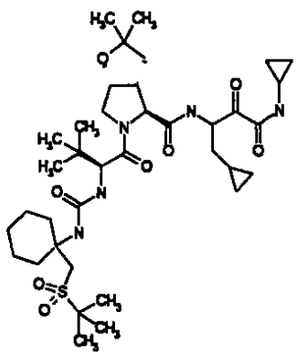
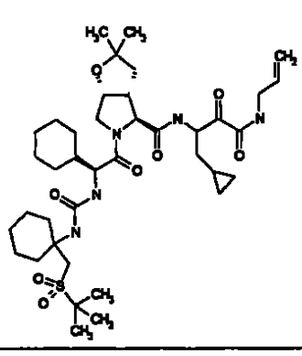
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553		746,0303	
554		719,992	
555		746,0303	

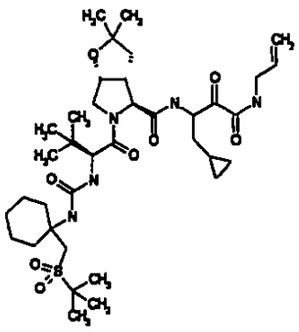
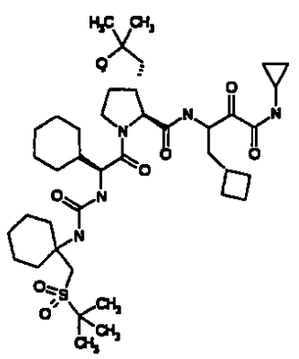
1144

556		750 0185	750,1
557		772,0685	

1145

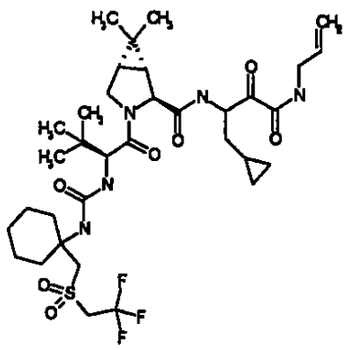
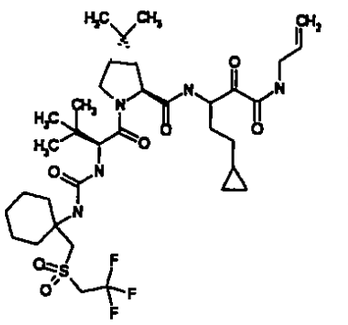
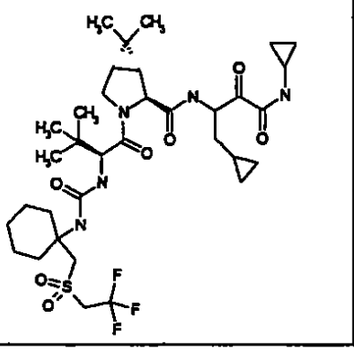
558		762,0297	
559		735,9914	
560		762,0297	

1146

561		735,9914	
562		776,0568	

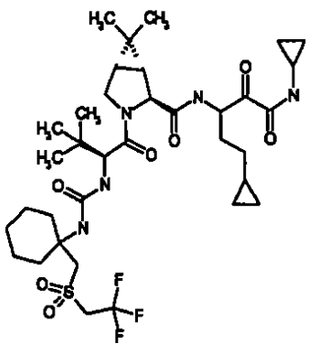
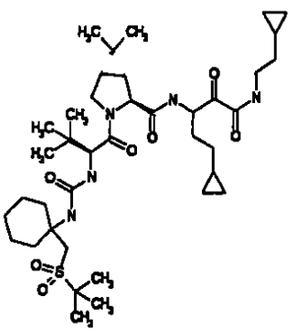
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1469

563		731,882	
564		745,9091	
565		731,882	

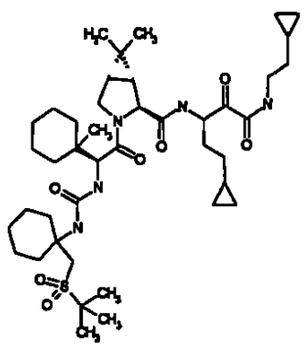
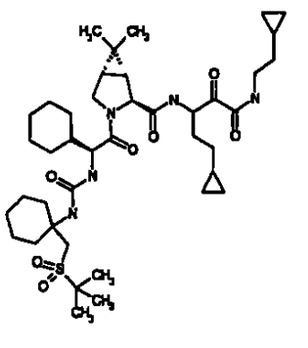
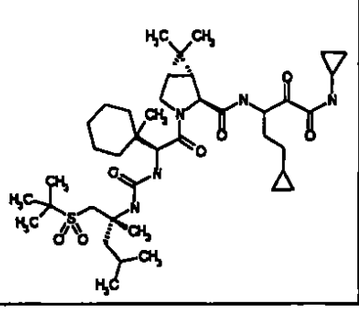
1148

A465

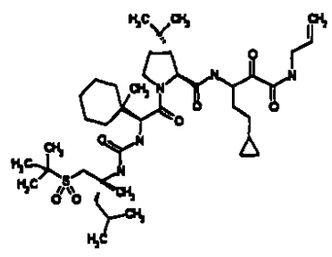
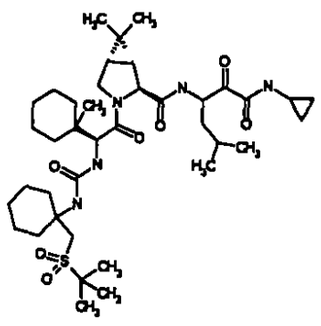
566		745,9091	
567		748,0462	

1149

1466

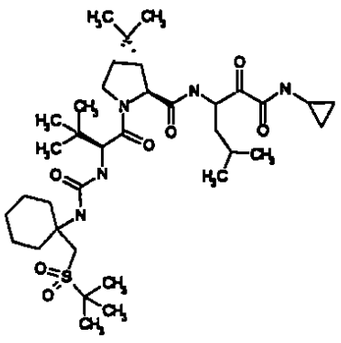
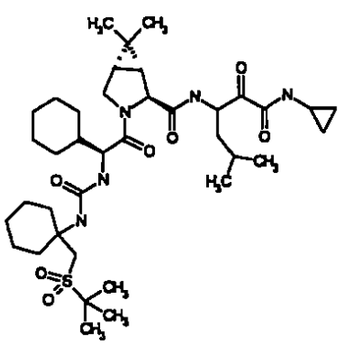
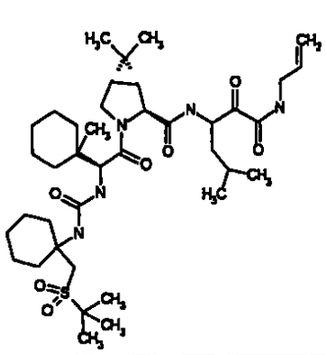
568		788,1115	
569		774,0844	
570		762,0733	763,1

1150 4469

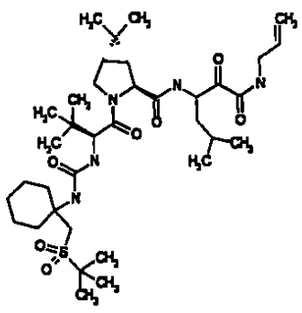
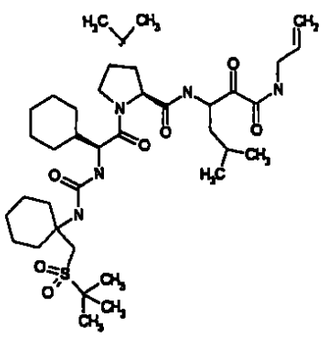
571		762,0733	763,1
572		748,0462	

A468

1151

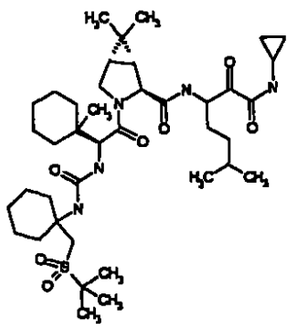
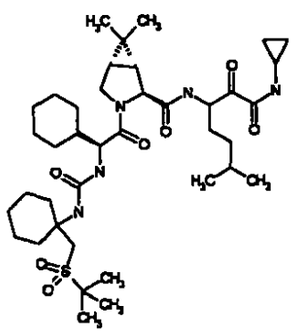
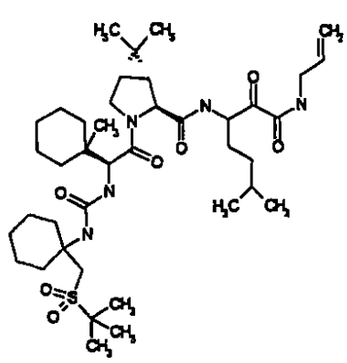
573		707,9809	
574		734,0191	
575		748,0462	

1152

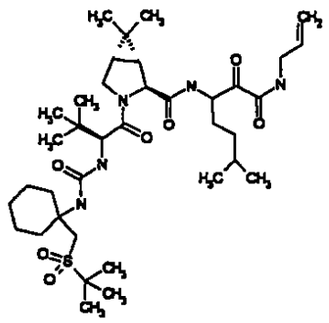
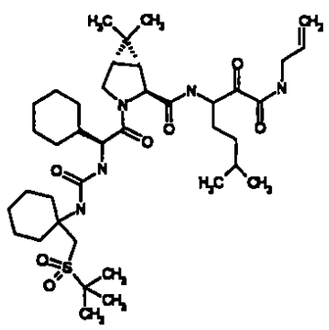
576		707,9809	
577		734,0191	

1153

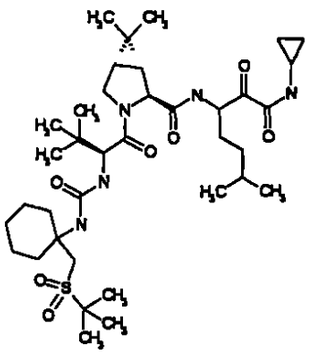
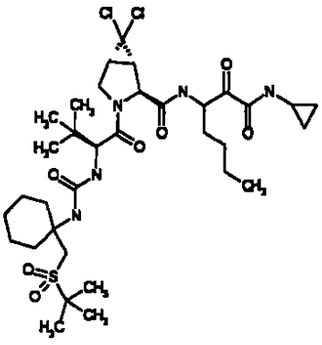
1120

578		762,0733	762,4
579		748,0462	748,4
580		762,0733	

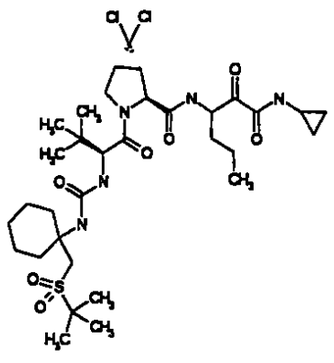
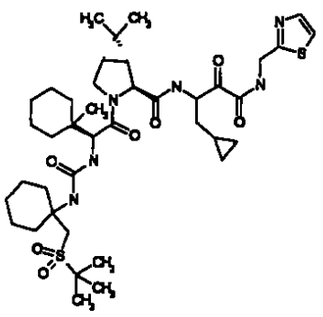
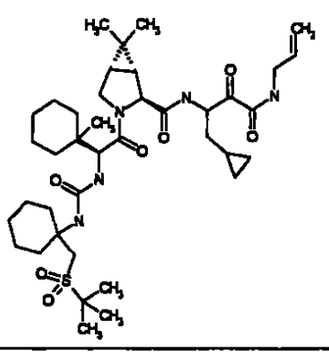
1154

581		722 008	
582		748,0462	

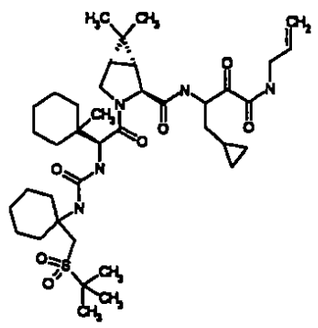
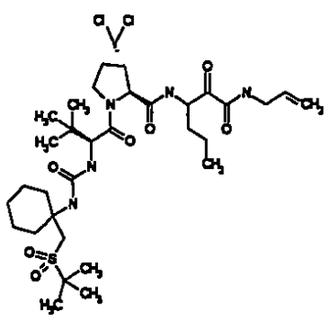
1155 A-42V

583		722 008	722,4
584		748,8168	748,4

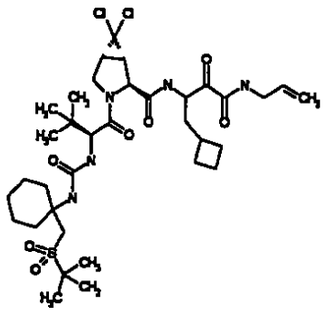
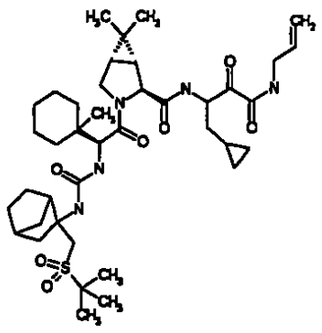
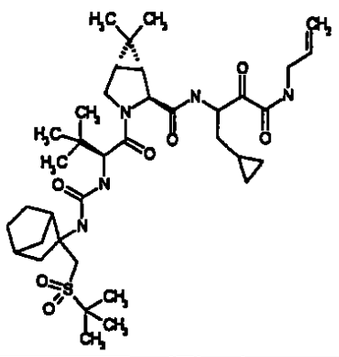
1156

585		734,7897	734,4
586		803,1041	803,4
587		746,0303	

1157

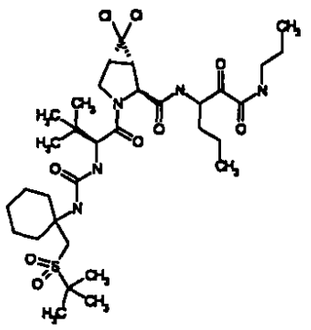
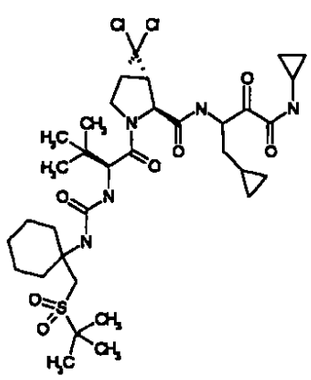
588		746,0303	
589		734,7897	734,1

1158

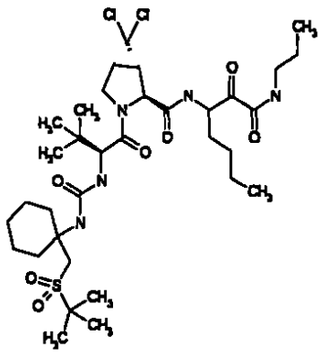
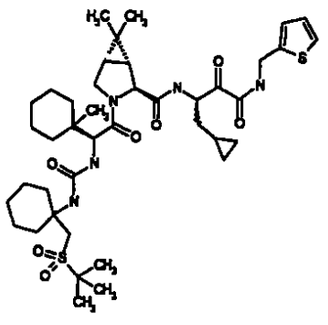
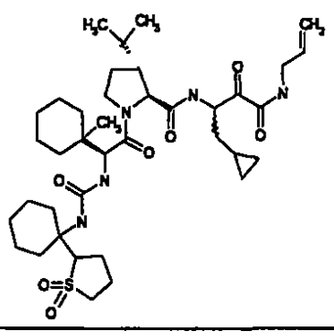
590		760,8279	760,1
591		758,0414	
592		717,9761	

A476

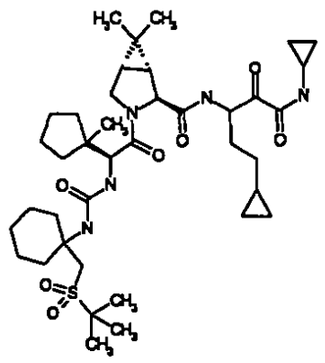
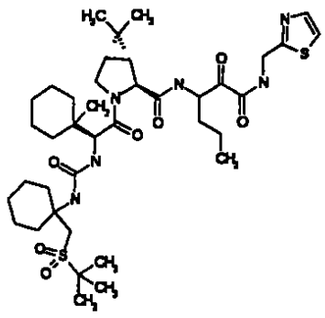
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593		736,8056	736,1
594		746,8008	746,1

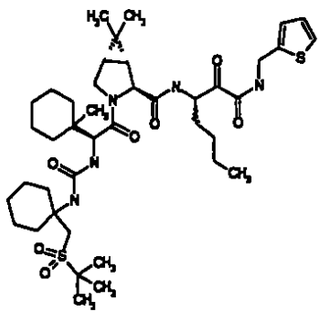
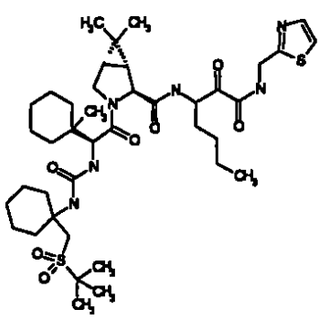
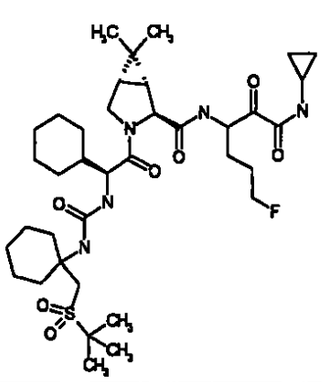
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595		750,8327	750,4
596		802,1166	802,5
597		729,9872	731,4

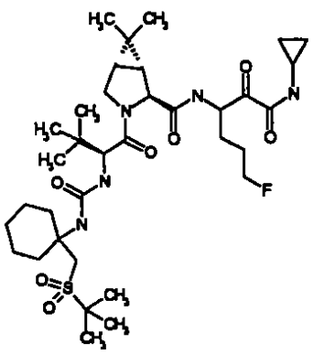
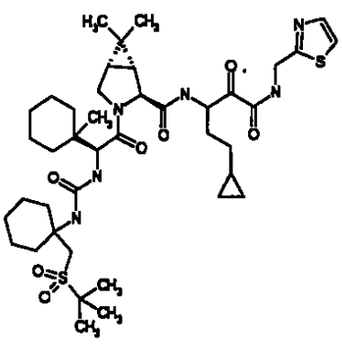
1161

598		746,0303	746,4
599		791,093	791,4

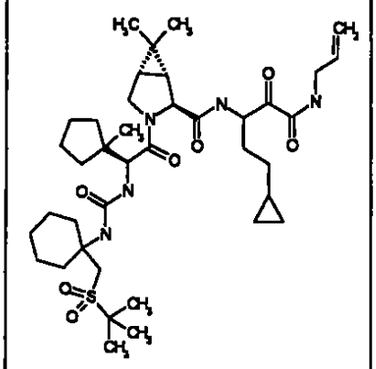
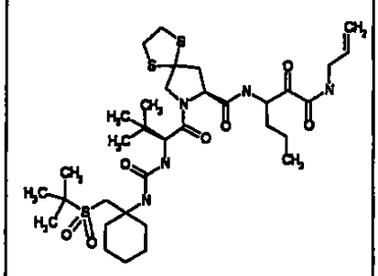
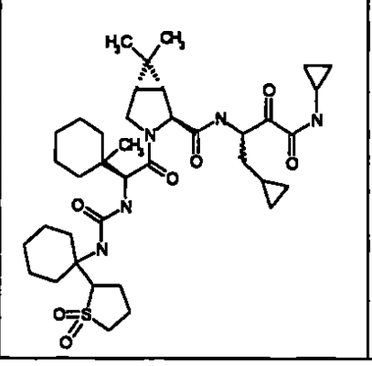
1162

600		804,1325	804,5
601		805,1201	805,4
602		737,9825	

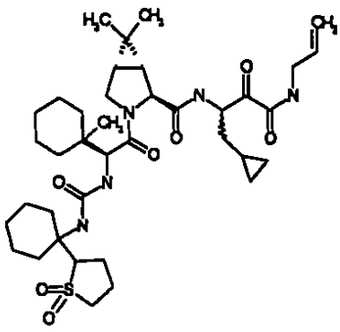
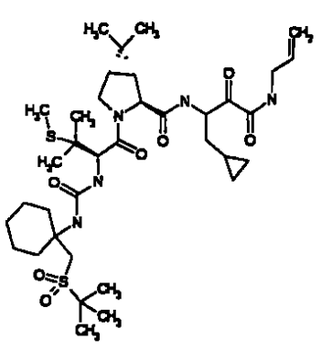
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603		711,9442	
604		817,1312	817,4

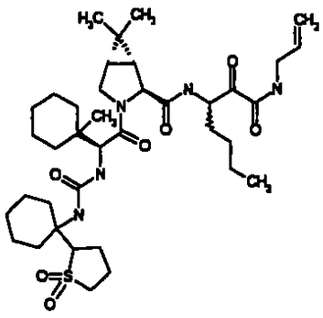
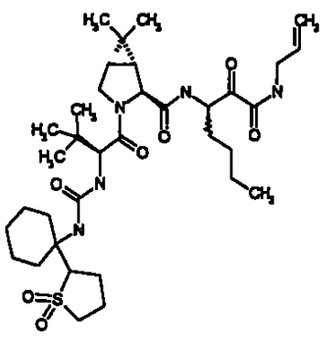
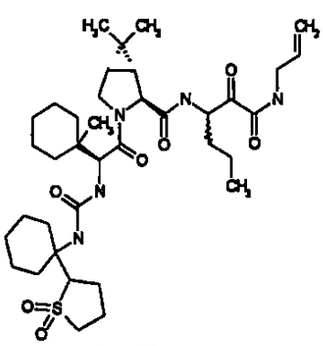
1164

605		746,0303	746,4
606		744,0547	745,1
607		729,9872	

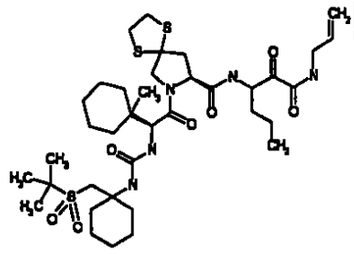
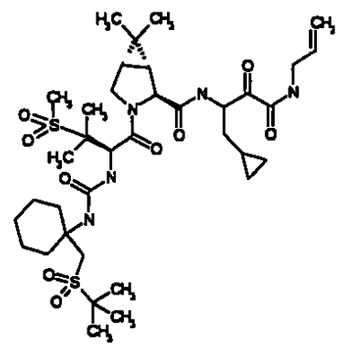
1165 7182

608		729,9872	730,4
609		738,0289	738,1

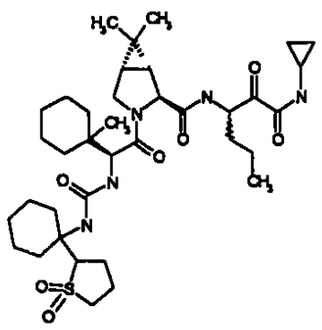
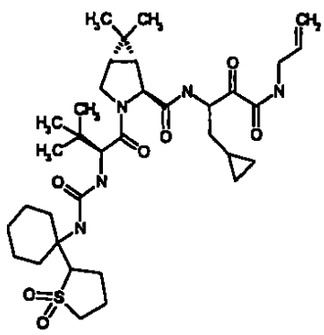
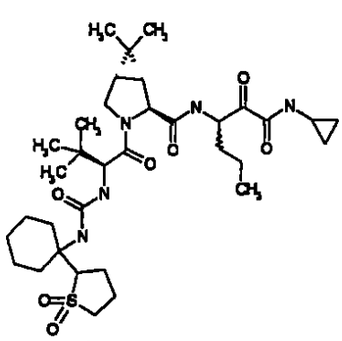
1166. 1183

610		732,0032	732,1
611		691,9378	692,1
612		717,9761	718,1

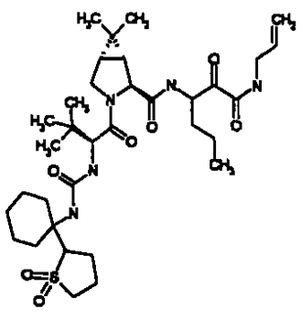
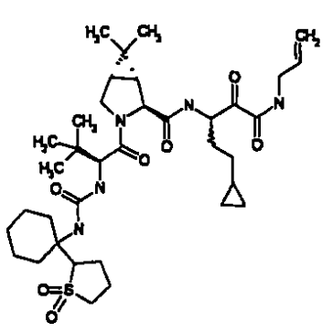
1167 1484

613		784,12	784,2
614		770,0277	770,2

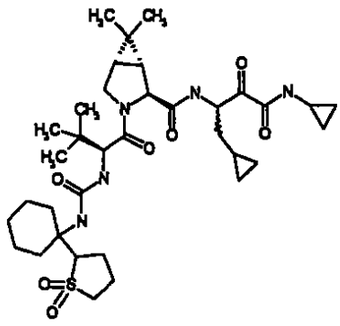
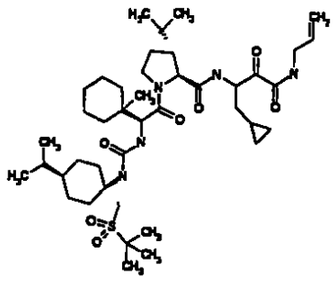
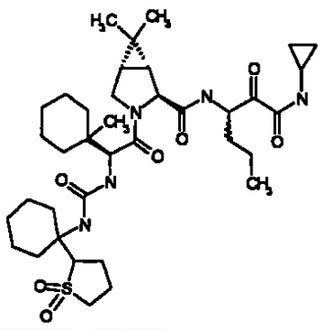
1168

615		717,9761	
616		689,9219	
617		677,9108	678,4

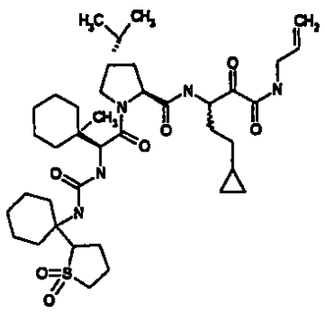
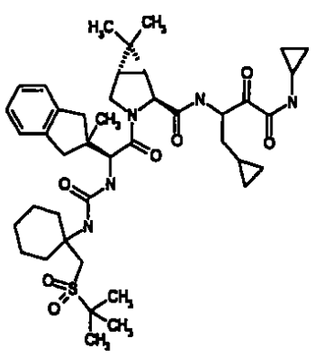
1169

618		677,9108	678,4
619		703,949	704,4

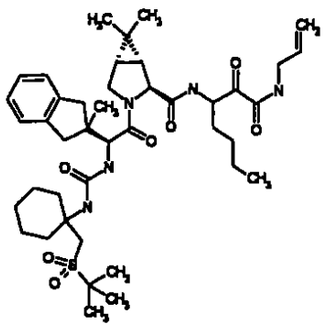
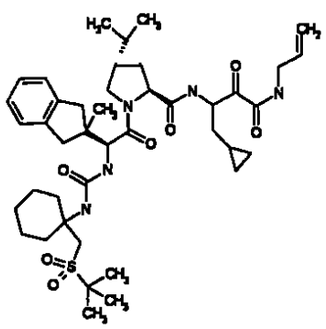
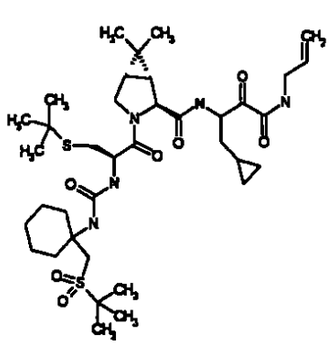
1170

620		689,9219	690,4
621		788,1115	789,4
622		717,9761	718,1

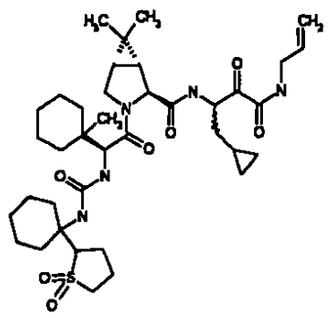
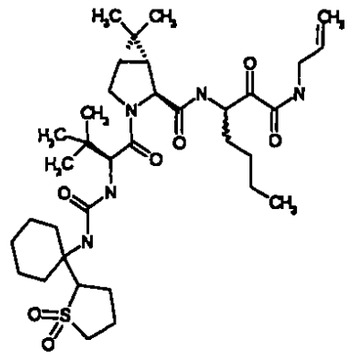
1171

623		744,0143	744,1
624		780,0478	780,5

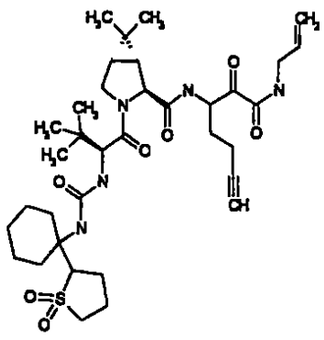
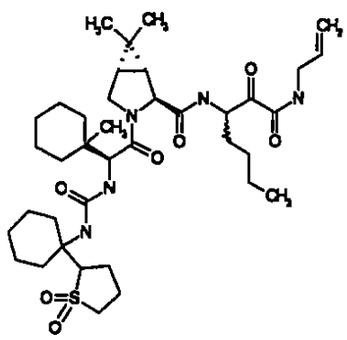
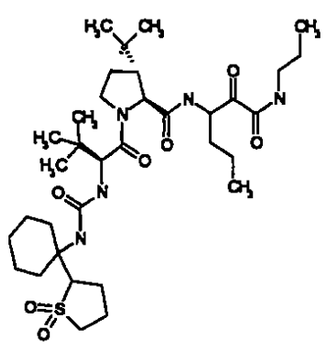
1172

625		782,0637	782,5
626		780,0478	780,5
627		752,056	752,1

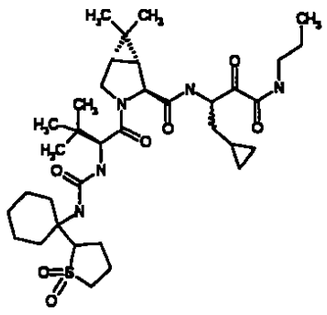
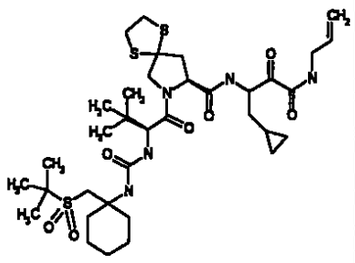
1173

628		729,9872	730,4
629		691,9378	692,4

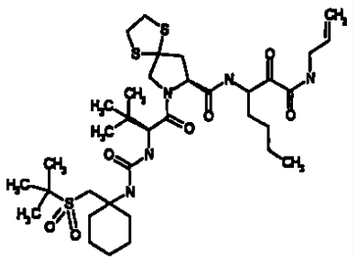
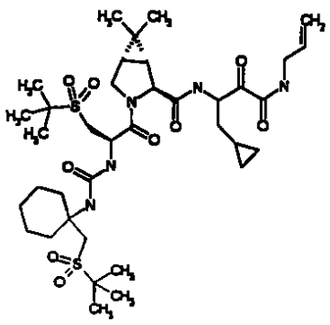
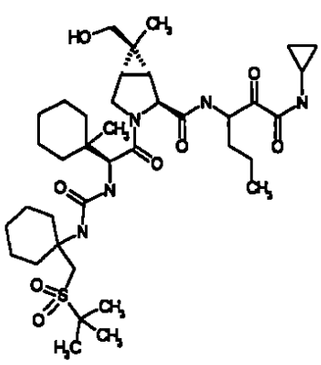
1174

630		687,906	688,4
631		732,0032	732,4
632		679,9267	680,4

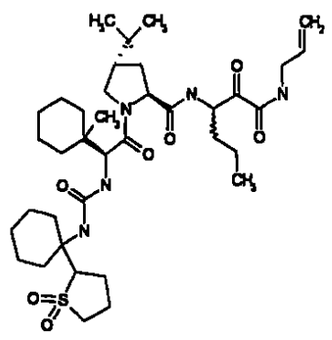
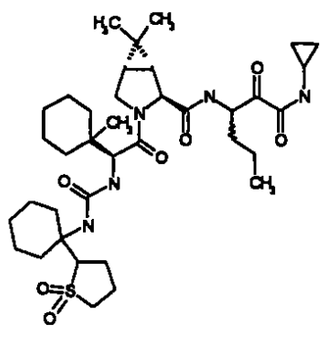
1175 A196

633		691,9378	692,4
634		756,0658	756,1

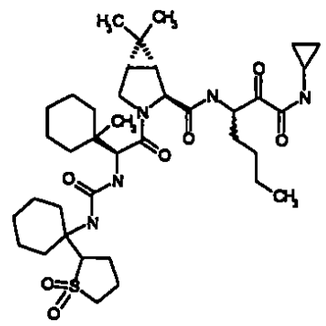
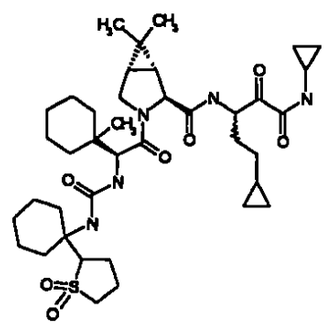
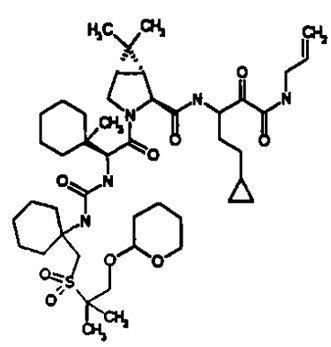
1176

635		758,0818	758,1
636		784,0548	784,2
637		750 0185	

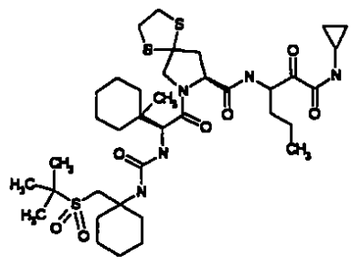
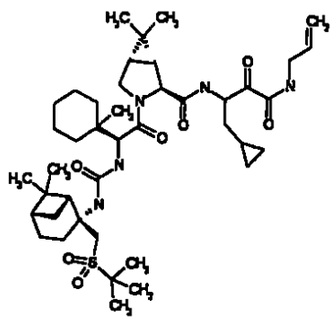
1177.

638		717,9761	718,4
639		717,9761	718,4

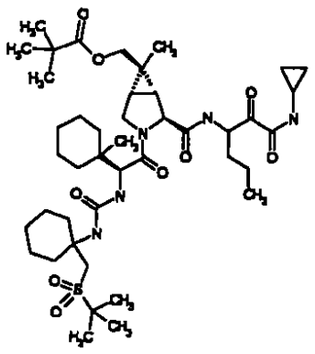
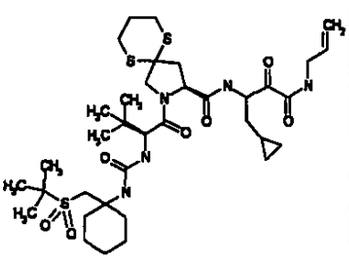
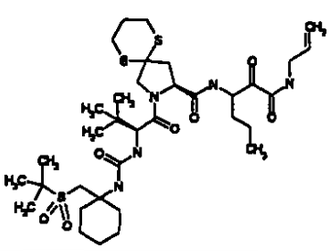
1178

640		732,0032	732,4
641		744,0143	744,4
642		860,1757	

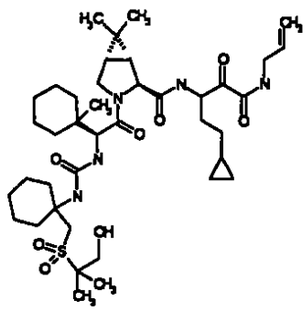
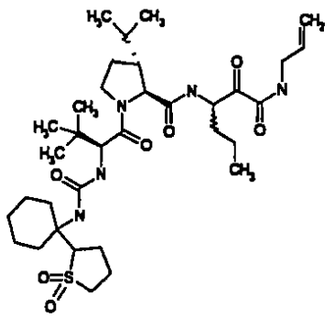
1179

643		784,12	
644		786,0956	

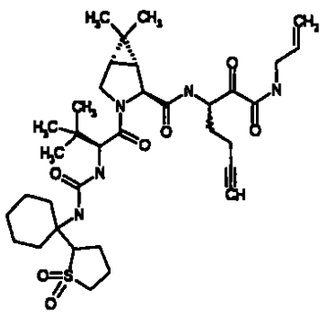
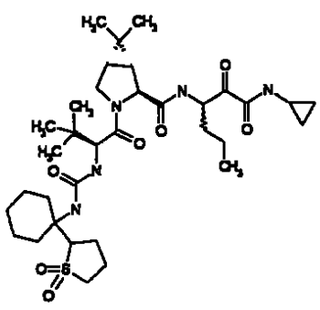
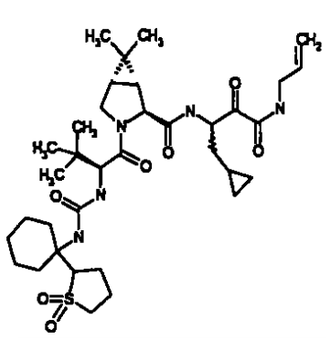
1180 A147

645		834,1374	
646		770,0929	770,2
647		758,0818	758,2

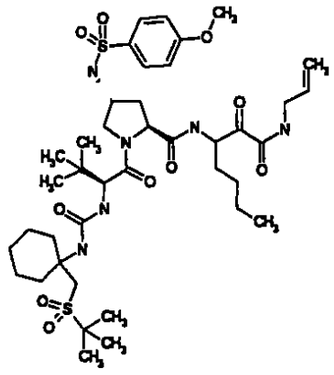
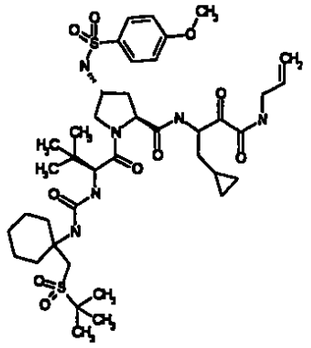
1181 1498

648		776,0568	
649		677,9108	678,2

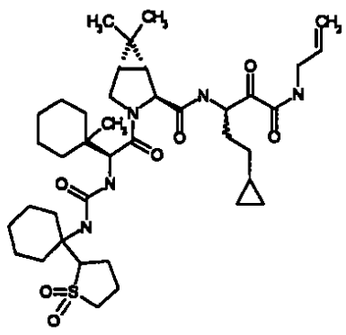
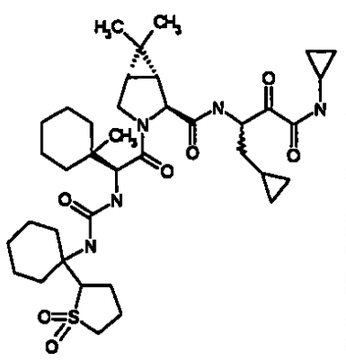
1182

650		687,906	688,2
651		677,9108	678,2
652		689,9219	690,2

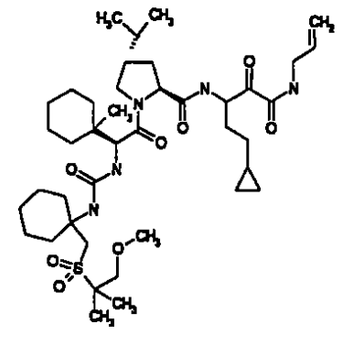
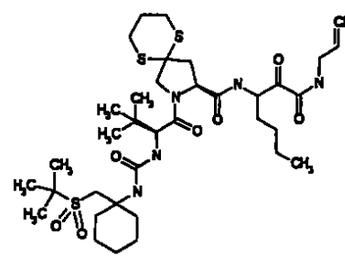
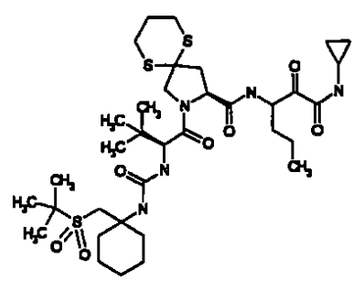
1183 +200

653		853,1183	853,4
654		851.1023	851,4

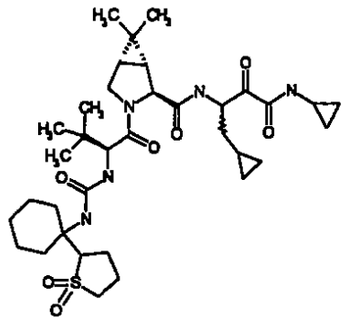
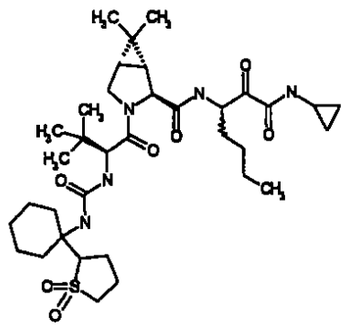
1184

655		744,0143	744,1
656		729,9872	730,1

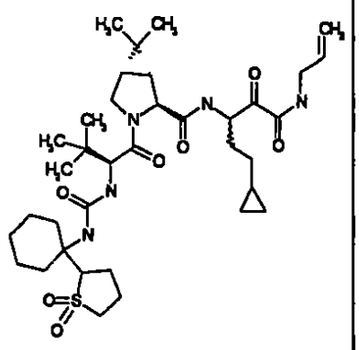
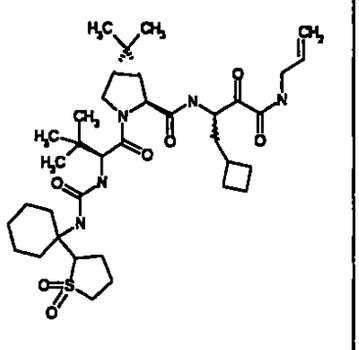
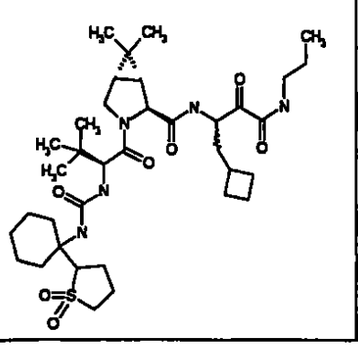
1185

657		790,0838	
658		772,1089	772,2
659		758,0818	758,2

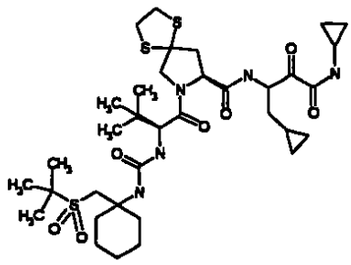
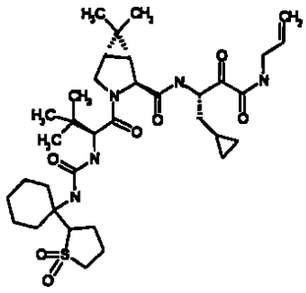
1186

660		689,9219	690,1
661		691,9378	692,1

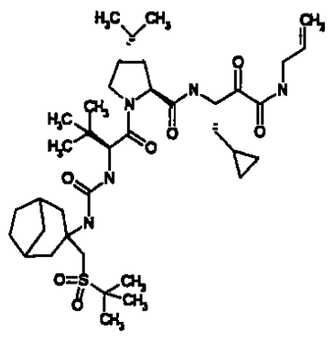
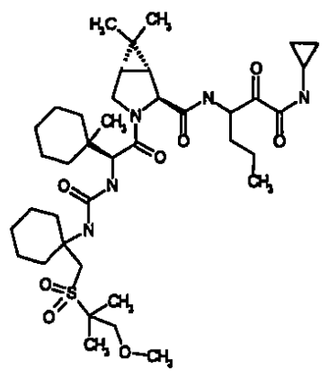
1187

662		703,949	704,1
663		703,949	704,1
664		705,9649	706,2

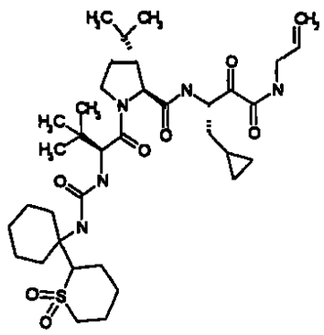
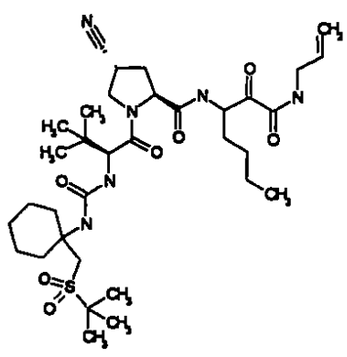
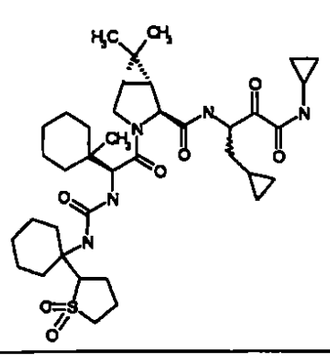
1188

665		756,0658	
666		689,9219	

1189

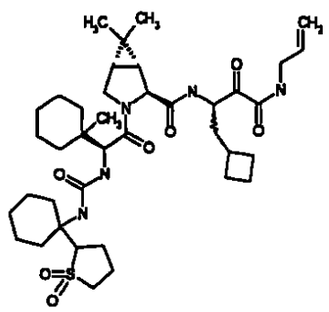
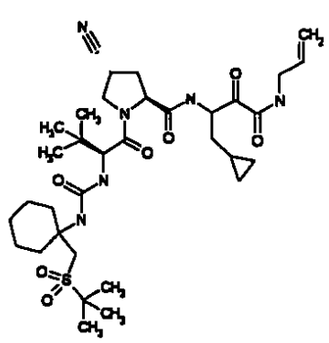
667		732,0032	
668		764,0456	

1190

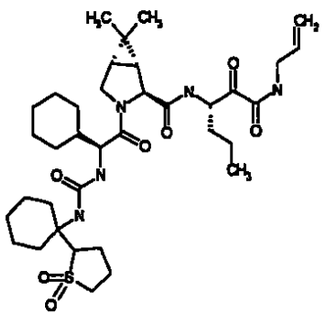
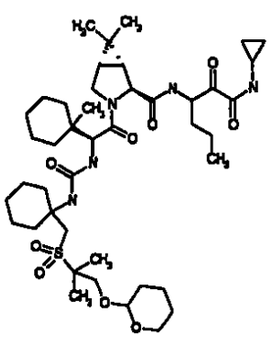
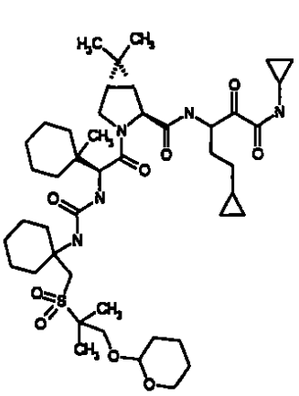
669		703,949	
670		692,9254	693,3
671		729,9872	730,1

1191

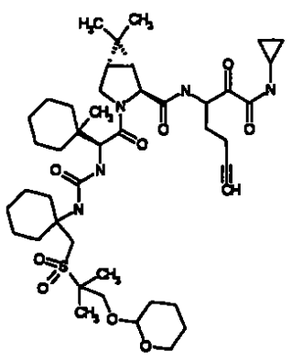
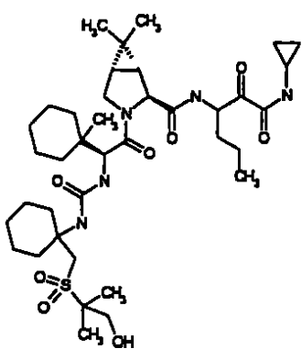
1908

672		744,0143	744,1
673		690,9095	691,35

1192

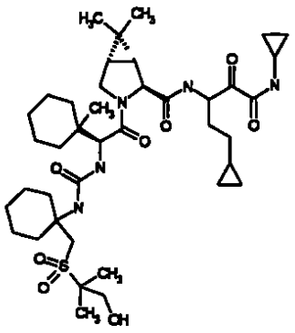
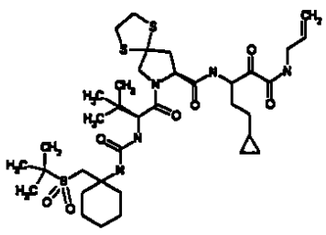
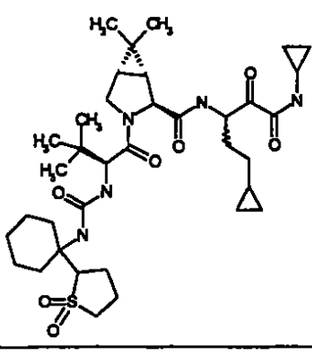
674		703,949	
675		834,1374	
676		860,1757	

1193

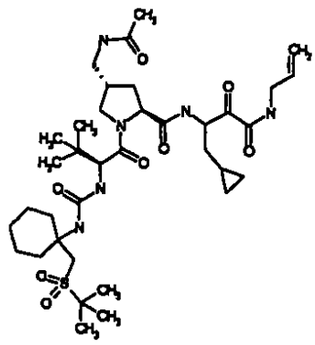
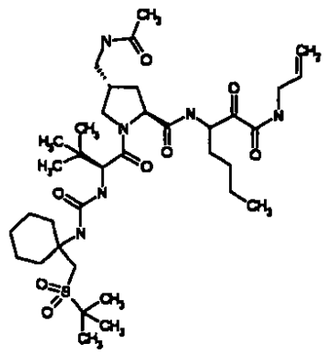
677		844,1326	
678		750 0185	

1194

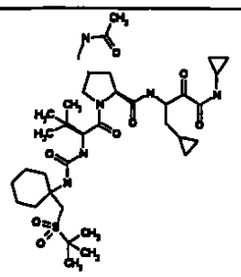
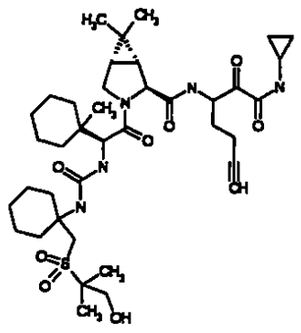
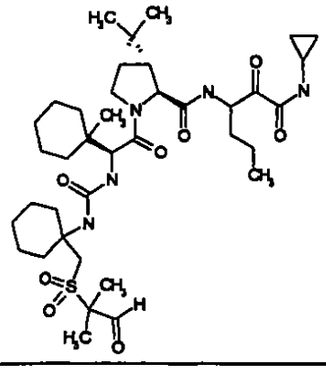
1217

679		776,0568	
680		770,0929	770,4
681		703,949	704,2

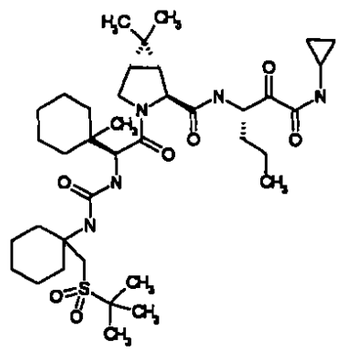
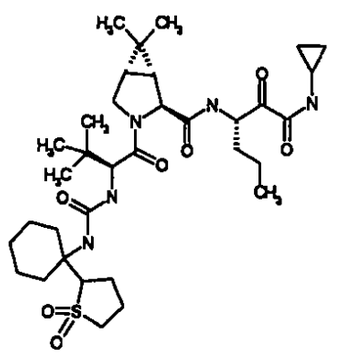
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682		736,979	737,5
683		738,9949	739,4

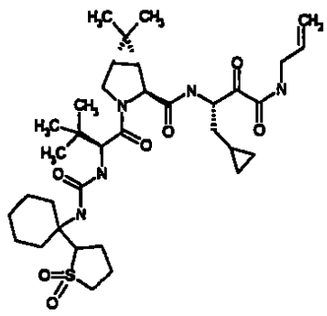
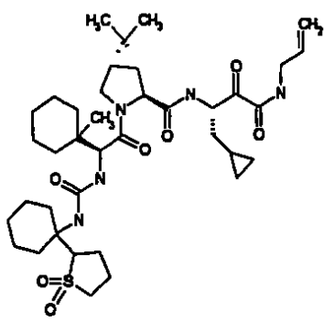
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684		736,979	737,4
685		760,0137	
686		748,0026	

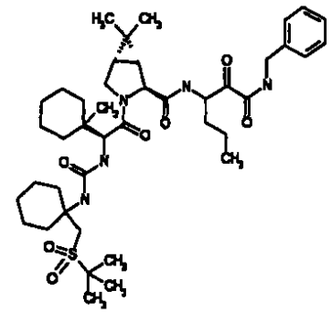
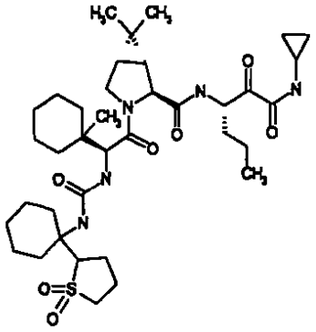
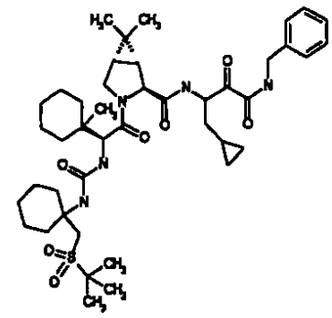
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687		734,0191	
688		677,9108	678,2

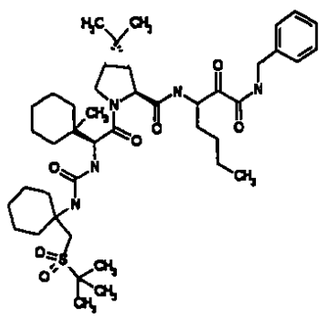
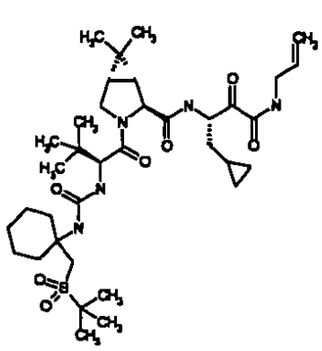
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689		689,9219	690,2
690		729,9872	730,2

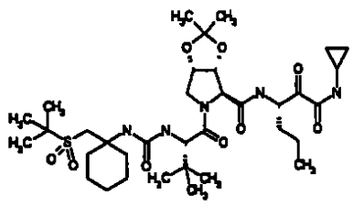
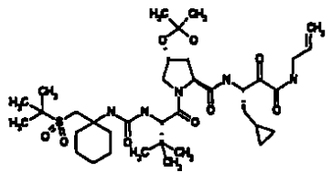
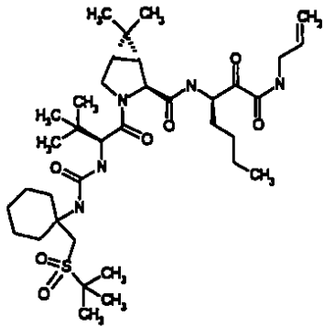
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691		784,0797	784,2
692		717,9761	
693		796,0908	796,2

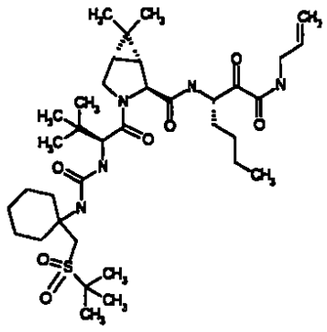
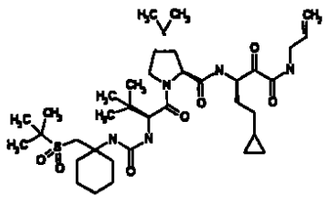
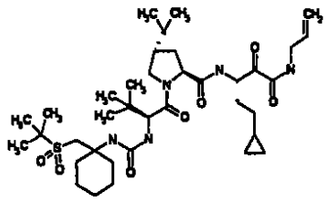
1200 1212

694		798,1067	798,2
695		705,9649	

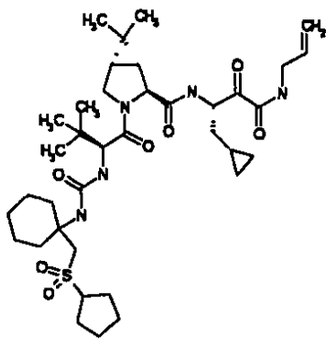
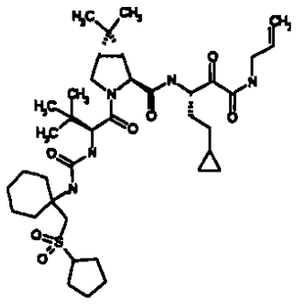
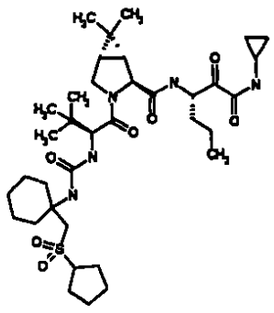
1201

696		725,9526	726,4
697		737,9637	738,4
698		707,9809	708,4

1202

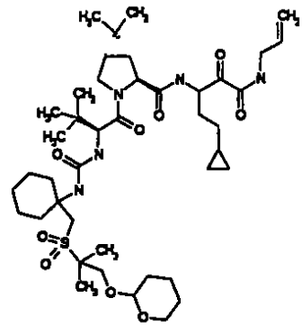
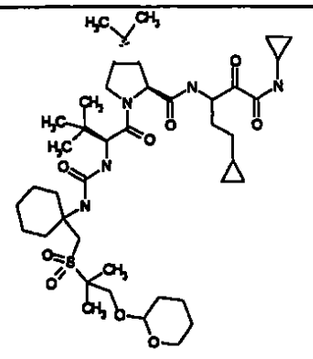
699		707,9809	708,4
700		719,992	
701		719,992	

1203

702		717,9761	718,60
703		732,0032	732,6
704		705,9649	706,6

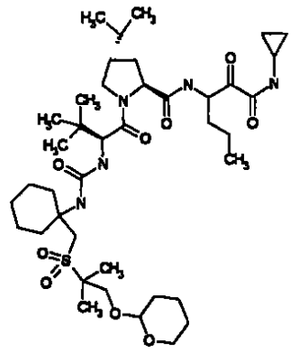
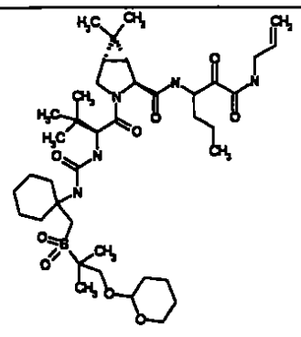
1204

1224

705		820,1103	
706		820,1103	

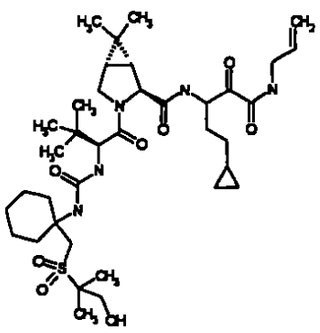
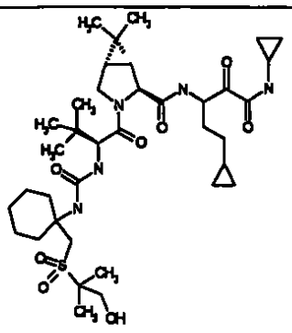
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1205

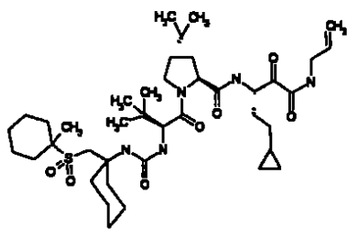
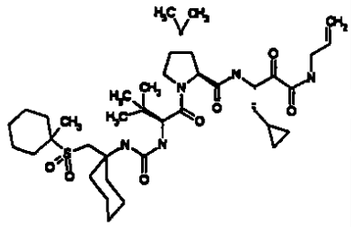
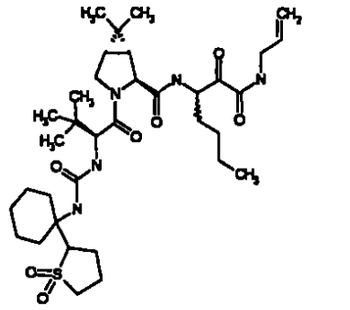
707		794,0721	
708		794,0721	

1206

1223

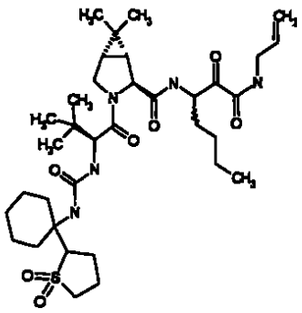
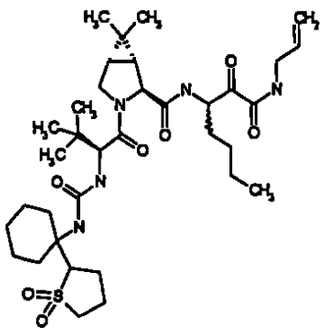
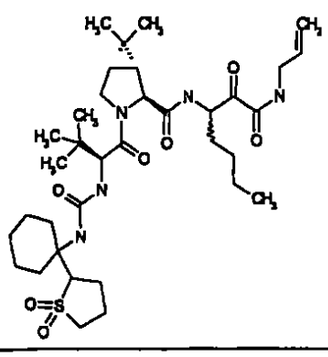
709		735,9914	
710		735,9914	

1207

711		760,0574	
712		746,0303	
713		691,9378	692,2

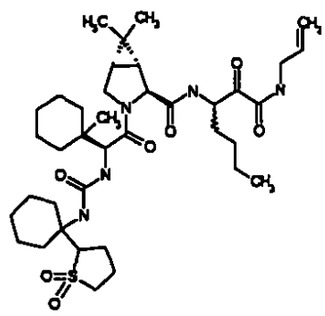
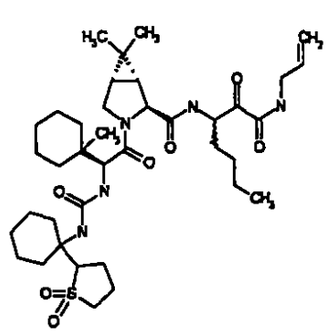
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1288

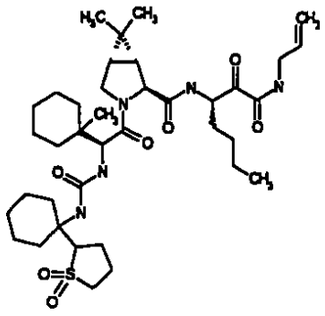
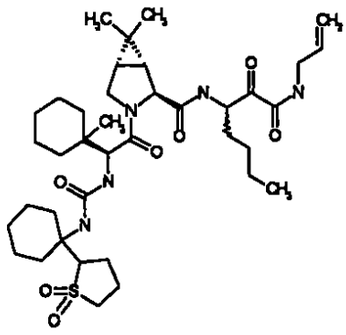
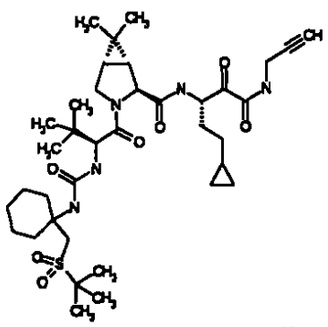
714		691,9378	692,2
715		691,9378	692,2
716		691,9378	692,2

1209

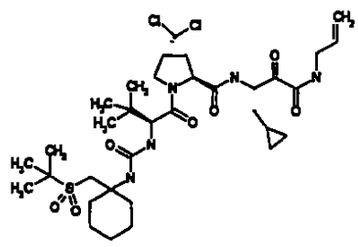
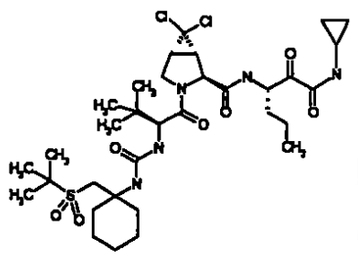
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717		732,0032	732,2
718		732,0032	732,2

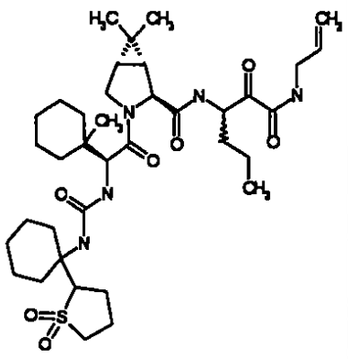
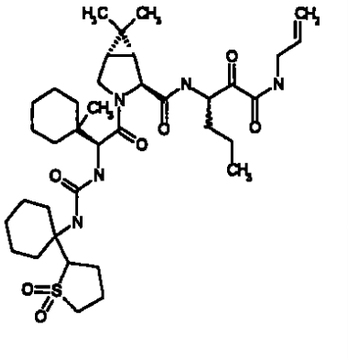
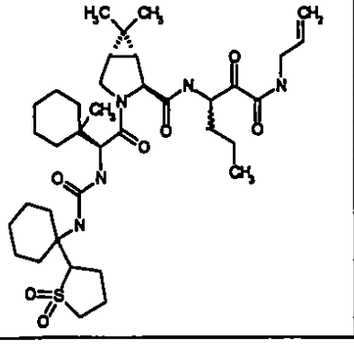
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719		732,0032	732,2
720		732,0032	732,2
721		717,9761	718,1

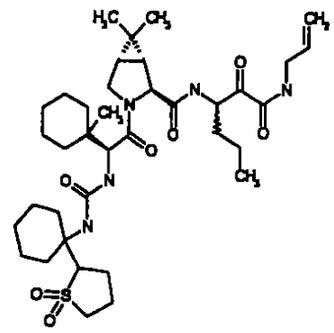
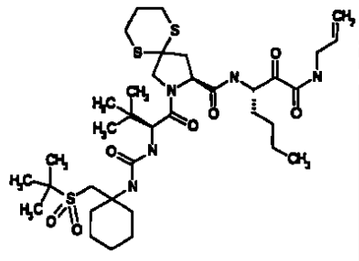
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722		746,8008	
723		734,7897	

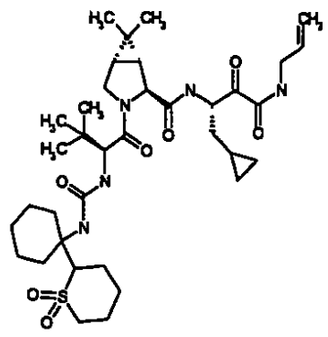
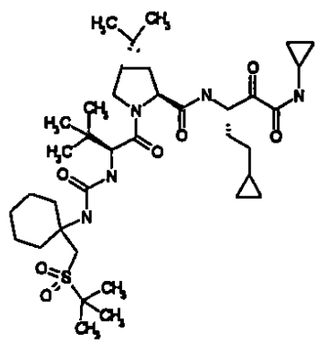
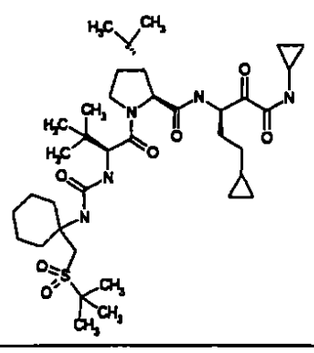
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724		717,9761	718,2
725		717,9761	718,2
726		717,9761	718,2

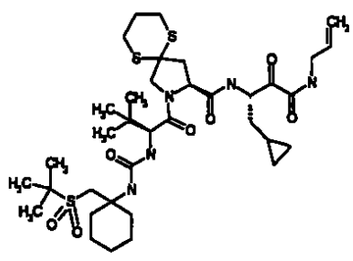
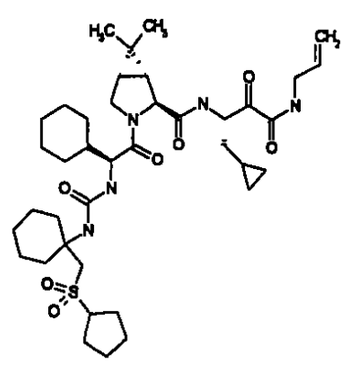
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727		717,9761	718,2
728		772,1089	

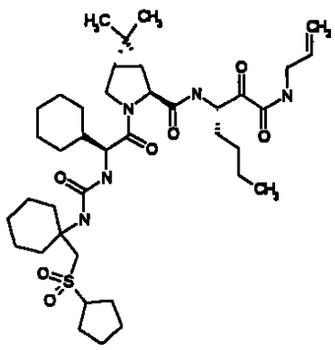
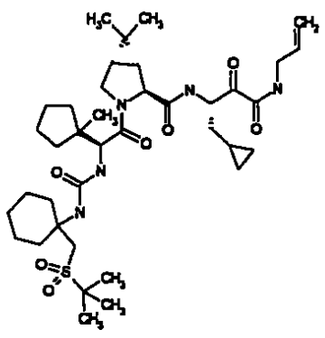
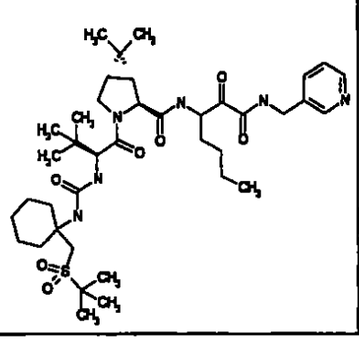
1214

729		703,949	704,2
730		719,992	
731		719,992	

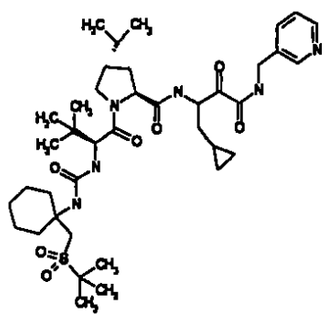
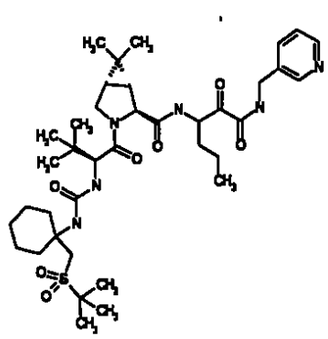
1215

732		770,0929	770,2
733		744,0143	744,3

1216

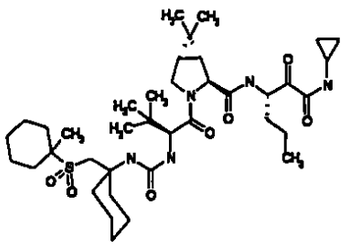
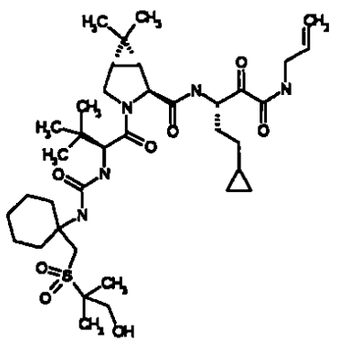
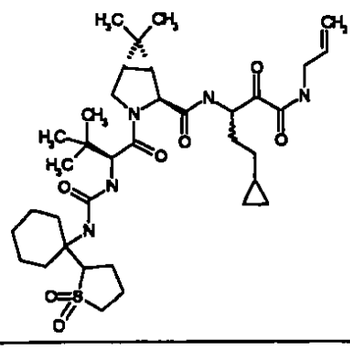
734		746,0303	746,2
735		732,0032	732,4
736		759,029	759,4

1217

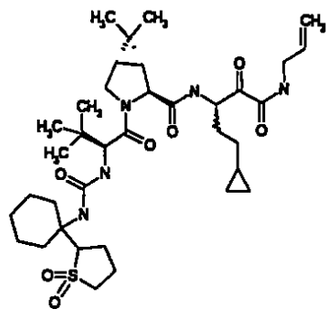
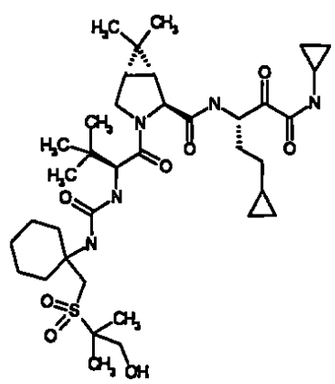
737		757,0131	757,4
738		745,0019	745,4

1218

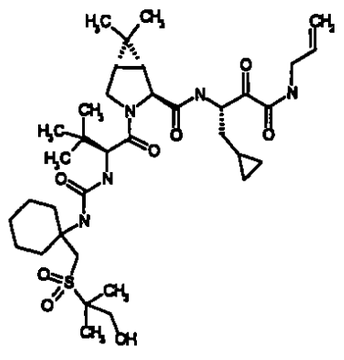
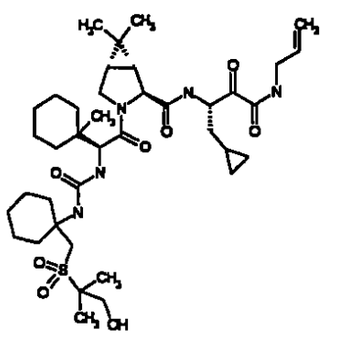
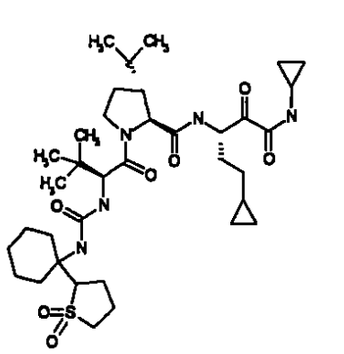
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739		734,0191	734,3
740		735,9914	
741		703,949	704,2

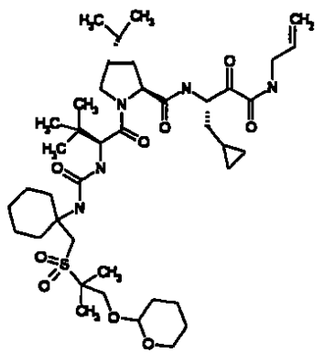
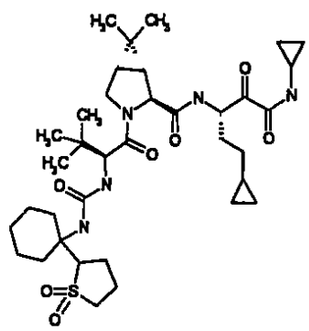
1219

742		703,949	704,2
743		735,9914	

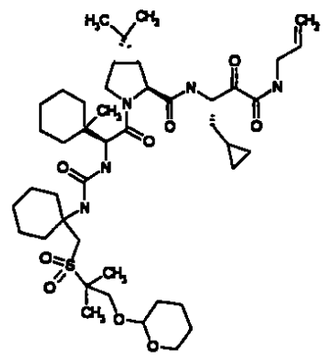
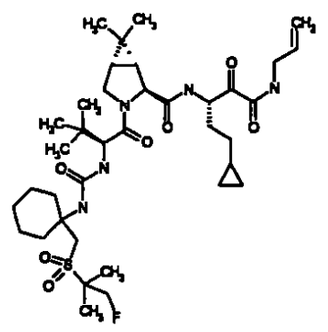
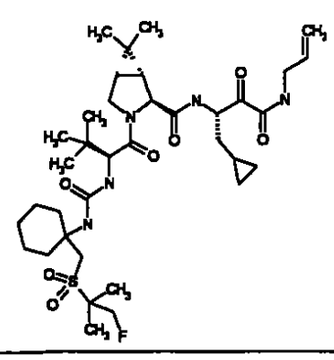
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744		721,9643	
745		762,0297	
746		703,949	704,2

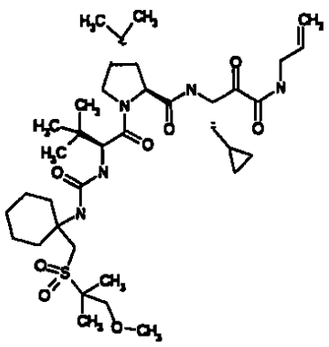
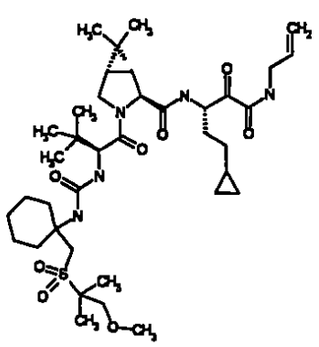
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747		806,0832	
748		703,949	704,2

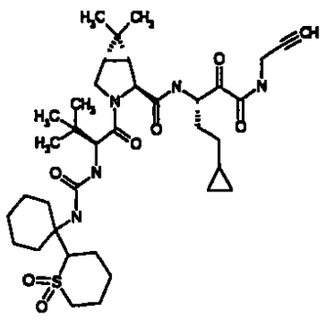
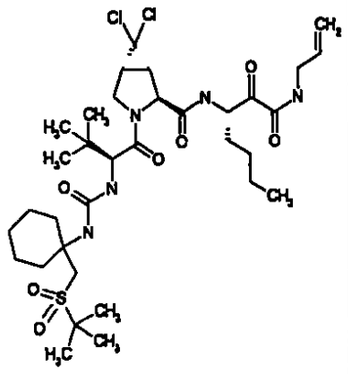
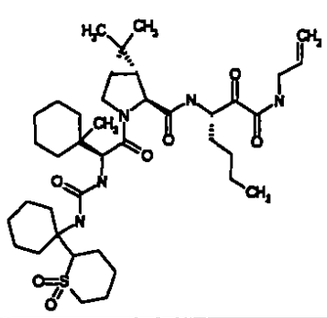
1222 · 1294 ·

749		846,1486	
750		737,9825	
751		723,9554	

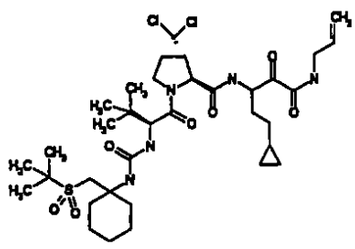
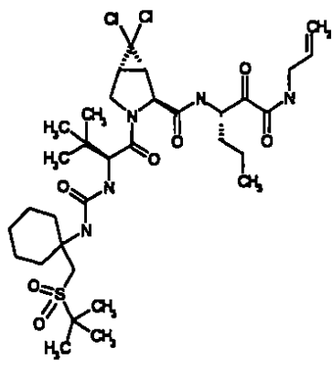
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752		735,9914	
753		750.0185	

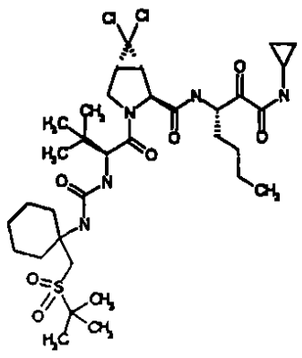
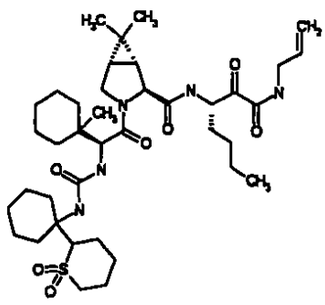
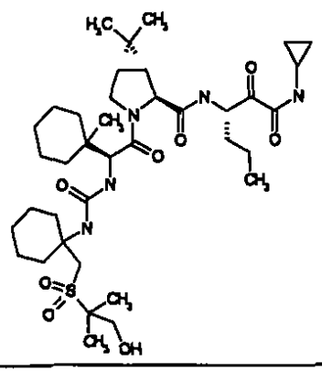
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754		715,9601	716,1
755		748,8168	748,1
756		746,0303	746,1

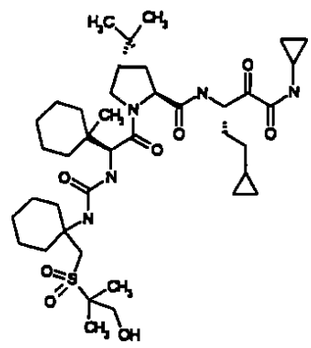
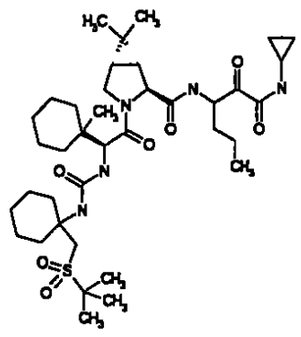
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757		760,8279	760,1
758		734,7897	734,1

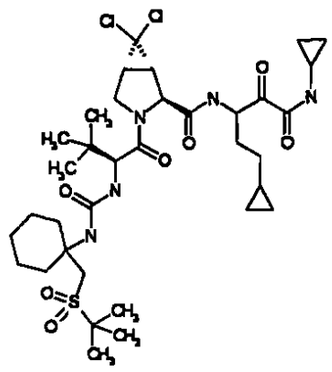
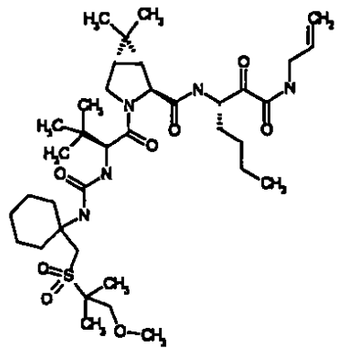
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759		748,8168	748,1
760		746,0303	
761		750 0185	

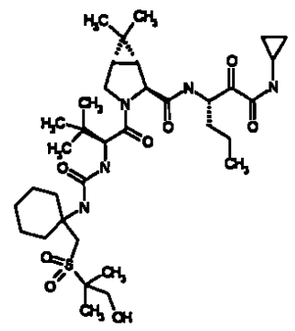
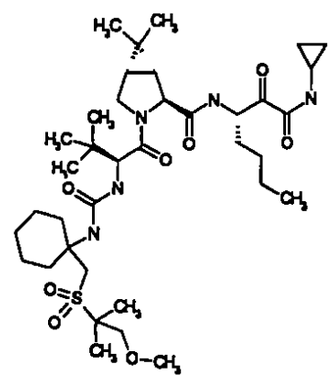
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762		776,0568	
763		734,0191	

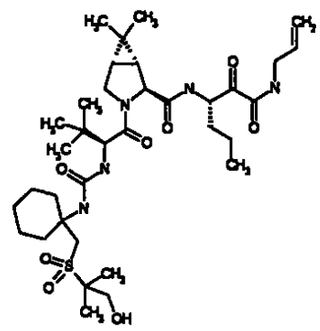
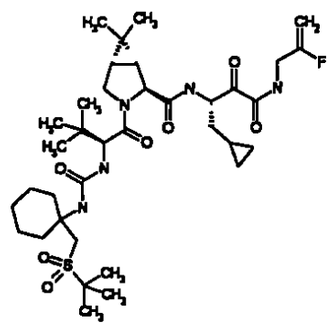
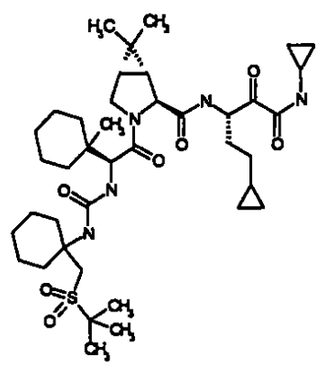
1228

764		760,8279	760,1
765		738,0074	

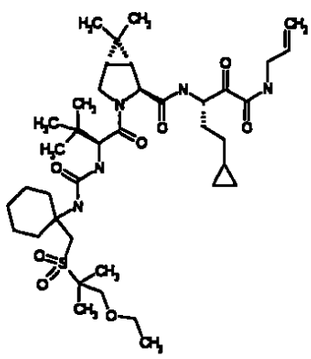
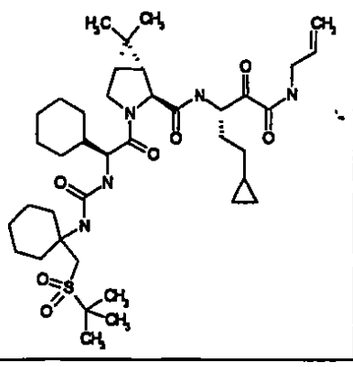
1229

766		709,9532	
767		738,0074	

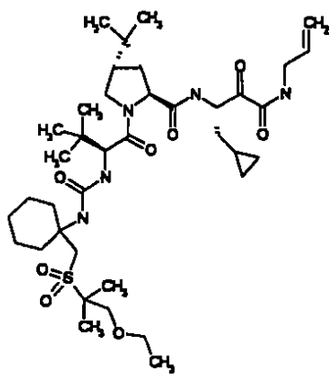
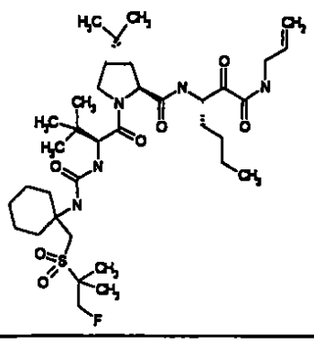
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768		709,9532	
769		723,9554	
770		760,0574	

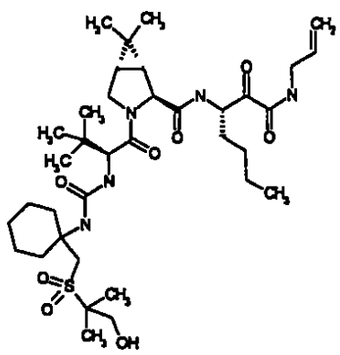
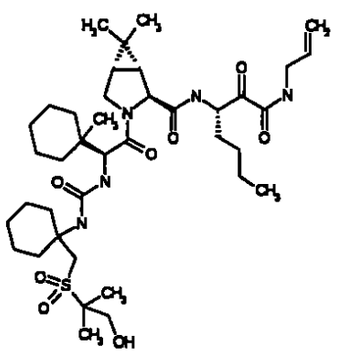
1231

771		764,0456	
772		746,0303	

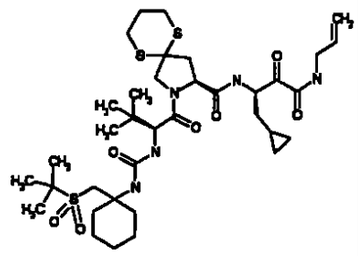
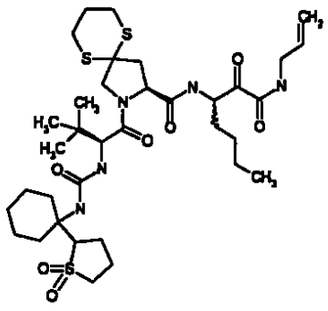
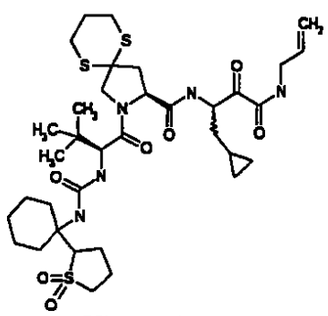
1232 1249

773		750 0185	
774		725,9713	

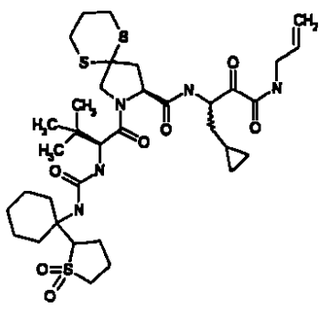
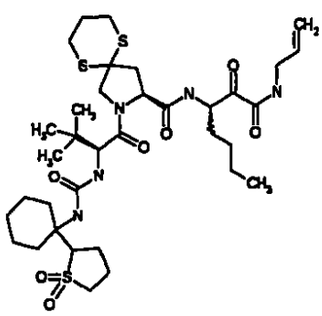
1233

775		723,9803	
776		764,0456	

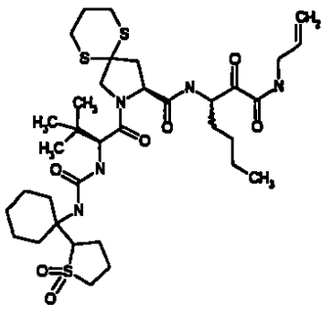
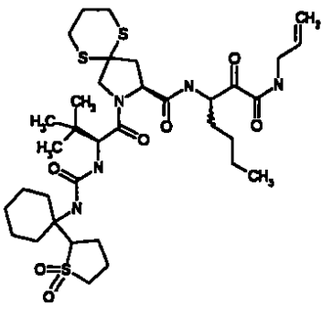
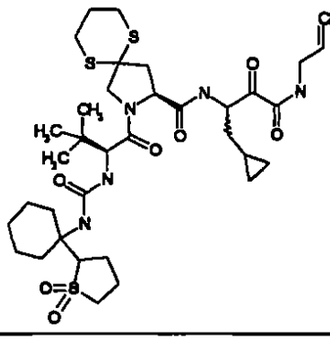
1234

777		770,0929	770,2
778		756,0658	756,1
779		754,0499	754,1

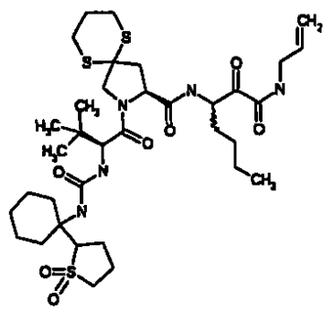
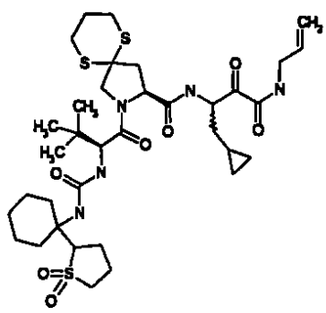
1235 1252

780		754,0499	754,1
781		756,0658	756,1

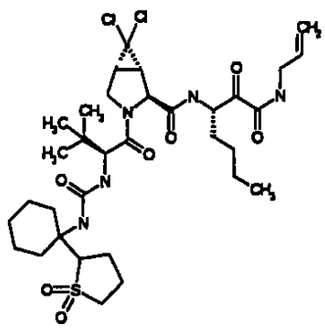
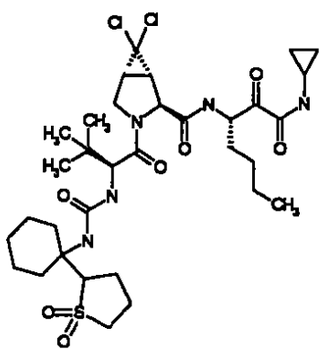
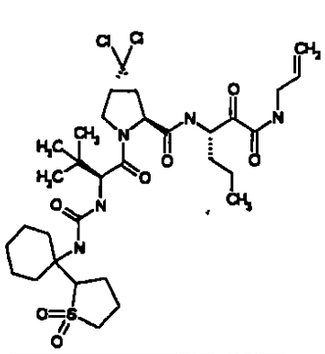
1236

782		756,0658	756,1
783		756,0658	756,1
784		754,0499	754,1

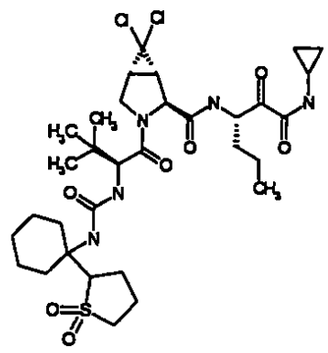
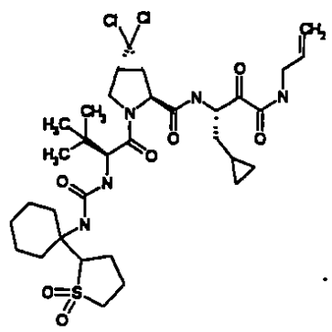
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785		756,0658	756,1
786		754,0499	754,1

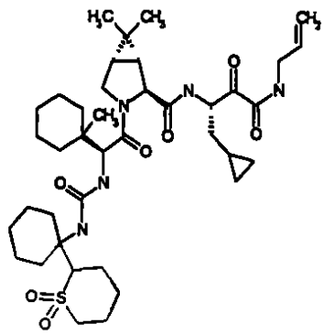
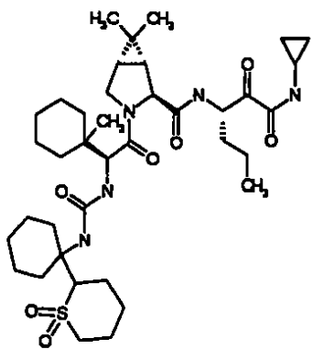
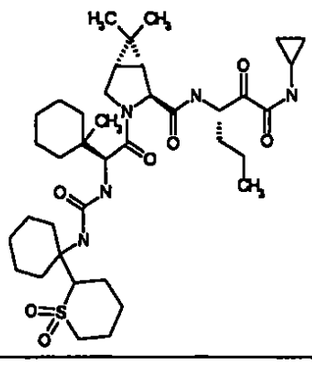
1238

787		732,7737	732,1
788		732,7737	732,1
789		718,7466	718,2

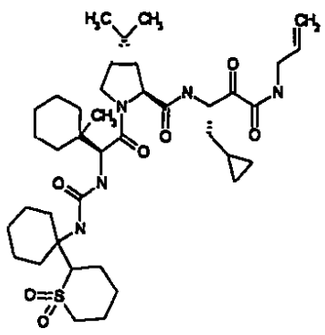
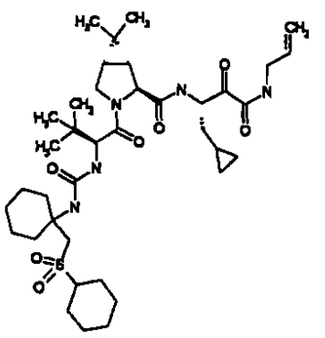
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790		718,7466	718,2
791		730,7578	730,2

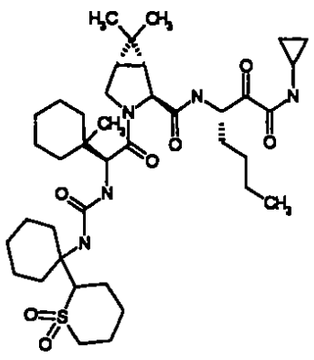
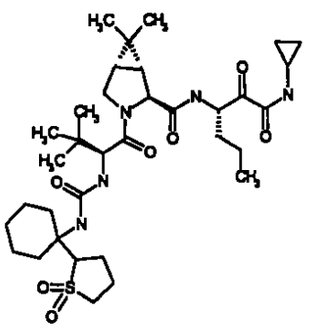
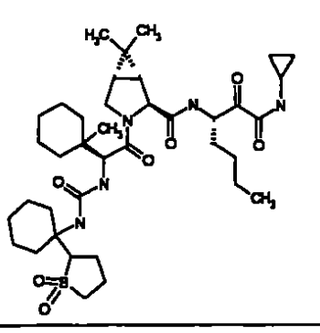
1240 1257

792		744,0143	
793		732,0032	732,1
794		732,0032	

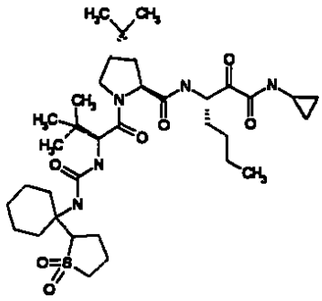
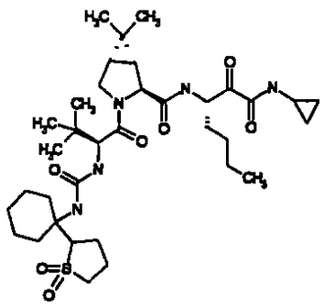
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795		744,0143	
796		732,0032	732,1

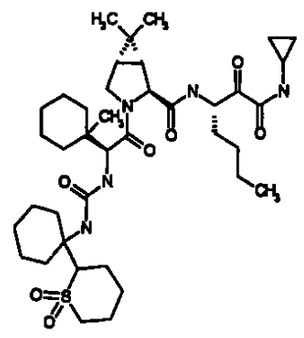
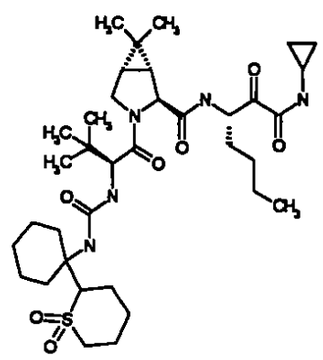
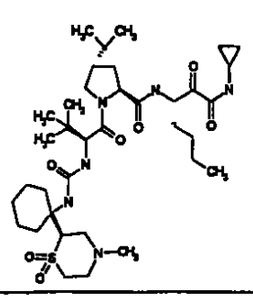
1242 +254

797		746,0303	
798		677,9108	678,1
799		732,0032	732,2

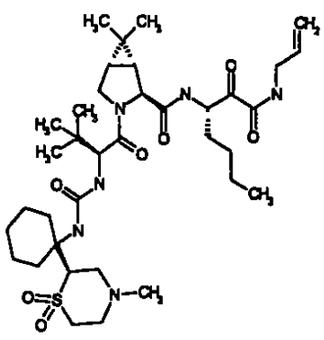
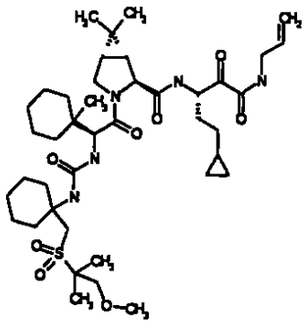
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800		691,9378	692,2
801		692	692,2

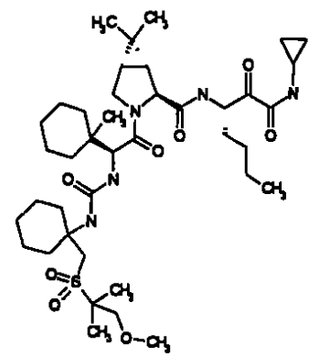
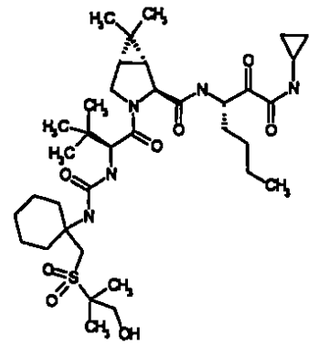
1244 1264

802		746,0303	
803		705,9649	
804		720,9796	

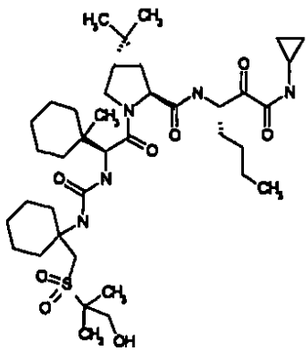
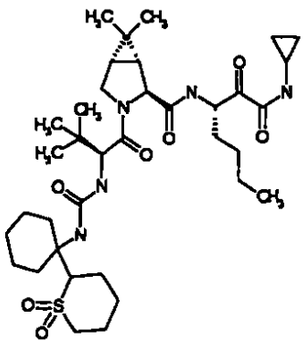
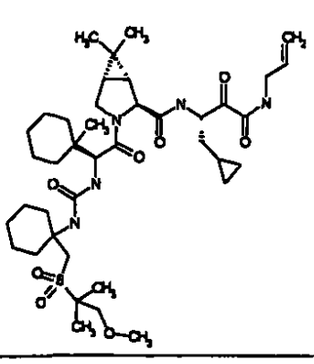
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805		720,9796	
806		790,0838	

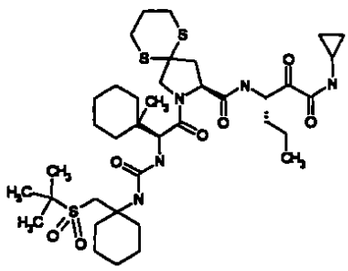
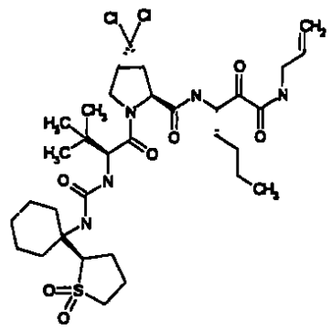
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807		778,0727	
808		723,9803	

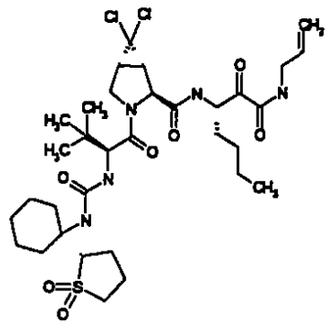
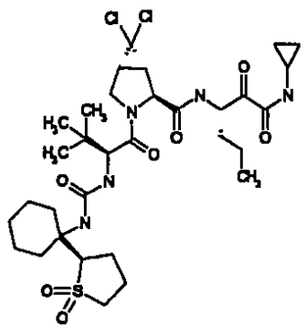
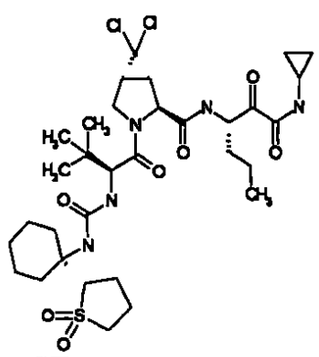
1247 1269

809		764,0456	
810		705,9649	706,4
811		776,0568	

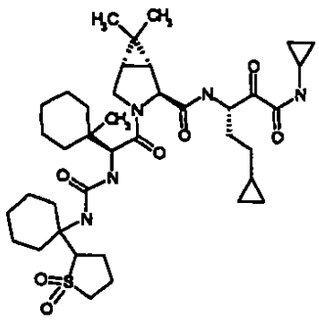
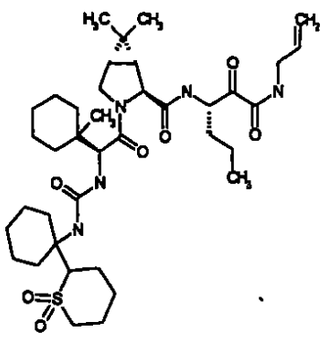
1248

812		798,1471	798,4
813		732,7737	732,1

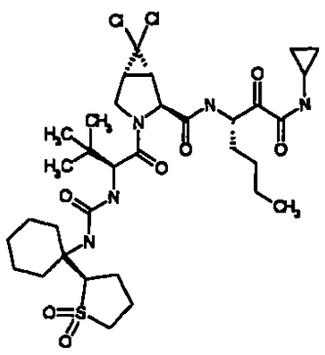
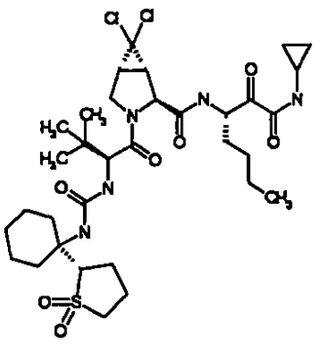
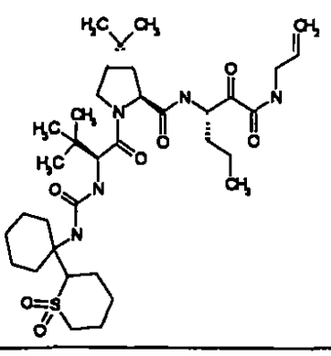
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814		732,7737	732,1
815		718,7466	718,1
816		718,7466	718,1

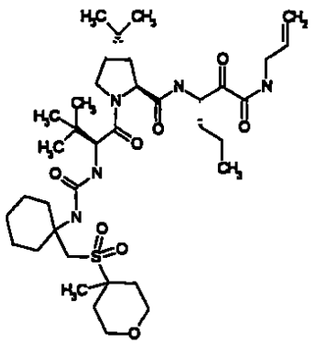
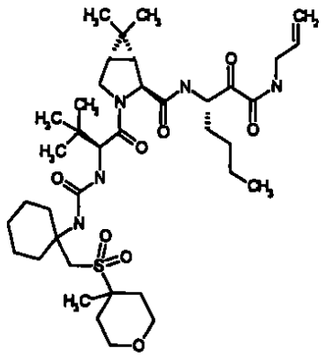
1250 - 1267

817		744,0143	744,1
818		732,0032	732,1

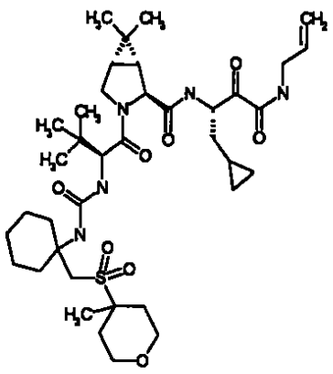
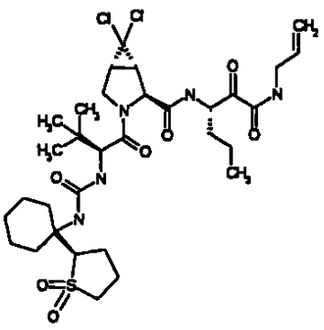
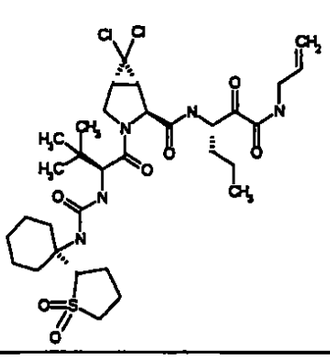
1251 1288

819		732,7737	732,1
820		732,7737	732,1
821		691,9378	692,1

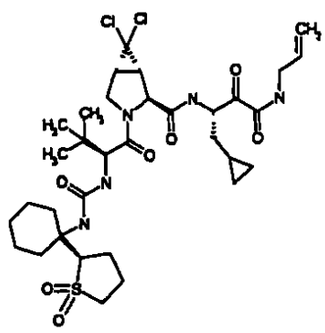
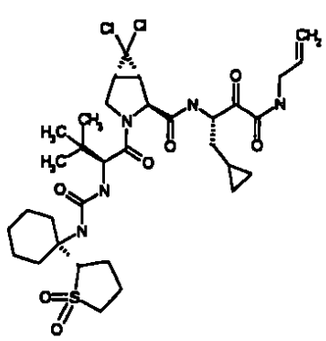
1252

822		735,9914	736,1
823		750 0185	750,1

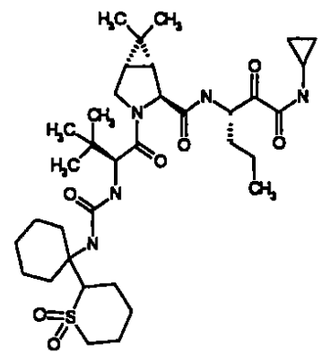
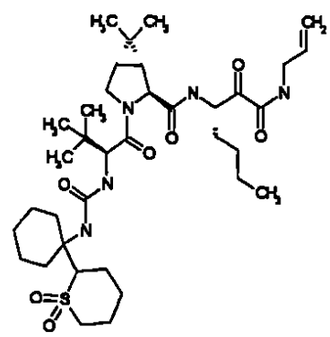
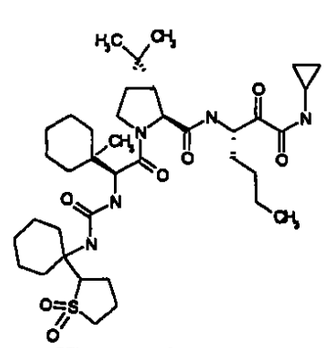
1253 1270

824		748,0026	748,1
825		718,7466	718,2
826		718,7466	718,2

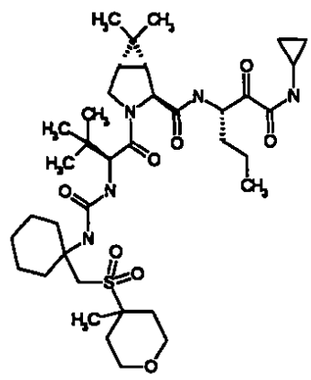
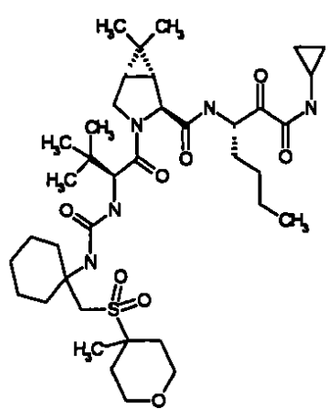
1254 1274

827		730,7578	730,2
828		730,7578	730,2

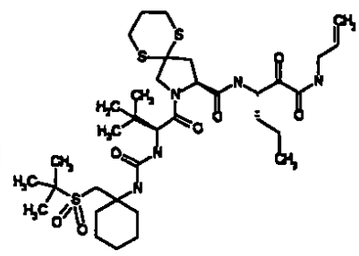
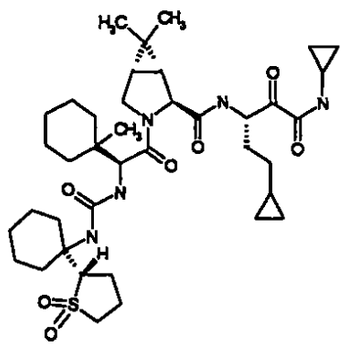
1255 : 1222

829		691,9378	
830		705,9649	706,1
831		732,0032	732,2

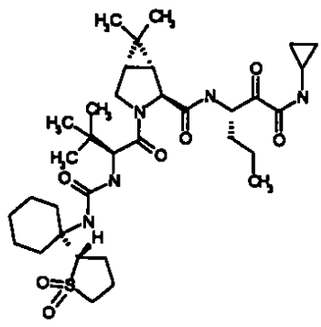
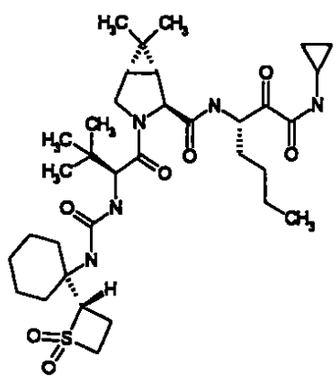
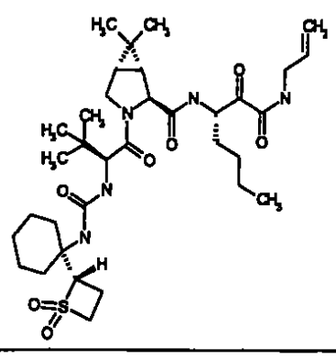
1256 F273

832		735,9914	736,1
833		750.0185	750,1

1257

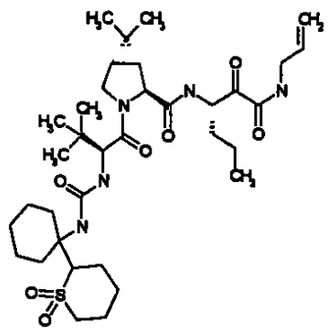
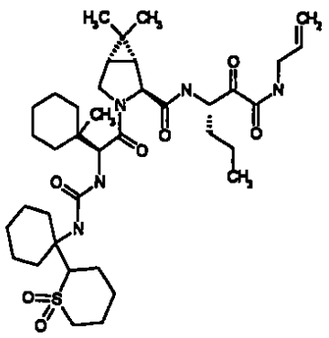
834		758,0818	758,2
835		744,0143	744,1

1258

836		677,9108	
837		677,9108	678,3
838		677,9108	678,3

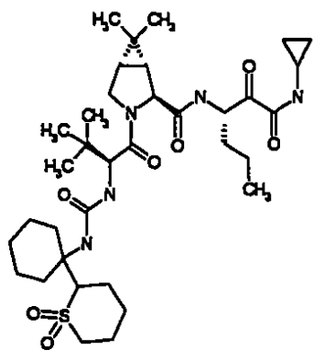
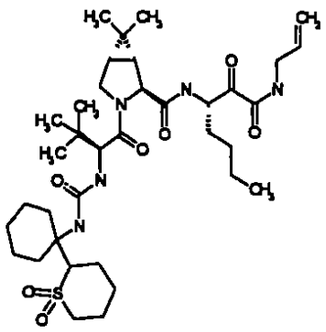
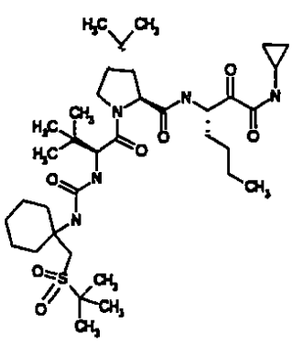
1276

1259

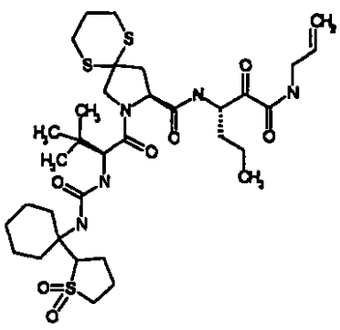
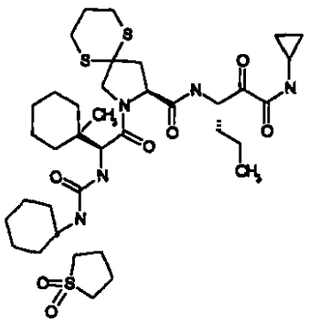
839		691,9378	
840		732,0032	

1260

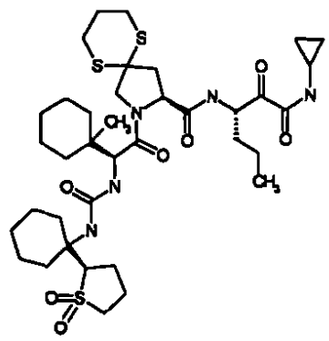
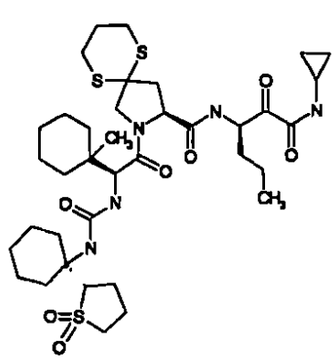
4227

841		691,9378	
842		705,9649	
843		707,9809	708,4

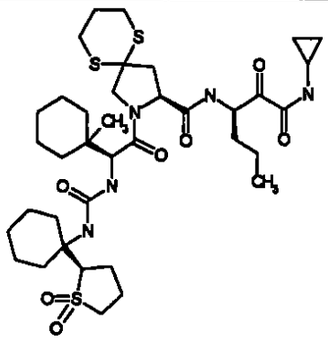
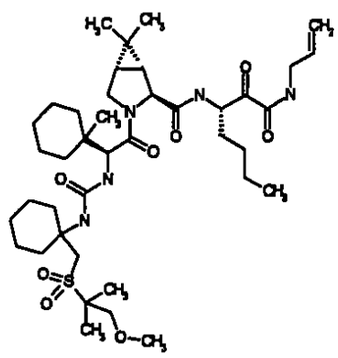
1261

845		742,0388	742,4
846		782,1041	782,4

1262 1279

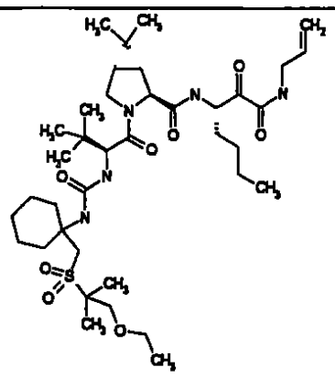
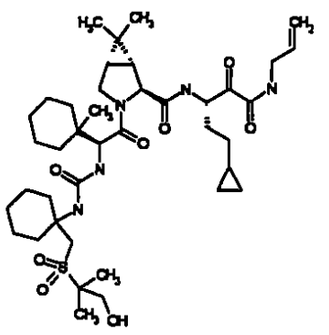
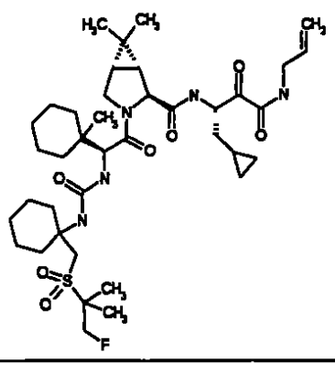
847		782,1041	782,4
848		782,1041	782,4
849		782,1041	782,4

1263

			
850		778,0727	
851		752,0345	

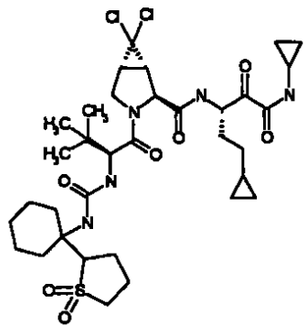
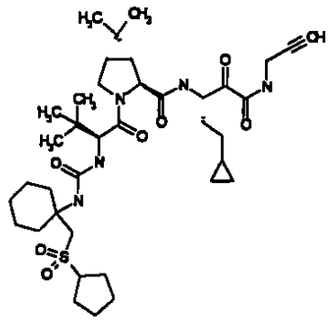
1264

4284

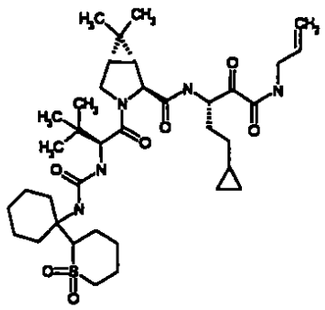
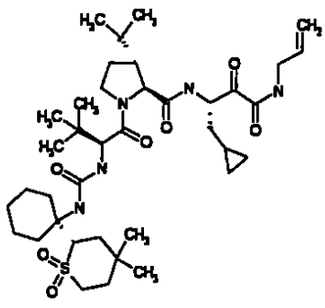
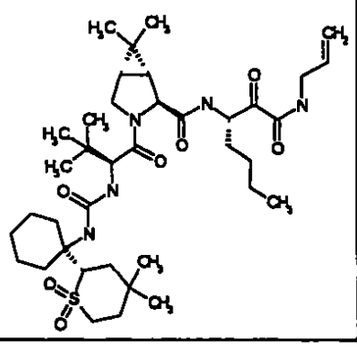
			
852		776,0568	
853		764,0207	

1265

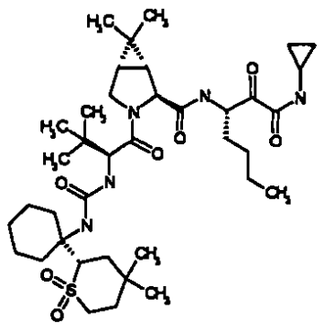
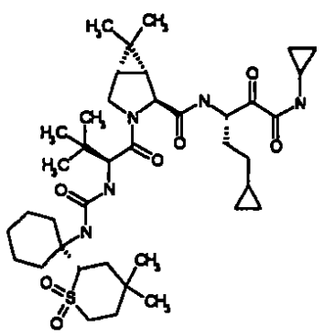
1282

854		744,7849	744,4
855		729,9872	730,2

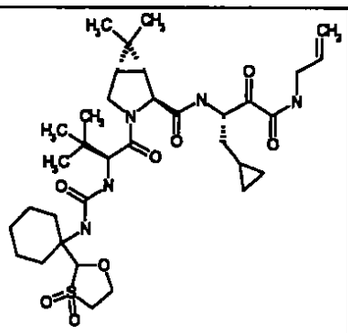
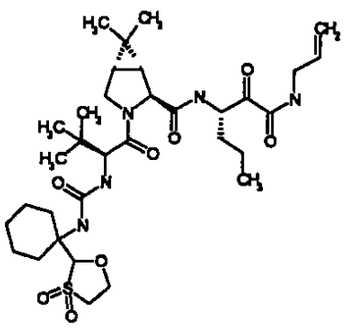
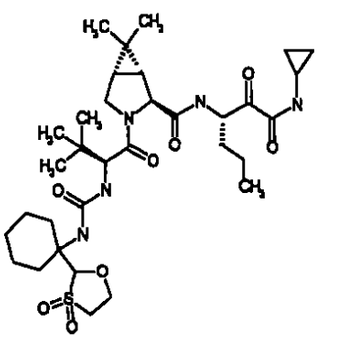
1266 1283

856		717,9761		5
857		732,0032	732,4	A
858		734,0191	734,4	A

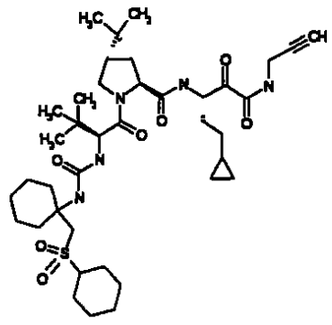
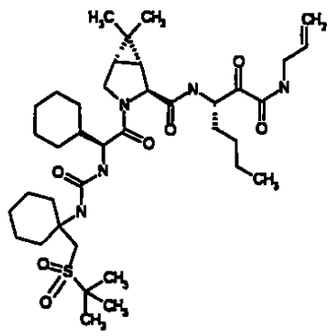
1267

859		734,0191	734,41	A
860		746,0303	746,5	A

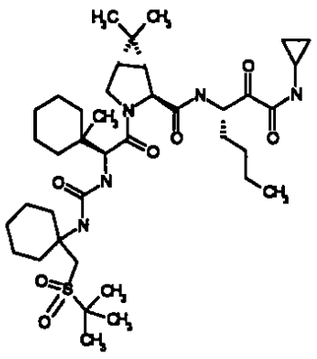
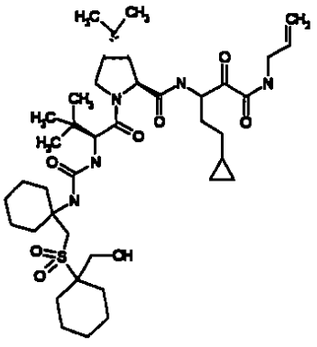
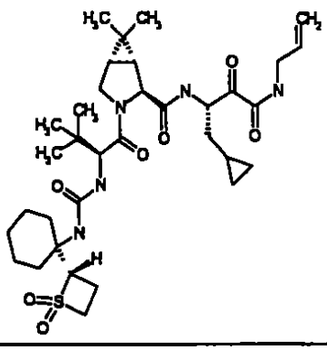
1268

861		691,8942	692,4	A
862		679,8831	680,38	A
863		679,8831	680,4	A

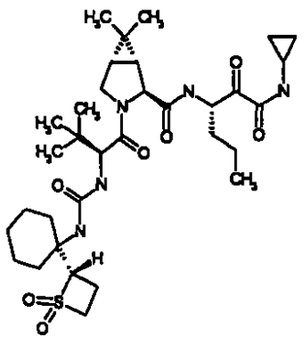
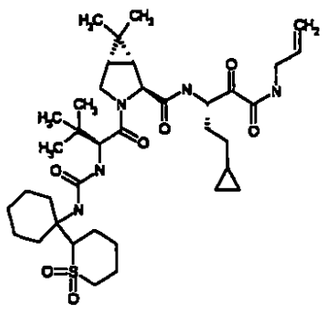
1269 1280

864		744,0143	744,1	A
865		734,0191	734,4	A

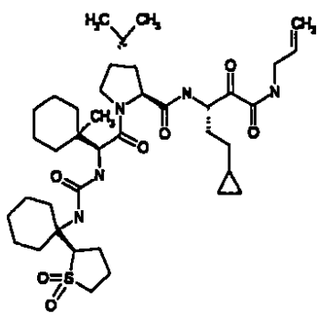
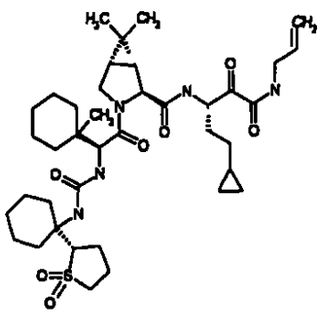
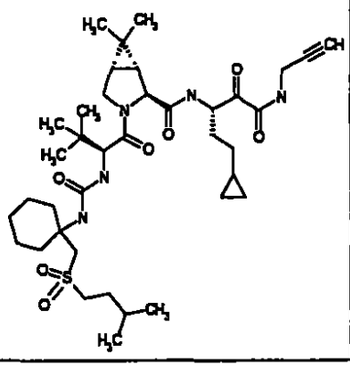
1270

866		748,0462	748,4	A
867		776,0568		A
868		675,8948		A

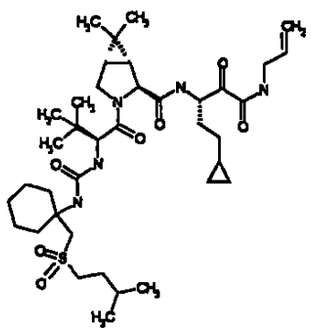
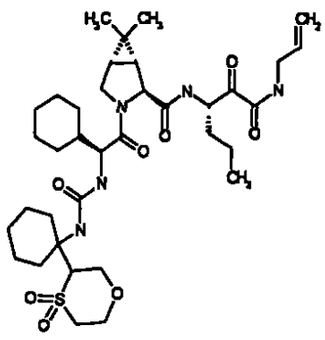
1271

869		663,8837		A
870		717,9761		A

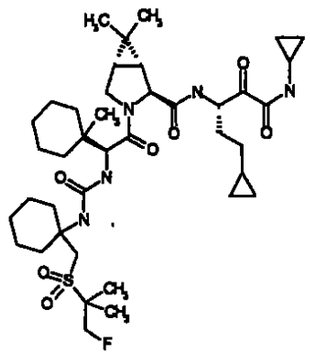
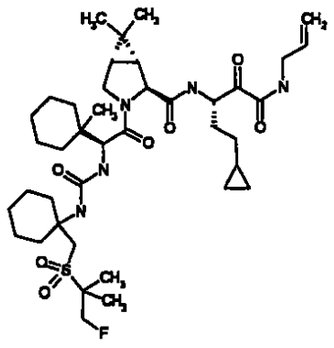
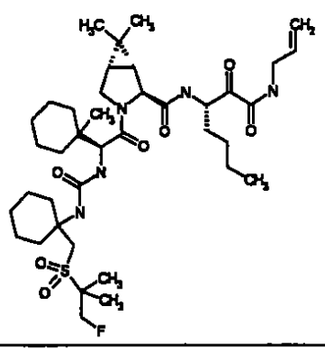
1272

871		744,0143		A
872		744,0143		A
873		732,0032	732,1	A

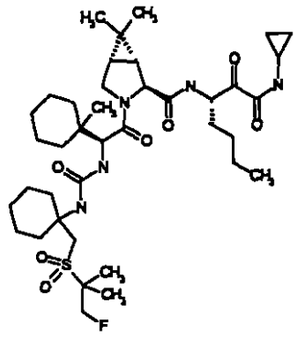
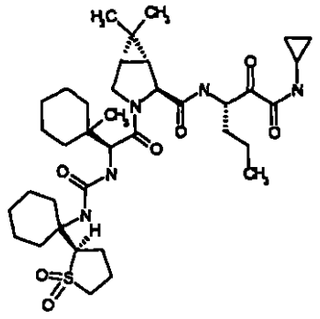
1273

874		734,0191	734,1	A
875		719,9484		A

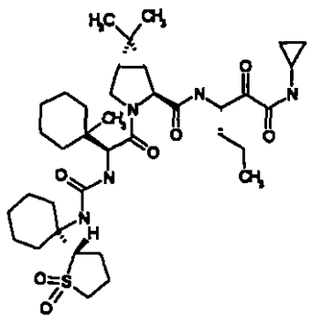
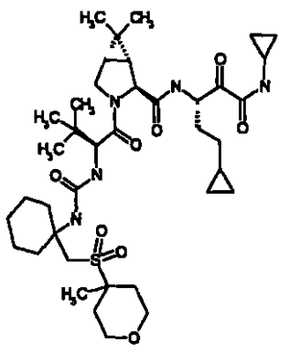
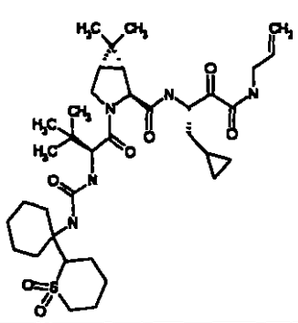
1274 1274

876		778,0478		A
877		778,0478		A
878		766,0366		A

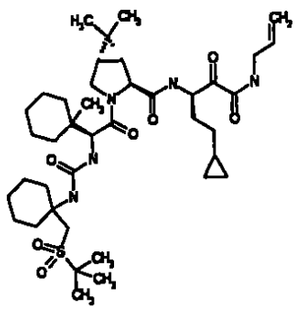
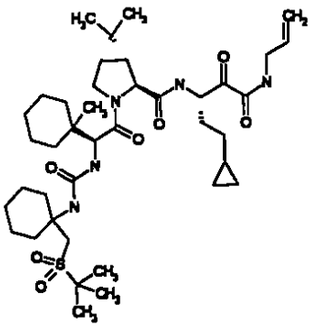
1275 1292

879		766,0366		A
880		717,9761	718,1	A

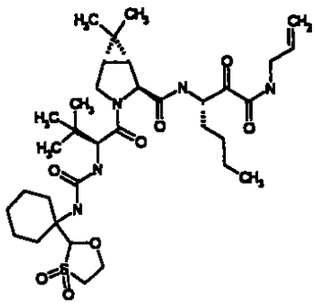
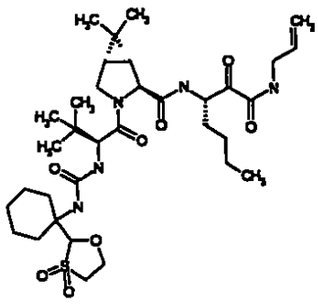
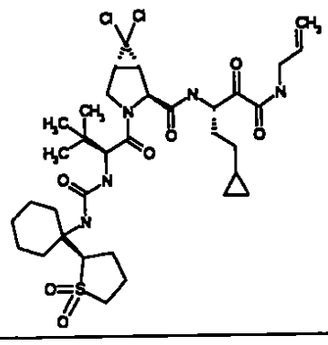
1276

881		717,9761	718,1	A
882		762,0297	762,1	A
883		703,949	704,1	A

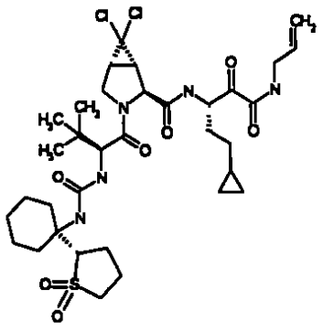
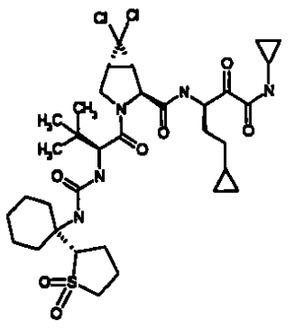
1277 F294

883-a			760,0574		B
883-b			760,0574		A

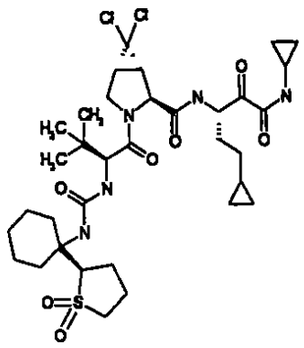
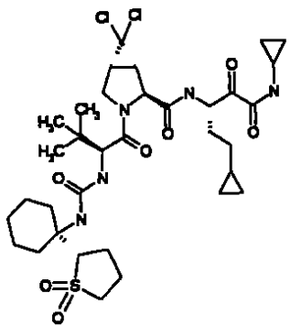
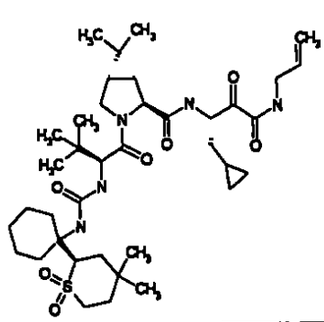
1278 1285

883-c		693,9102		3
883-d		693,9102		A
883-e		744,7849		A

1279

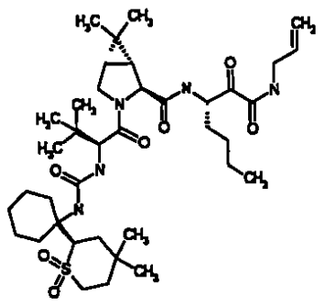
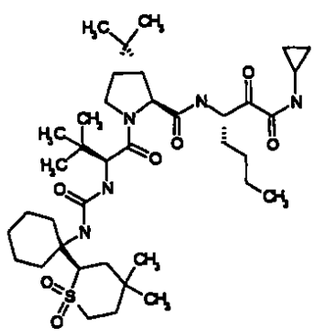
883-f		744,7849		A
883-fa		744,7849		A

1280 1284

883-g		744,7849		A
883-h		744,7849		A
883-i		732,0032		A

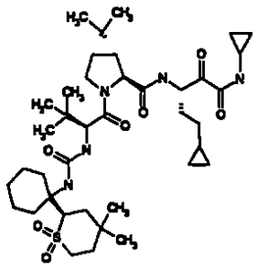
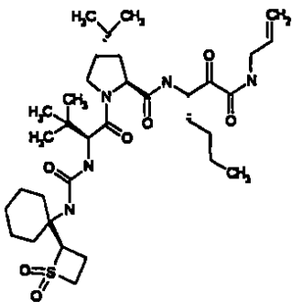
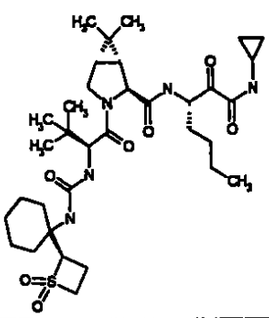
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1281

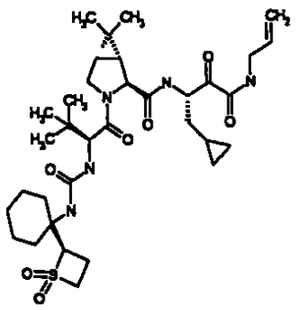
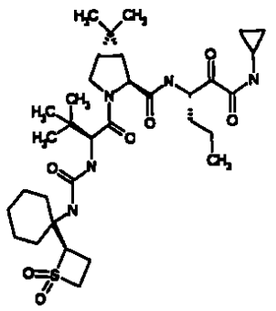
883-j		734,0191		A
883-k		734,0191		A

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1282

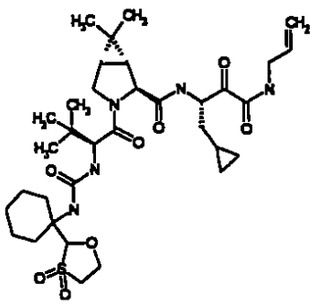
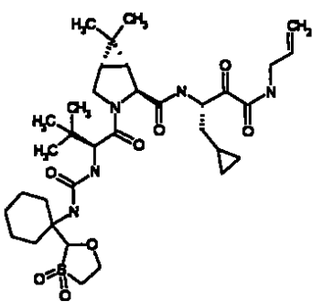
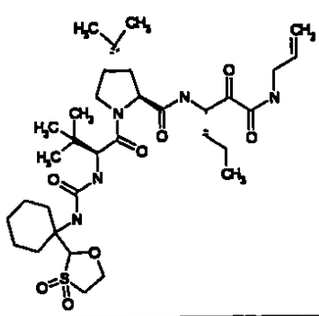
883-l		746,0303		A
883-m		677,9108		A
883-n		677,9108		A

1283

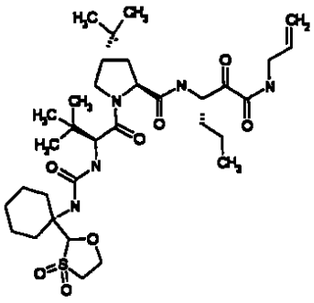
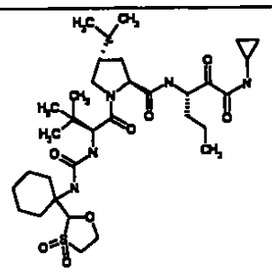
883-o		675,8948		A
883-p		663,8837		A

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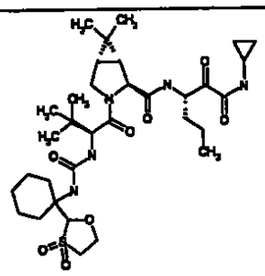
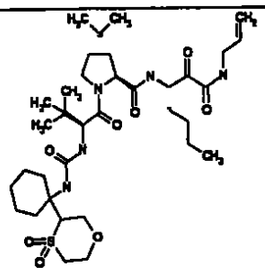
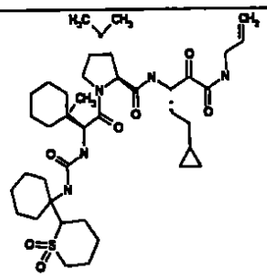
1284

883-q		691,8942		A
883-r		691,8942		A
883-s		679,8831		A

1285

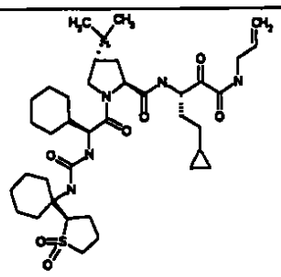
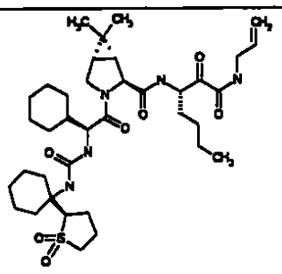
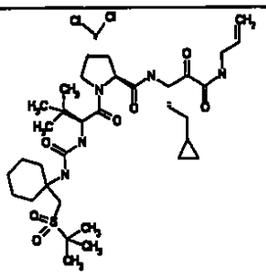
883-t		679,8831		A
883-u		679,8831		A

1286

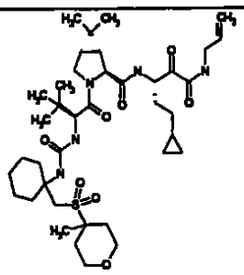
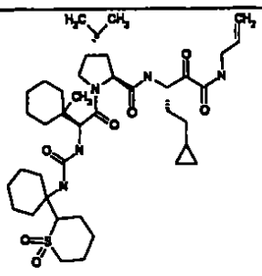
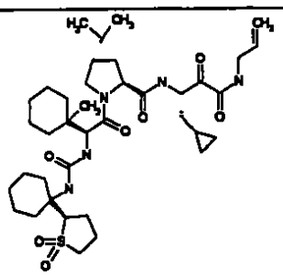
883-v		679,8831		A
883-w		707,9372		3
883-x		758,0414		A

~~1304~~

1287

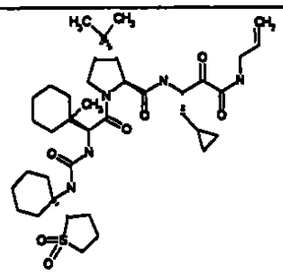
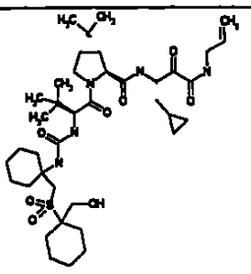
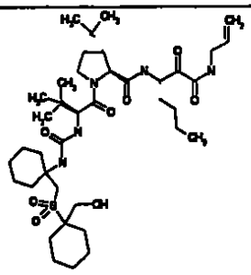
883-y		729,9872		A
883-z		717,9761		A
883-aa		760,8279		A

1288

883-ab		762,0297		A
883-ac		758,0414		A
883-ad		729,9872		A

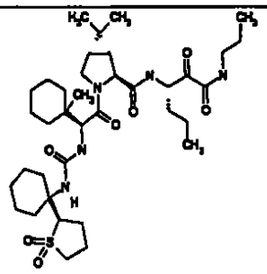
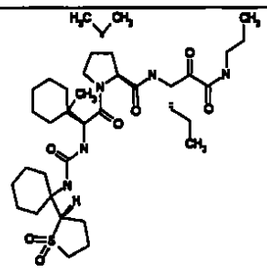
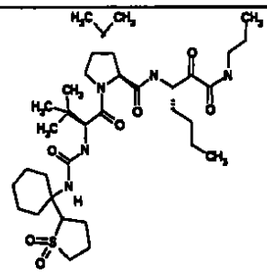
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1289

883-ae		729,9872		A
883-af		762,0297		A
883-ag		764,0456		A

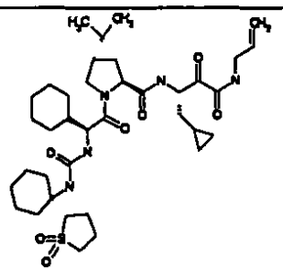
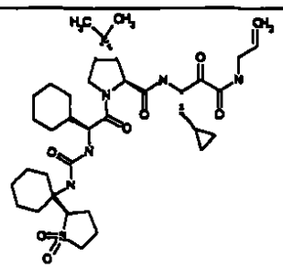
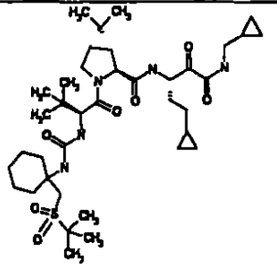
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1290

883-ah		719,992		A
883-ai		719,992		A
883-aj		693,9538		A

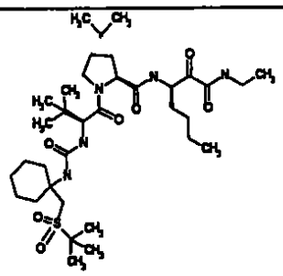
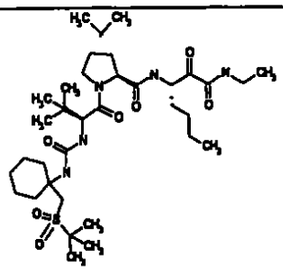
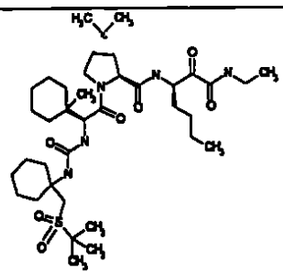
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1291

883-ak		715,9601		A
883-al		715,9601		A
883-am		734,0191		A

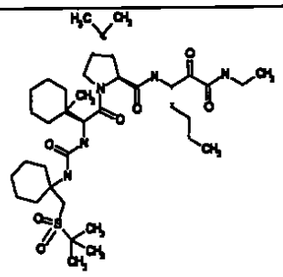
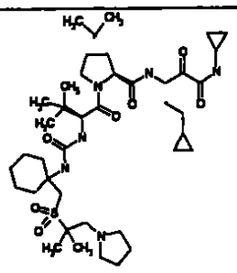
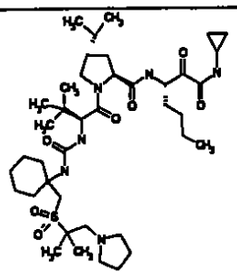
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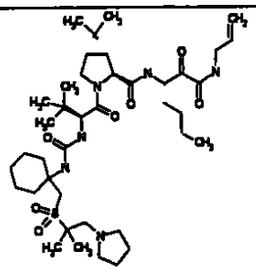
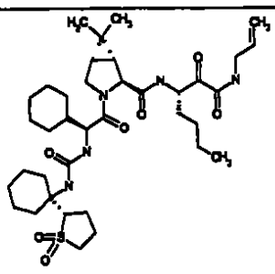
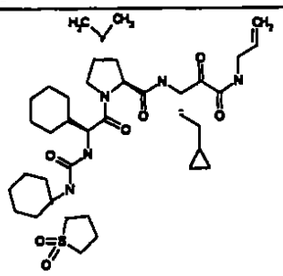
883-an		695,9697		C
883-ao		695,9697		A
883-ap		736,0351		B

~~1310~~

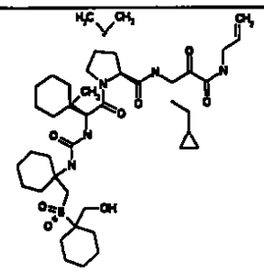
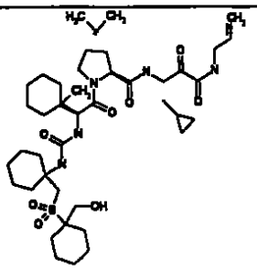
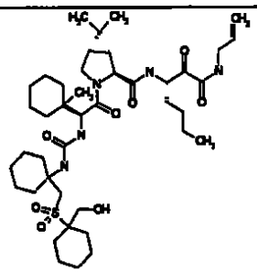
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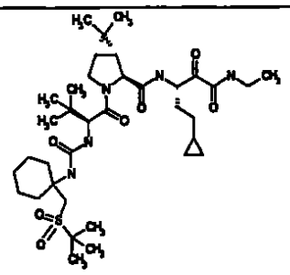
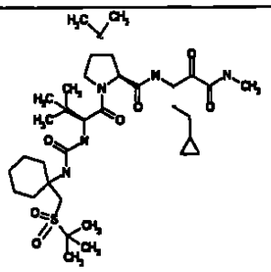
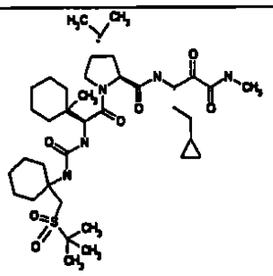
883-aq		736,0351		A
883-ar		789,0991		A
883-as		777,088		A

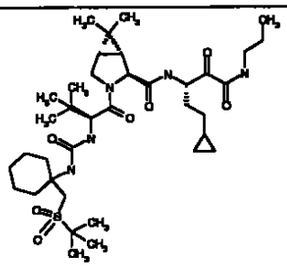
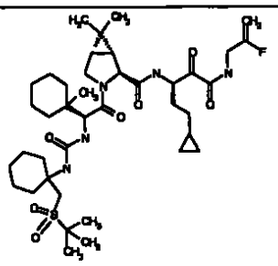
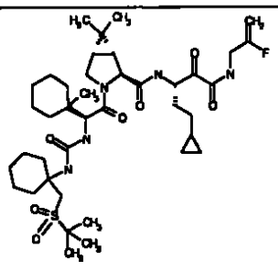
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883-at		777,088		A
883-au		717,9761		A
883-av		729,9872		A

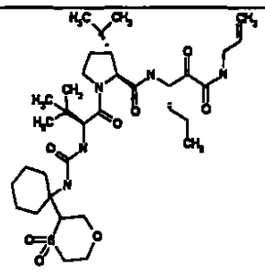
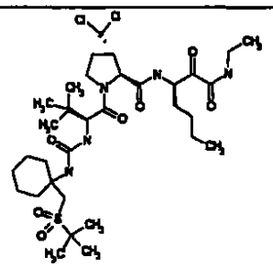
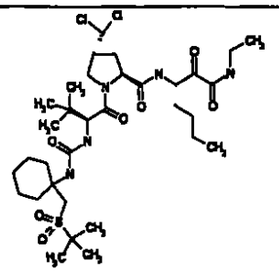
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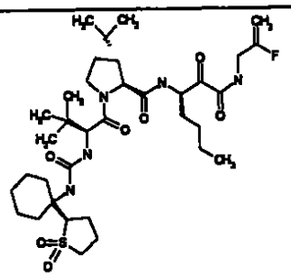
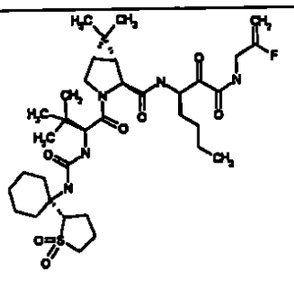
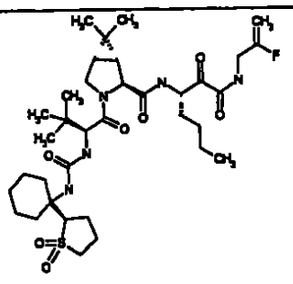
883-aw		816,1221		A
883-ax		802,095		A
883-ay		804,1109		A

883-az		707,9809		A
883-ba		693,9538		A
883-bb		734,0191		A

883-bc		722 008		A
883-bd		778,0478		b
883-be		778,0478		A

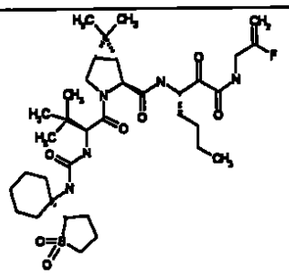
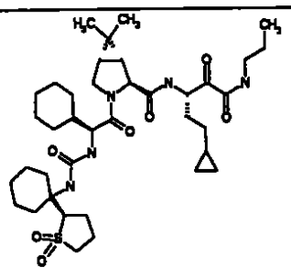
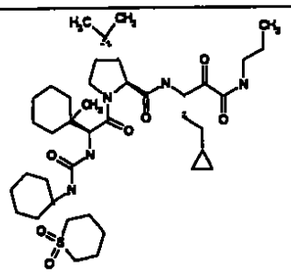
1298

883-bf		693,9102		A
883-bg		736,8056		B
883-bh		736,8056		A

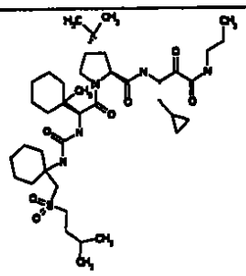
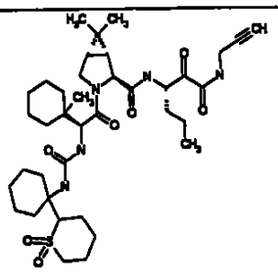
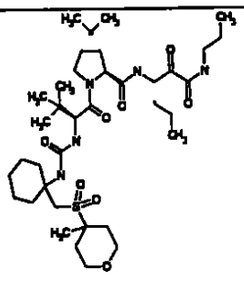
883-bi		709,9283		B
883-bj		709,9283		B
883-bk		709,9283		A

1317

1300

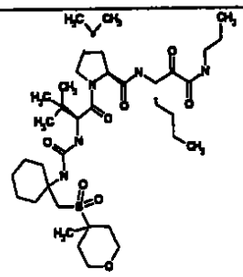
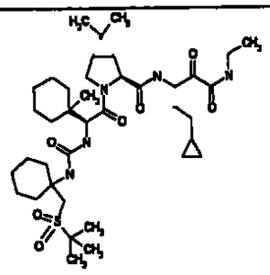
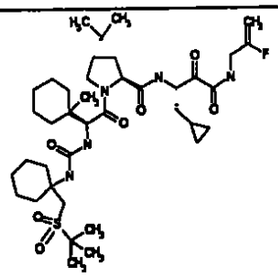
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883-bm		732,0032		A
883-bn		760,0574		A

1301

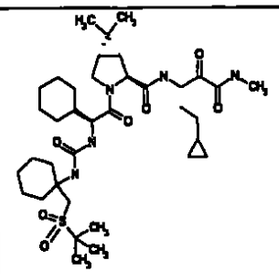
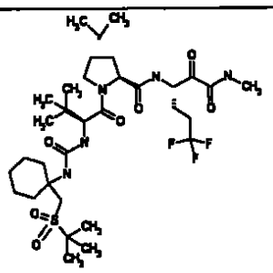
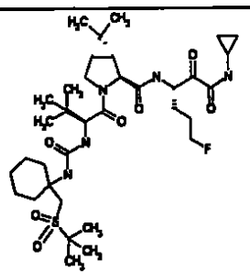
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883-bp		729,9872		A
883-bq		738,0074		A

1319

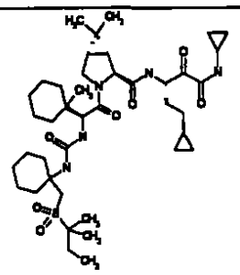
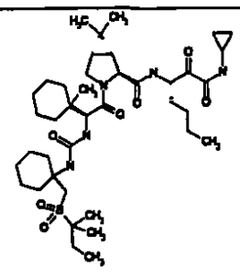
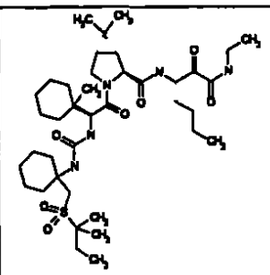
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883-bs		748,0462		A
883-bt		764,0207		A

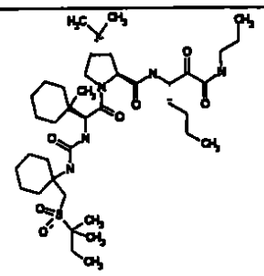
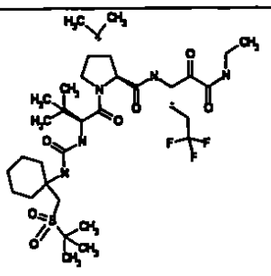
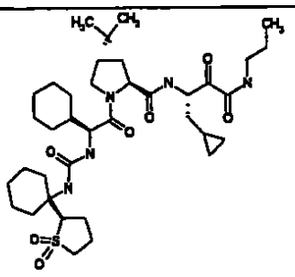
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883-bv		721,8868		A
883-bw		711,9442		A

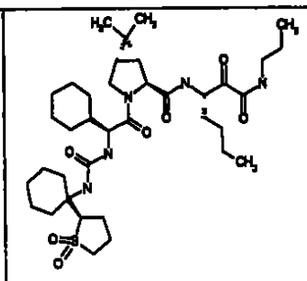
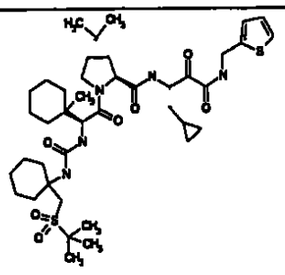
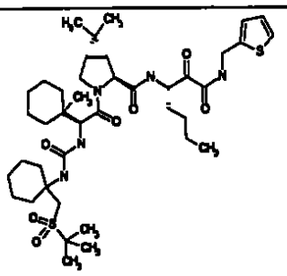
1304

883-bx		774,0844		A
883-by		762,0733		A
883-bz		750.0621		A

1305

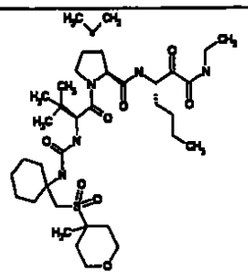
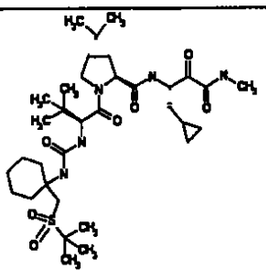
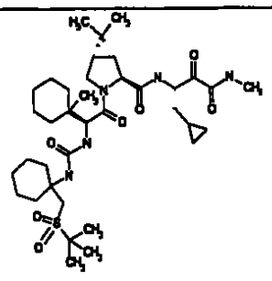
883-ca		764,0892		A
883-cb		735,9139		A
883-cc		717,9761		A

1306

883-cd		719,992		A
883-ce		802,1166		A
883-cf		804,1325		A

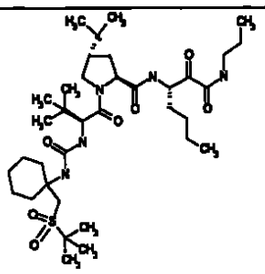
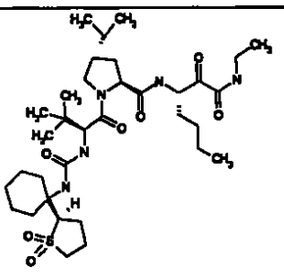
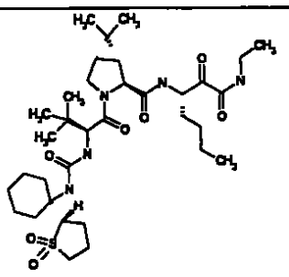
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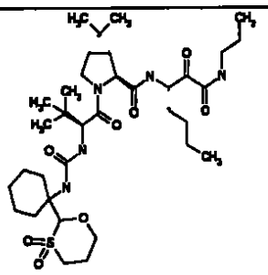
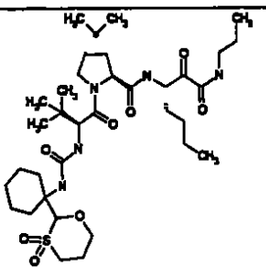
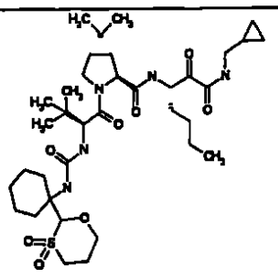
883-cg		738,0074		A
883-ch		679,9267		A
883-ci		719,992		A

1325

1308

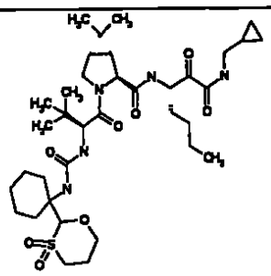
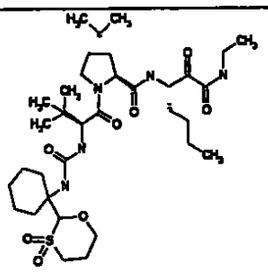
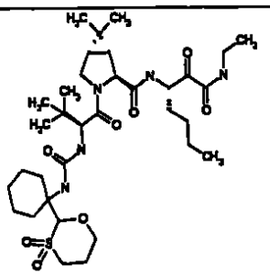
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883-ck		679,9267		A
883-cl		679,9267		A

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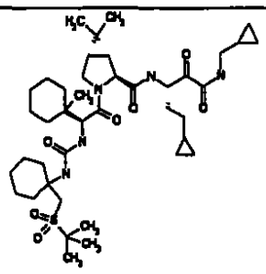
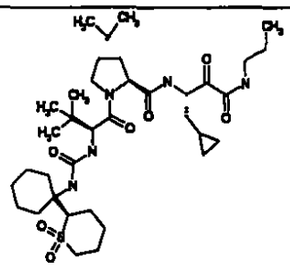
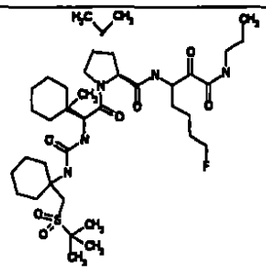
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883-cn		709,9532		A
883-co		721,9643		A

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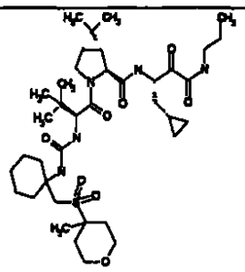
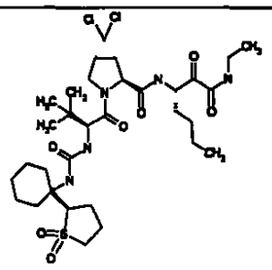
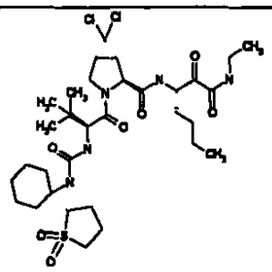
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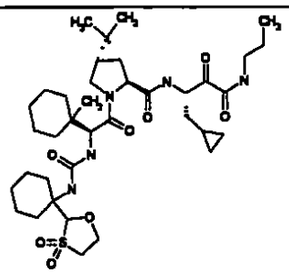
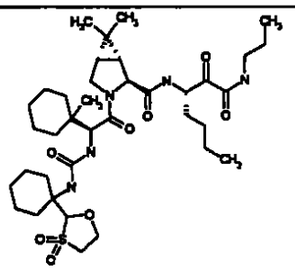
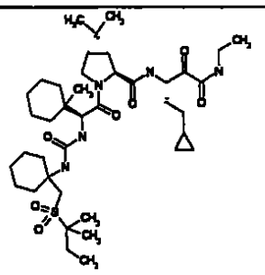
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883-cq		695,9261		A
883-cr		695,9261		B

1311

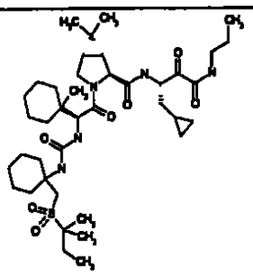
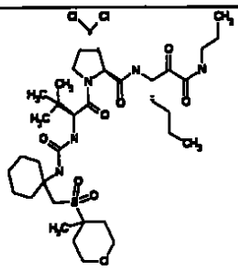
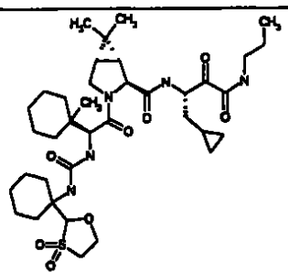
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883-ct		705,9649		A
883-cu		768,0526		A

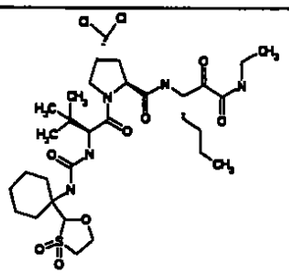
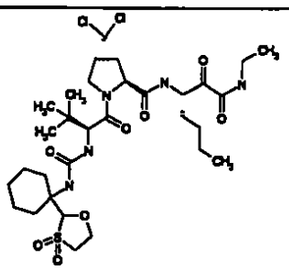
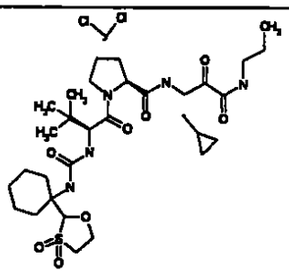
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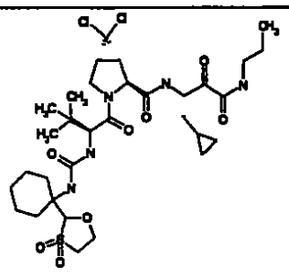
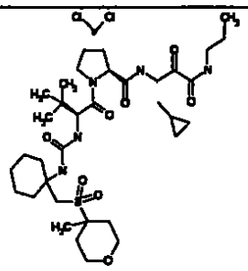
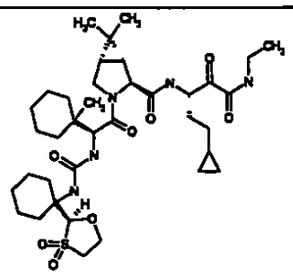
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883-CW		720,7626		A
883-CX		720,7626		A

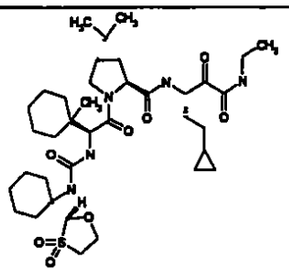
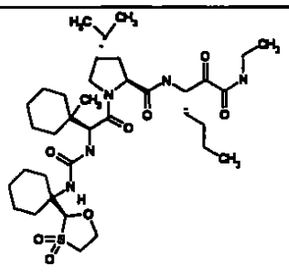
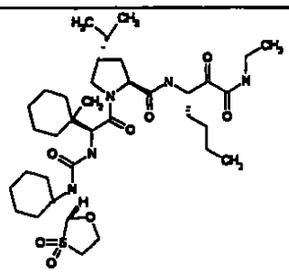
883-cy		733,9755		A
883-cz		735,9914		A
883-da		762,0733		A

1314

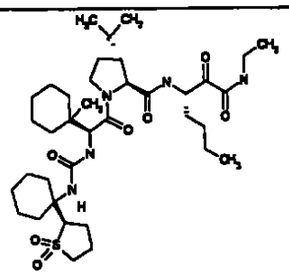
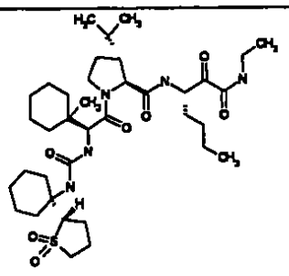
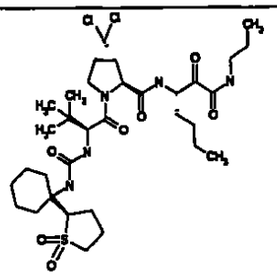
883-db		762,0733		A
883-dc		792,8703		A
883-dd		733,9755		A

883-de		722,7349		A
883-df		722,7349		A
883-dg		734,746		A

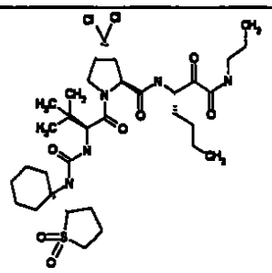
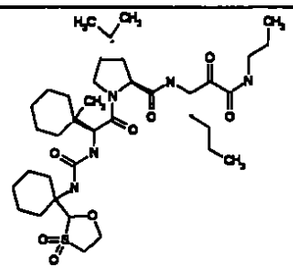
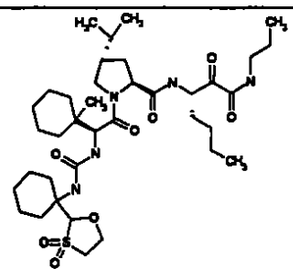
883-dh		734,746		A
883-di		790,8544		A
883-dj		733,9755		A

883-dk		733,9755		A
883-dl		721,9643		A
883-dm		721,9643		A

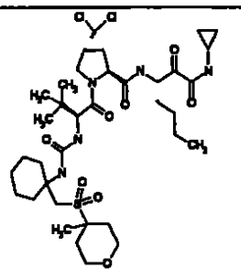
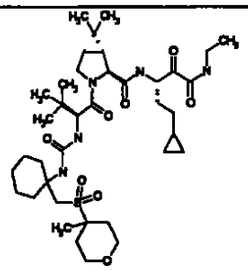
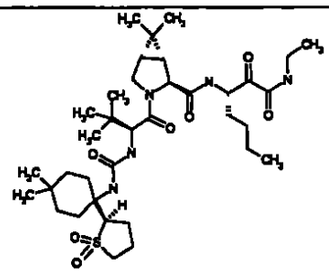
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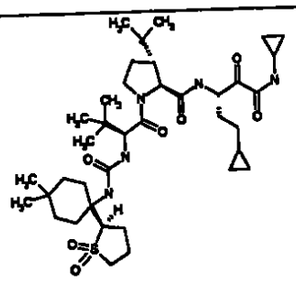
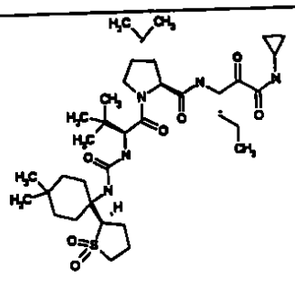
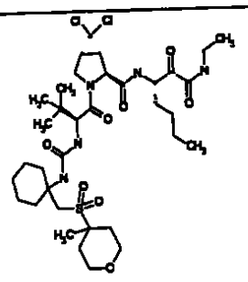
883-dn		719,992		A
883-do		719,992		A
883-dp		734,7897		A

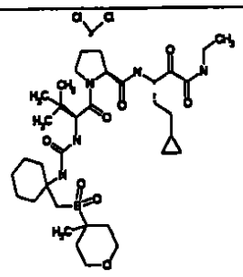
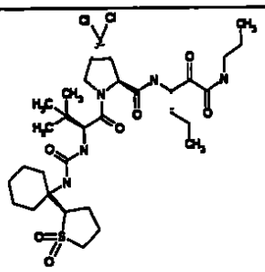
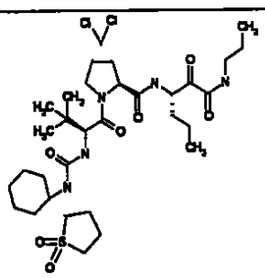
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883-dr		735,9914		A
883-ds		735,9914		A

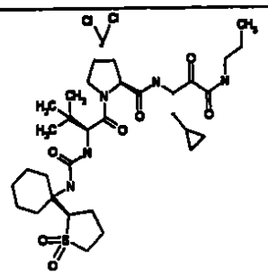
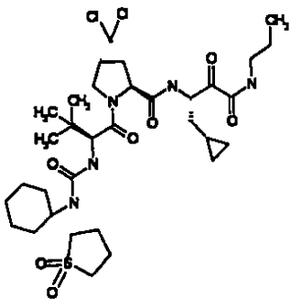
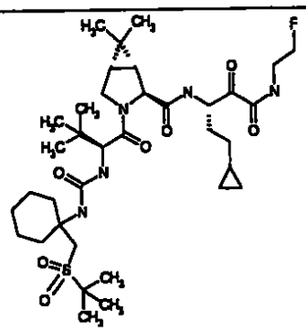
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883-dt		790,8544		A
883-du		750 0185		A
883-dv		707,9809		A

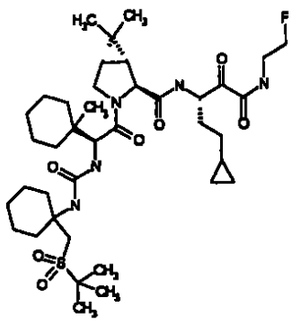
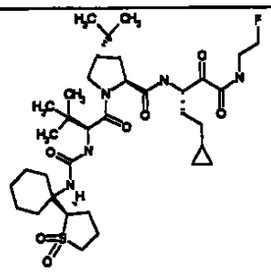
883-dw		732,0032		A
883-dx		705,9649		A
883-dy		778,8432		A

883-dz		790,8544		A
883-ea		720,7626		A
883-eb		720,7626		A

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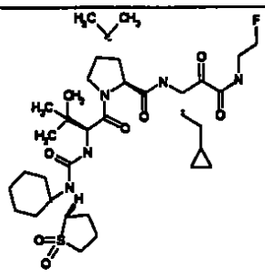
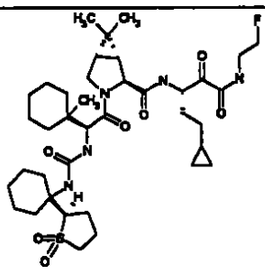
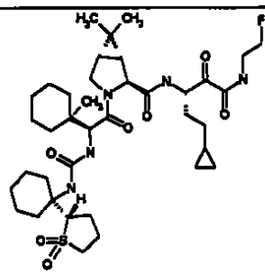
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883-ed		732,7737		A
883-ee		725,9713		A

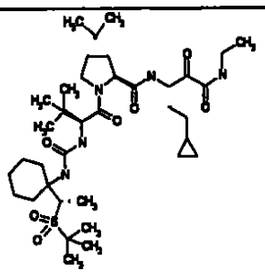
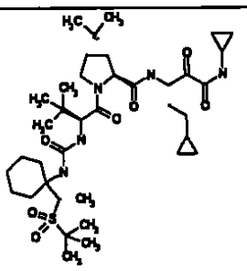
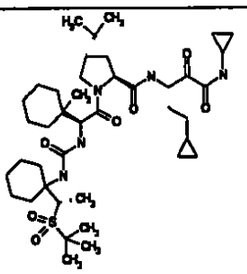
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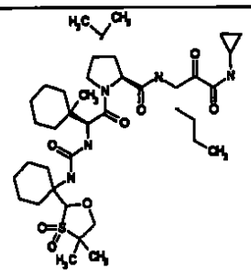
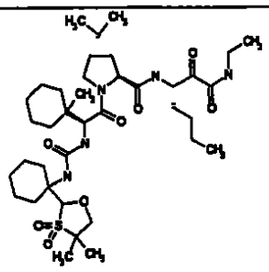
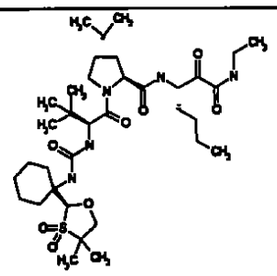
883-ef		766,0366		A
883-eg		709,9283		A

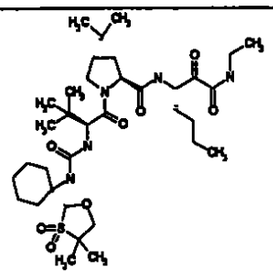
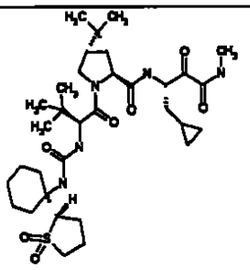
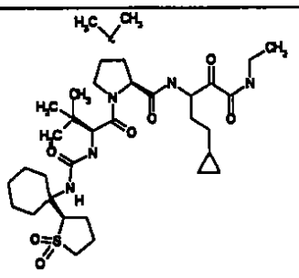
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1325

883-eh		709,9283		A
883-ei		749,9936		A
883-ej		749,9936		A

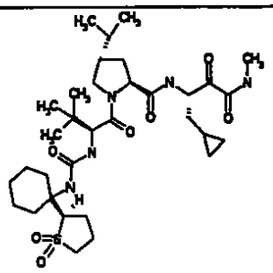
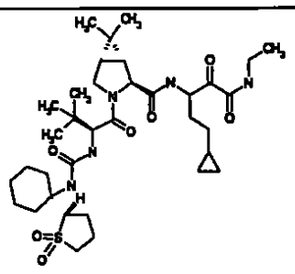
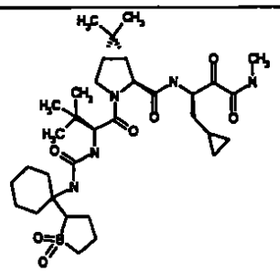
883-ek		722.008		A
883-el		734,0191		A
883-em		774,0844		A

883-en		762,0297		A
883-eo		750.0185		A
883-ep		709,9532		A

883-eq		709,9532		A
883-er		663,8837		A
883-es		691,9378		A

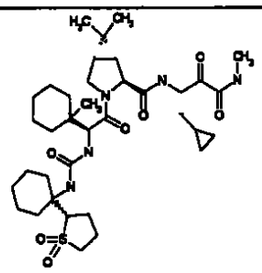
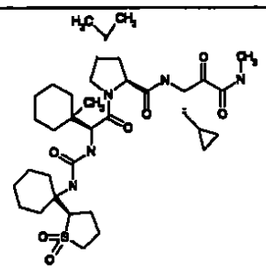
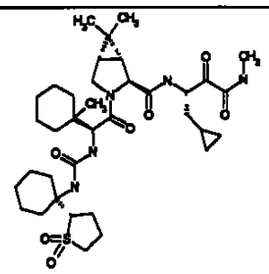
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1329

883-et		663,8837		A
883-eu		691,9378		A
883-ev		663,8837		A

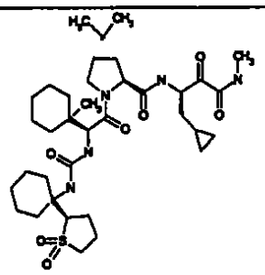
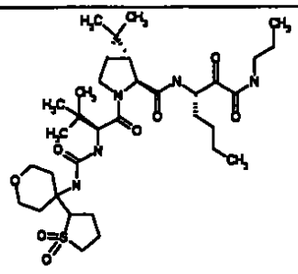
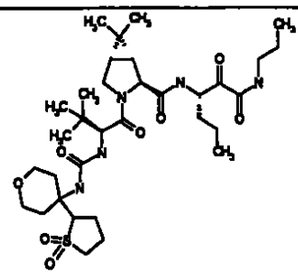
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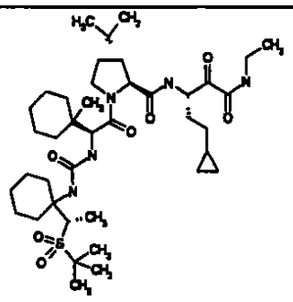
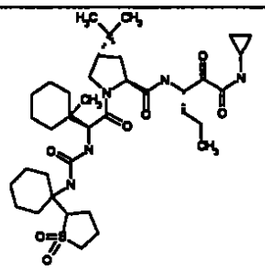
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883-ew		703,949		A
883-ex		703,949		A
883-ey		703,949		A

1348

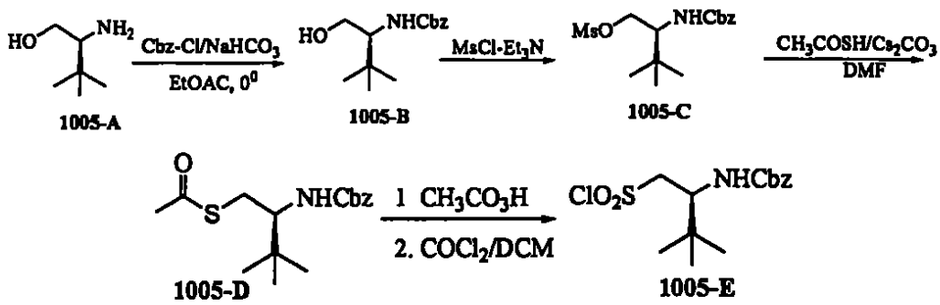
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883-ez		703,949		A
883-fa		695,9261		B
883-fb		681,899		A

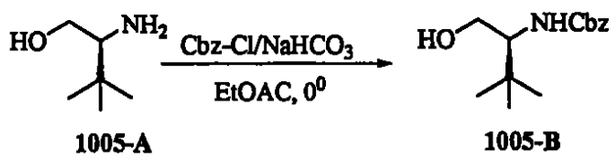
883-fc		762,0733		A
883-fd		717,9761		A

También se describen los siguientes compuestos en la **Tabla 4 y Tabla 4A.** La preparación de los compuestos de la **Tabla 4 y Tabla 4A** se describe a continuación:

EJEMPLO 1005:



PASO 1



A una solución de 5g de **1005-A** (disponible comercialmente de Aldrich) en 100 ml de EtOAc a 0°C se agregaron 40 ml de solución saturada de $NaHCO_3$ seguida de 6,5 ml de Cbz-Cl en una porción La mezcla resultante se agitó durante 2h y las capas se separaron. La fase acuosa se volvió a extraer con 50 ml de EtOAc. La fase orgánica combinada se lavó una vez con salmuera, se secó sobre $MgSO_4$ y se concentró hasta un líquido incoloro que solidificó al reposar Se obtuvieron 10,7g de **1005-B** como sólido blanco.

MS: 274 $[M+Na]^+$.

PASO 2



1005-B **1005-C**

A una solución de 10,7g de **1005-B** en 120 ml de DCM a 0°C se agregaron 7,04 ml de trietilamina y 4,05 ml de cloruro de metansulfonilo. La mezcla se agitó a 0°C por 10 minutos y 1,5h a temperatura ambiente. La mezcla se lavó con solución 1M de $KHSO_4$, agua, salmuera y se secó sobre $MgSO_4$. La concentración del solvente dio el producto en bruto que se purificó en columna de gel de sílice eluyendo con DCM. Se obtuvieron 13g de **1005-C** como aceite incoloro espeso.

EM: 352 $[M+Na]^+$.

PASO 3

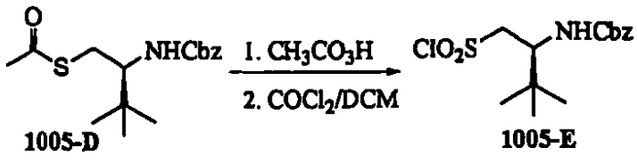


1005-C **1005-D**

A una suspensión de 8,3g de Cs_2CO_3 en 100 ml de DMF anhidra se agregaron 3,3 ml de ácido tioacético A la suspensión marrón oscura se agregó una solución de 12,97g de **1005-C** en 30 ml de DMF anhidra. La mezcla resultante se agitó hasta la mañana siguiente a temperatura ambiente, se diluyó con 300 ml de hielo-agua y se extrajo con 2x250 ml de EtOAc. La fase orgánica

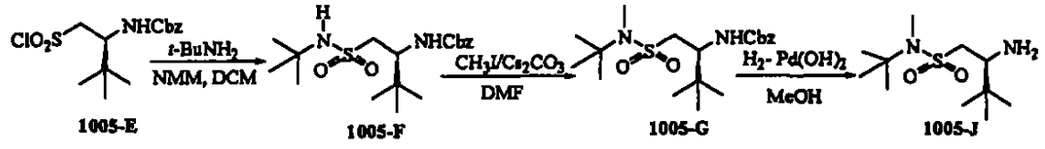
combinada se lavó con agua, salmuera y se secó sobre $MgSO_4$. La evaporación del solvente dio ~10g del producto en bruto que se purificó en columna de gel de sílice con EtOAc 10% en Hexano. Se obtuvieron 4,8g de **1005-D** como sólidos blancos. EM: 310 $[M+H]^+$, 332 $[M+Na]^+$.

PASO 4



1005-D 1005-E

A una solución de 4,4g de **1005-D** en 15 ml de AcOH se agregó una solución de 15 ml de H_2O_2 30% y 30 ml de AcOH. La solución resultante se agitó a temperatura ambiente durante 20 h. Se agregaron 75 mg de Pd/C al 10% y la mezcla se agitó durante 1h, se filtró a través de un taco de celite y se enjuagó con MeOH. El filtrado concentrado se concentró y co-evaporó con 3x100 ml de tolueno para dar sólidos. Se agregaron 90 ml de DCM anhidra para disolver los sólidos y a la solución se agregaron 15 ml de fosgeno al 20% en tolueno (Fluka) seguido de 1,8 ml de DMF anhidra. El gas evolucionó y la mezcla se agitó a temperatura ambiente durante 2 h y se concentró para producir un residuo sólido. La purificación sobre gel de sílice eluyendo con DCM dio 3,94 g de **1005-E** como sólido EM: 356, 358 $[M+Na]^+$.



1005-E 1005-F 1005-G 1005-J

PASO 5

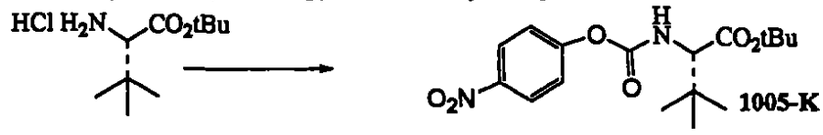
Una mezcla de 900 mg de **1005-E**, 1,0 ml de t-butilamina y 0,4 ml de NMM en 40 ml de DCM se agitó a temperatura ambiente durante 0,5 h, se lavó con solución 1M de $KHSO_4$, salmuera y se secó sobre $MgSO_4$. La evaporación del solvente dio 445 mg del producto en bruto, que se purificó sobre gel de sílice con DCM y EtOAc 5% en DCM. Se obtuvieron 617 mg de **1005-F**. EM: 379 $[M+Na]^+$.

PASO 6

Una mezcla de 600 mg de **1005-F**, 2,64 g de carbonato de cesio y 0,5 ml de yoduro de metilo en 10 ml de DMF anhidra se agitó a temperatura ambiente hasta la mañana siguiente, se diluyó con 50 ml de hielo-agua fría y se extrajo con 2x50 ml EtOAc. La solución orgánica combinada se lavó dos veces con agua, una vez con salmuera, se secó sobre $MgSO_4$ La eliminación del solvente al vacío dio 620 mg de **1005-G** como sólido blanco. EM: 385 $[M+H]^+$.

PASO 7

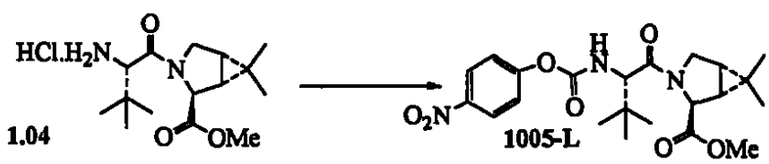
Una solución de **1005-G** (600 mg) y $Pd(OH)_2$ (70mg) en MeOH se colocó bajo una atmósfera de hidrógeno hasta la mañana siguiente. El sólido se filtró y se lavó minuciosamente con MeOH. Los volátiles se eliminaron a presión reducida para dar la amina (**1005-J**; 380mg) EM: 251 $[M+H]^+$.



PASO 8

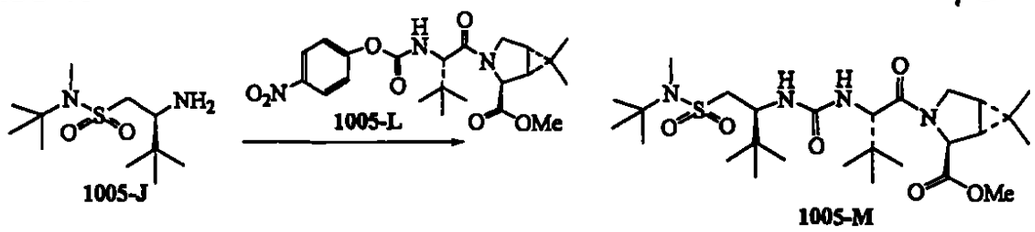
A una solución del clorhidrato (Bachem; 2,24g) en diclorometano (50 ml) se agregó NMM (2,6 ml) seguido de cloroformiato de p-nitrofenilo (2,42g) y la mezcla resultante se agitó a temperatura ambiente hasta la mañana siguiente. La mezcla de reacción se lavó con HCl 1N frío acuoso, bicarbonato de sodio ac sat., se secó y los volátiles se eliminaron a presión reducida. El producto de la reacción en bruto se purificó mediante cromatografía en gel de sílice usando EtOAc:Hexanos (1:10) como eluyente para dar el carbamato (**1005-K**; 2,97g)

PASO 9



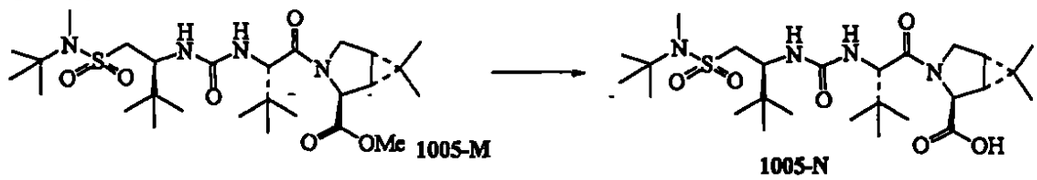
Usando el procedimiento establecido en el **PASO 8** el carbamato **1005-L** se preparó a partir del clorhidrato de amina **1.04**.

PASO 10



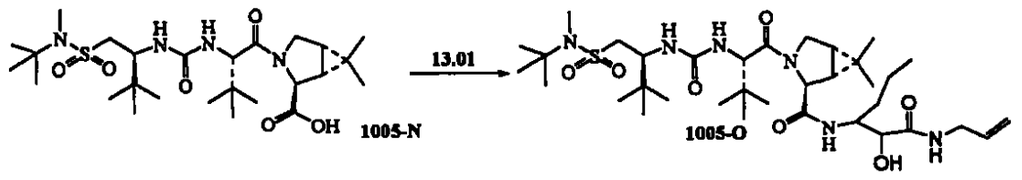
Se agregó NMM (0,12 ml) a una mezcla de la amina (**1005-J**; 0,20 g) y el carbamato (**1005-L**, 0,375 g) en acetonitrilo (15 ml) y la mezcla resultante se agitó a temperatura ambiente, bajo una atmósfera de nitrógeno, hasta la mañana siguiente Los volátiles se eliminaron a presión reducida y el residuo se repartió entre EtOAc y agua. Se separó la fase orgánica, se secó y se concentró. El producto de la reacción en bruto se purificó por cromatografía en columna de gel de sílice usando EtOAc Hexanos (2:3) como eluyente, dando la urea deseada (**1005-M**; 0,43g). EM: 559,28 $[M+H]^+$.

PASO 11



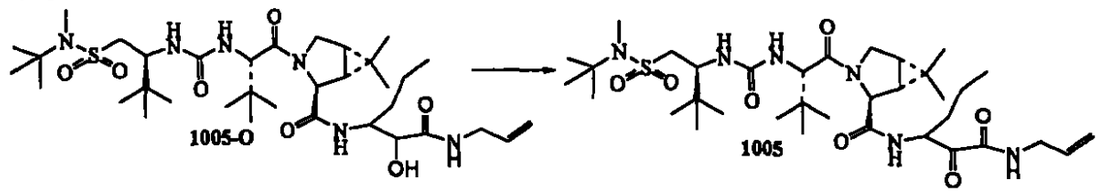
Se agregó hidróxido de litio (0,020 g) en agua (2 ml) a una solución del metil éster (1005-M; 0,41g) en dioxano (15 ml) y la mezcla resultante se agitó a temperatura ambiente hasta la mañana siguiente. Se agregó HCl acuoso (0,01N) y los compuestos orgánicos se extrajeron en EtOAc. Se separó la fase orgánica, se secó y se concentró para dar el ácido carboxílico (**1005-N**; 0,395 g). EM: 545,32 $[M+H]^+$.

PASO 12



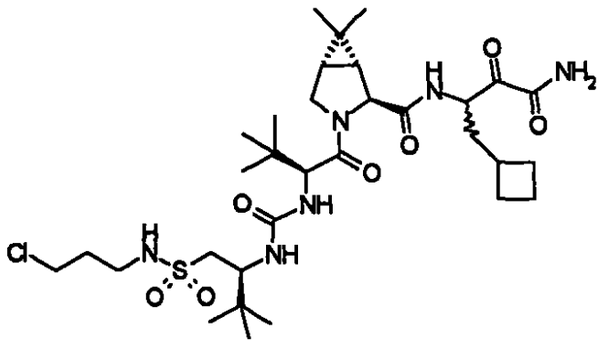
Se agregó base de Hunigs (0,050 ml) a una mezcla del ácido carboxílico (**1005-N**; 0,030 g) y el clorhidrato (**13.01**; 0,015 g) en diclorometano (5 ml) a –20°C, bajo una atmósfera de nitrógeno. La reacción se mantuvo a esta temperatura durante un período de 20h. El procesamiento acuoso dio un producto de reacción en bruto (**1005-O**) que se usó en el Paso **13**, a continuación.

PASO 13



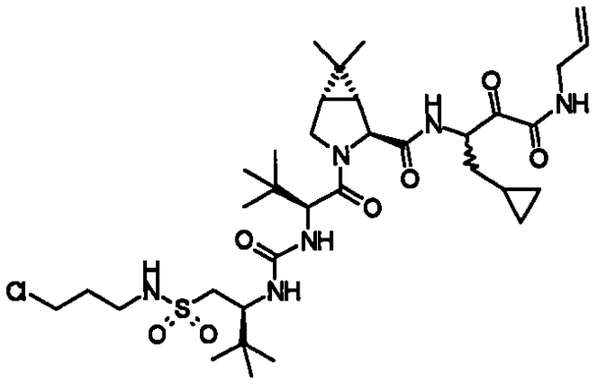
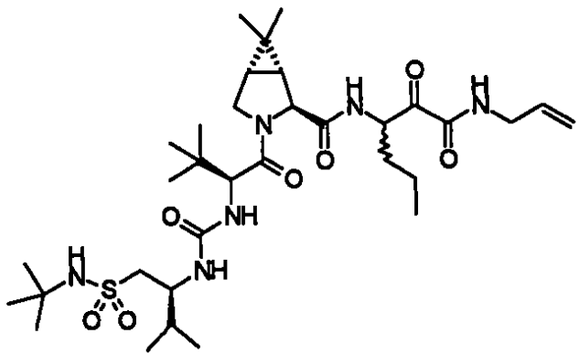
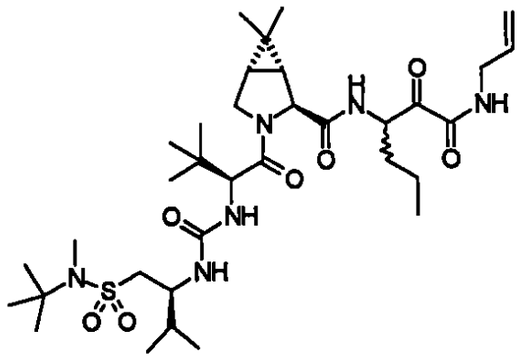
Al producto bruto (**1005-O**, en el Paso **12** anterior) en diclorometano (3ml) se agregó Periodinano de Dess-Martin (0,050 g) y la mezcla resultante se agitó a temperatura ambiente durante un período de 24h. El procesamiento acuoso y la cromatografía en placa de gel de sílice usando diclorometano:metanol (20:1) como eluyente dio la α-ceto-amida deseada (0,0282g), como un sólido blanco Los rangos de Ki* son: A = <75 nM; B = 75 - 250 nM; C = >250 nM

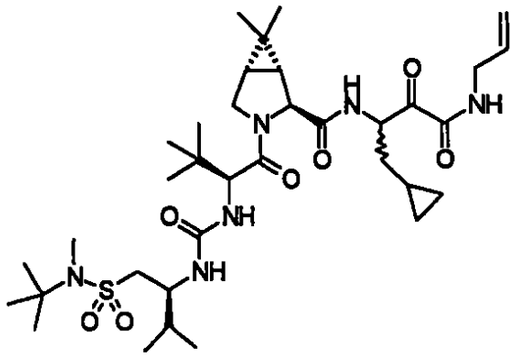
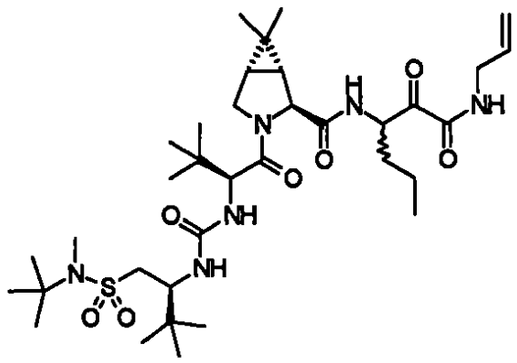
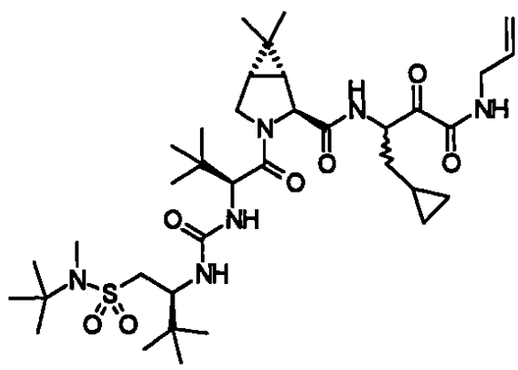
Tabla 4

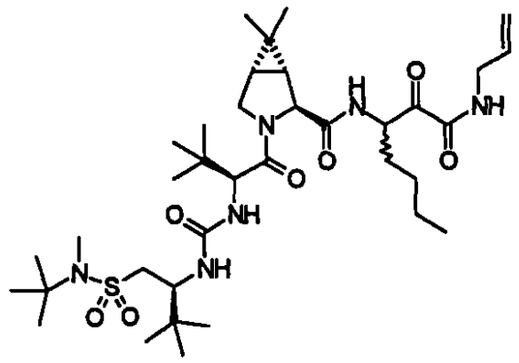
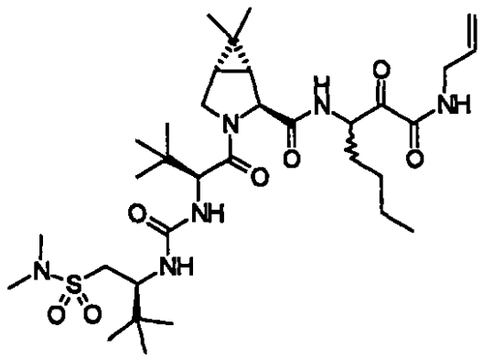
Ej. de Prep.	COMPUESTO	FABMS: MH+	rango de Ki*
1000		703,7	A

1355

1338

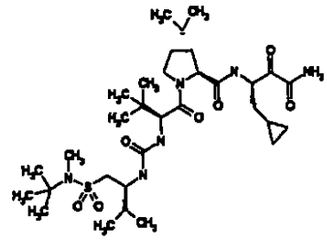
1001		729,7	B
1002		683,3	C
1003		697,3	A

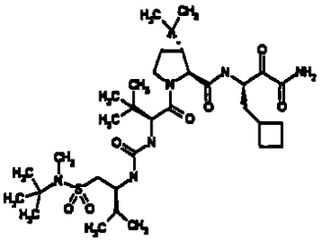
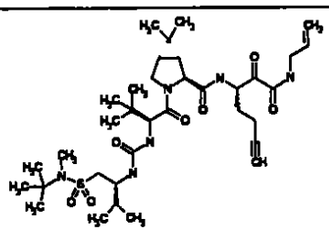
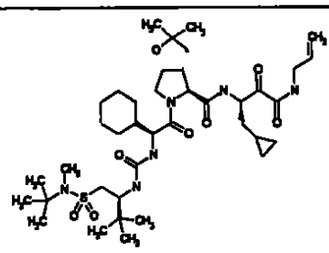
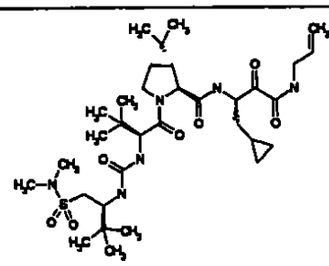
1004		709,3	A
1005		711,3	B
1006		723,3	B

1007		725,3	B
1008		683,3	B

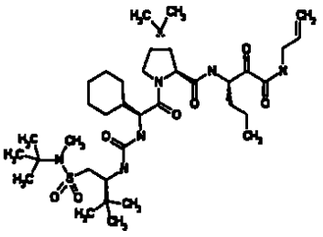
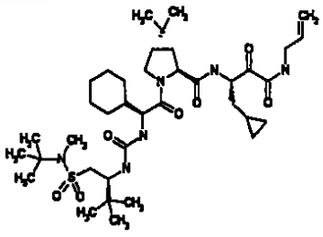
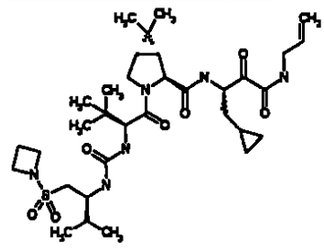
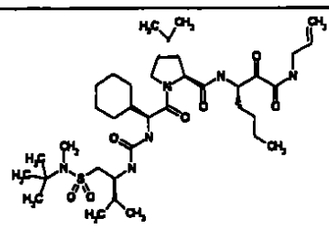
La Tabla 4A enumera compuestos aun adicionales que representan la presente invención:

Tabla 4A

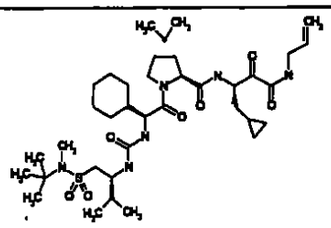
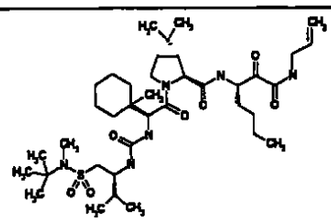
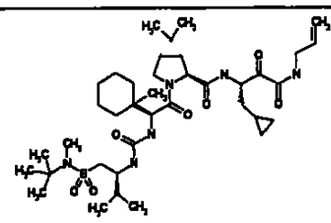
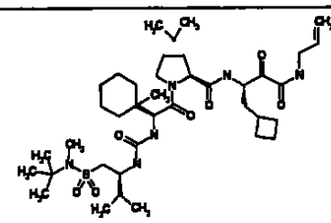
Ej. de prep.	Compuesto	Datos de Espectro de masa selec	Rango de Ki*
1100			A

1101			A
1102			A
1103			B
1104			B

1342

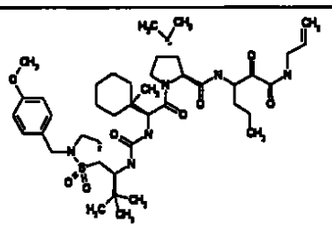
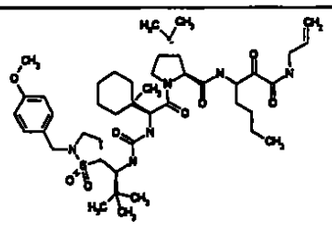
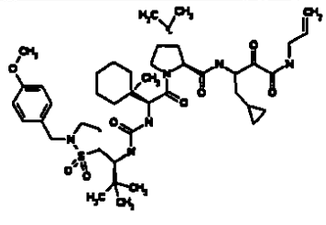
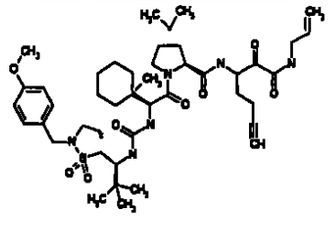
1105			B
1106			B
1107			A
1108			A

1343

1109			B
1110			A
1111			C
1112			A

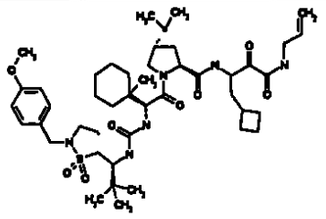
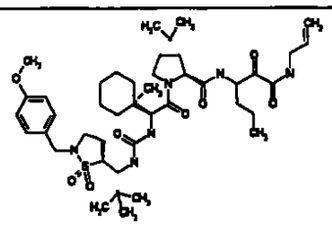
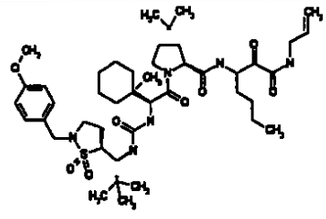
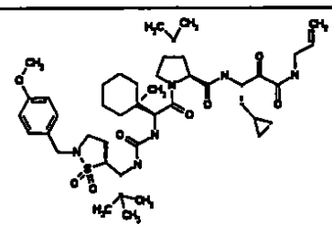
~~1361~~

1347

1113			C
1114			C
1115			C
1116			C

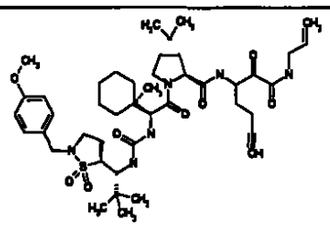
1362

1345

1117			C
1118			C
1119			C
1120			

1363

1346

1121			C

La presente invención se refiere a nuevos inhibidores de la proteasa del VHC. Esta utilidad puede manifestarse en su capacidad para inhibir a la serina proteasa NS2/NS4a del VHC. Un procedimiento general para tal demostración se ilustra por medio del siguiente ensayo *in vitro.*

Ensayo para la Actividad Inhibitoria de la Proteasa del VHC:

Ensayo Espectrofotométrico el ensayo espectrofotométrico para la serina proteasa del VHC puede realizarse sobre los compuestos de la invención siguiendo el procedimiento descripto por R. Zhang *et al*, *Analytical Biochemistry*, 270 (1999) 268-275, cuya revelación se incorpora a la presente a modo de referencia. El ensayo basado en la proteólisis de sustratos cromogénicos con grupo éster es adecuado para el monitoreo continuo de la actividad de la proteasa NS3 del VHC. 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 cromóforos diferentes (3- o 4-nitrofenol, 7-hidroxi-4-metil-cumarina, o 4-fenilazofenol). Se ilustran más abajo la síntesis, caracterización y aplicación de estos nuevos sustratos espectrofotométricos con grupo éster a la selección de alto rendimiento y a la evaluación cinética detallada de los inhibidores de la proteasa NS3 del VHC.

Materiales y Métodos:

Materiales: los reactivos químicos para los buffers relacionados con los ensayos ase obtienen de Sigma Chemical Company (St. Louis, Missouri). Los

reactivos para la síntesis de péptidos fueron de Aldrich Chemicals, Novabiochem (San Diego, California), Applied Biosystems (Foster City, California) y Perseptive Biosystems (Framingham, Massachusetts). Los péptidos se sintetizan manualmente o en un sintetizador automatizado ABI modelo 431A (de Applied Biosystems). El Espectrómetro UV/VIS modelo LAMBDA 12 fue de Perkin Elmer (Norwalk, Connecticut) y las placas de 96 pocillos se obtuvieron de Corning (Corning, New York). El bloque de pre-calentamiento puede ser de USA Scientific (Ocala, Florida) y el mezclador de vórtice para placas de 96 pocillos es de Labline Instruments (Melrose Park, Illinois). Se obtiene una lectora de placas de microtitulación Spectramax Plus con monocromador de Molecular Devices (Sunnyvale, California).

Preparación de Enzimas La proteasa recombinante heterodimérica NS3/NS4A del VHC (cepa 1a) se prepara usando los procedimientos publicados previamente (D. L. Sali *et al*, *Biochemistry*, 37 (1998) 3392-3401). Las concentraciones de proteína se determinan por el método del colorante de Biorad usando patrones de proteasa recombinante del VHC previamente cuantificados por análisis de aminoácidos. Antes del inicio del ensayo, el buffer de almacenamiento de enzimas (fosfato de sodio 50 mM, pH 8,0, NaCl 300 mM, 10% de glicerol, 0,05% de lauril maltósido y DTT 10 mM) se intercambia por buffer de ensayo (MOPS 25 mM, pH 6,5, NaCl 300 mM, 10% de glicerol, 0,05% de lauril maltósido, EDTA 5 µM y DTT 5 µM), utilizando una columna pre-empacada Biorad Bio-Spin P-6.

Síntesis y Purificación de Sustratos: La síntesis de los substrates se realiza como lo informan R. Zhang *et al*, (*ibid*) y se inicia por anclaje de Fmoc-Nva-OH a una resina de cloruro de 2-clorotritilo usando un protocolo estándar (K. Barlos *et al*, *Int. J. Pept. Protein Res.*, 37 (1991), 513-520). Los péptidos se ensamblan posteriormente, usando química de Fmoc, ya sea manualmente o en un sintetizador de péptidos automático ABI modelo 431. Los fragmentos peptídicos

N-acetilados y totalmente protegidos se escinden de la resina ya sea mediante ácido acético (HOAc) al 10% y trifluoroetanol (TFE) al 10% en diclorometano (DCM) durante 30 min, o mediante ácido trifluoroacético (TFA) al 2% en DCM durante 10 min. El filtrado combinado y el lavado de DCM se evapora azeotrópicamente (o se extrae repetidamente mediante solución acuosa de Na_2CO_3) para eliminar el ácido usado en la ruptura La fase DCM se seca sobre Na_2SO_4 y se evapora

The éster sustratos se ensamblan usando procedimientos de acoplamiento ácido-alcohol estándar (K. Holmber *et al, Acta Chem. Scand.*, B33 (1979) 410-412). Los fragmentos peptídicos se disuelven en piridina anhidra (30-60 mg/ml) a la cual se agregaron 10 equivalentes molares de cromóforo y una cantidad catalítica (0,1 eq) de ácido para-toluensulfónico (pTSA) Se agrega diciclohexil-carbodiimida (DCC, 3 eq.) para iniciar las reacciones de acoplamiento. La formación de productos se monitorea por HPLC y puede encontrarse que es completa luego de 12-72 horas de reacción a temperatura ambiente El solvente piridina se evapora al vacío y se continúa eliminando por evaporación azeotrópica con tolueno. El éster del péptido se deprotege con TFA 95% en DCM durante dos horas y se extrae tres veces con etil éter anhidro para eliminar el exceso de cromóforo. El sustrato desprotegido se purifica por HPLC en fase reversa en una columna C3 o C8 con un gradiente de acetonitrilo 30% a 60% (usando seis volúmenes de columna). El rendimiento global luego de la purificación por HPLC puede ser de aproximadamente 20-30%. La masa molecular puede confirmarse mediante espectroscopía de masa por ionización por electroaspersión. Los sustratos se conservan en forma de polvo bajo acción desecante

Espectros de Sustratos y Productos: los espectros de sustratos y los correspondientes productos cromóforos se obtienen en buffer de ensayo de pH 6,5. Los coeficientes de extinción se determinan a la longitud de onda óptima de

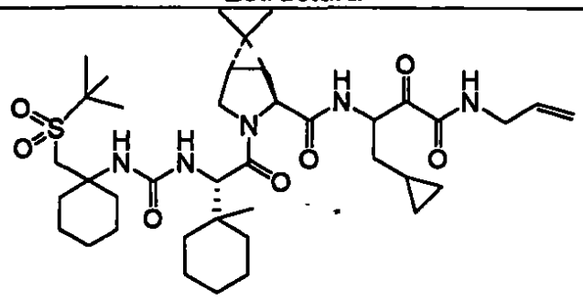
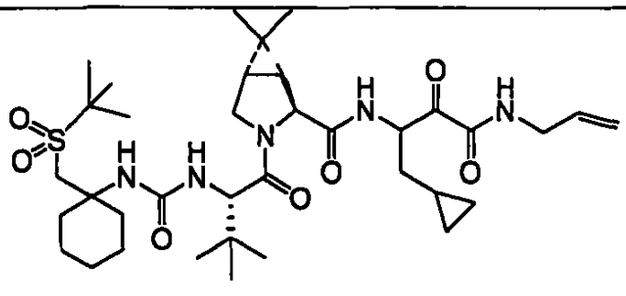
1349

pico máximo 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 de pico máximo se define como la longitud de onda que produce la máxima diferencia fraccionaria en absorbancia entre sustrato y producto (DO del producto - DO del sustrato)/DO del sustrato).

Ensayo de Proteasa: los ensayos de proteasa del VHC se realizan a 30°C usando una mezcla de reacción de 200 µl en una placa de microtitulación de 96 pocillos Las condiciones del buffer de ensayo (MOPS 25 mM, pH 6,5, NaCl 300 mM, 10% de glicerol, 0,05% de lauril maltósido, EDTA 5 µM y DTT 5 µM) se optimizan para el heterodímero NS3/NS4A (D. L. Sali *et al*, *ibid*)). Normalmente, se colocan mezclas de 150 µl de buffer, sustrato e inhibidor en los pocillos (concentración final de DMSO ≤ 4% v/v) y se deja preincubar a 30°C durante aproximadamente 3 minutos. Luego se utilizan cincuenta µl de proteasa precalentada (12 nM, 30°C) en buffer de ensayo, para iniciar la reacción (volumen final 200 µl). Se monitorean las placas a lo largo del ensayo (60 minutos) para observar cambios en la absorbancia a la longitud de onda apropiada (340 nm para 3-Np y HMC, 370 nm para PAP, y 400 nm para 4-Np) usando una lectora de placas de microtitulación Spectromax Plus equipada con un monocromador (pueden obtenerse resultados aceptables con lectoras de placas que utilizan filtros de corte). La ruptura proteolítica del enlace éster entre el Nva y el cromóforo se monitorea a la longitud de onda apropiada contra un blanco sin enzima como control para hidrólisis no enzimática. La evaluación de parámetros cinéticos del sustrato se efectúa en un rango de concentración de un factor 30 (~6-200 µM). Las velocidades iniciales se determinan usando regresión lineal y las constantes cinéticas se obtienen 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 recambio (k_{cat}) se calculan suponiendo que la enzima es totalmente activa.

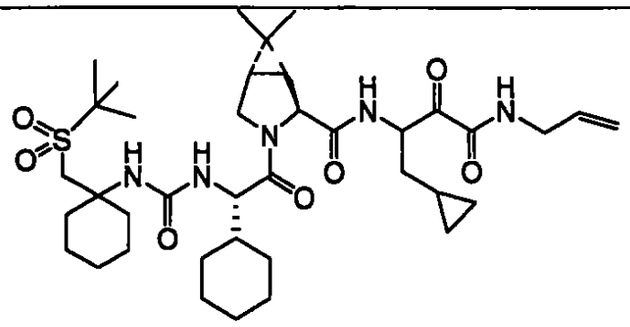
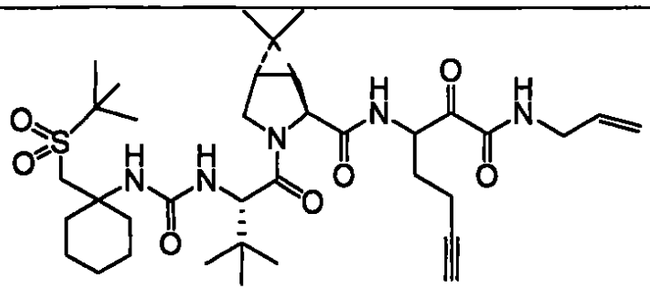
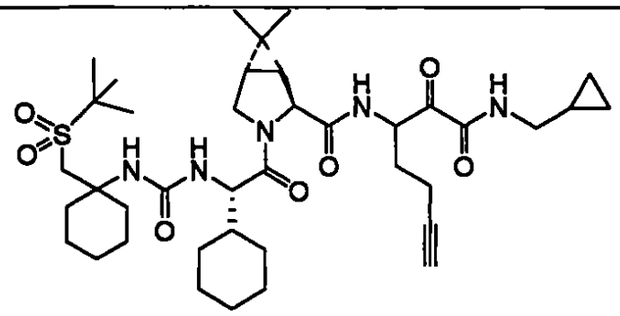
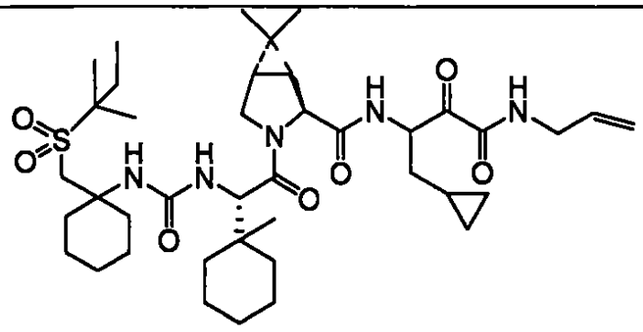
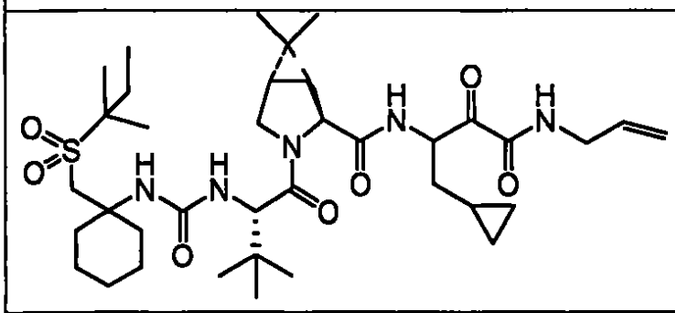
Evaluación de Inhibidores e Inactivadores: Las constantes de inhibición (K_i) para los inhibidores competitivos Ac-D-(D-Gla)-L-I-(Cha)-C-OH (27), Ac-DTEDVVA(Nva)-OH y Ac-DTEDVVP(Nva)-OH se determinan experimentalmente a concentraciones fijas de enzima y sustrato graficando v_o/v_i vs. concentración de inhibidor ($[I]_o$) de acuerdo con la ecuación de Michaelis-Menten reordenada para 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 a cualquier concentración dada de inhibidor ($[I]_o$), y $[S]_o$ es la concentración de sustrato usada. Los datos resultantes se ajustan usando regresión lineal y la pendiente resultante, $1/(K_i(1+[S]_o/K_m)$, se utiliza para calcular el valor de K_i. La **Tabla 5** siguiente enumera los valores de Ki* obtenidos (en nanoMolar) para algunos de los compuestos de la invención Se destacan otros varios en las **Tablas** de páginas anteriores.

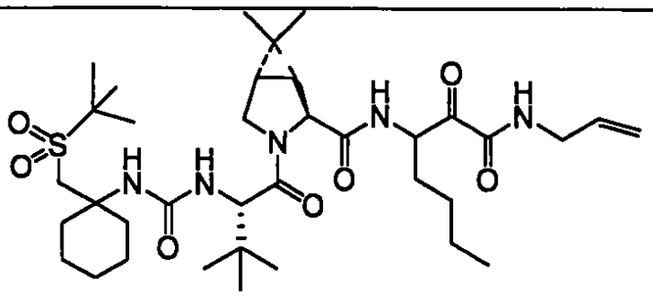
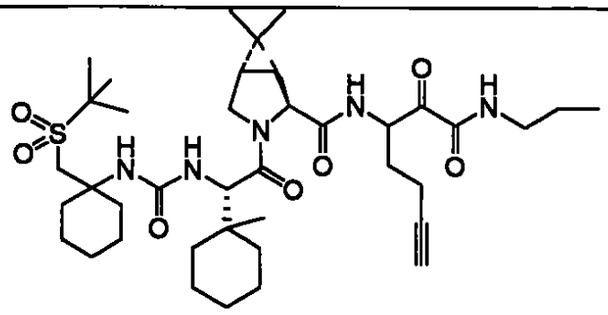
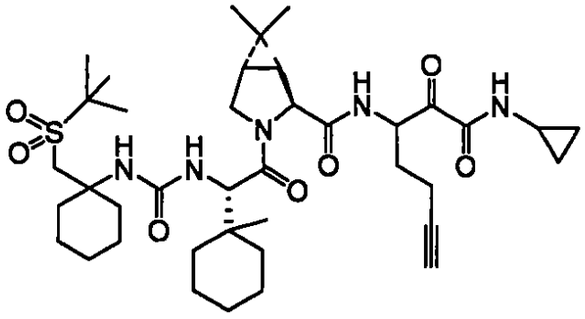
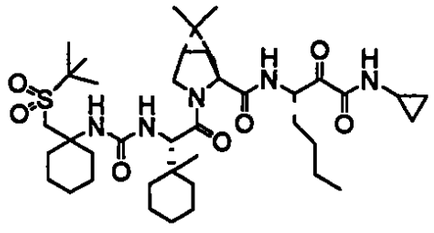
Tabla 5

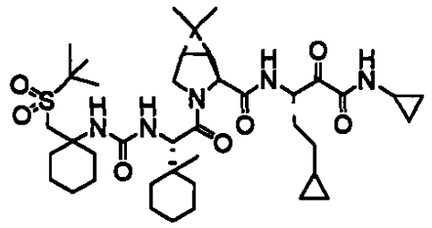
Estructura	Ki* (nM)
	10
	14

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	4,1
	2
	19
	9
	14

	11
	4
	6
	5

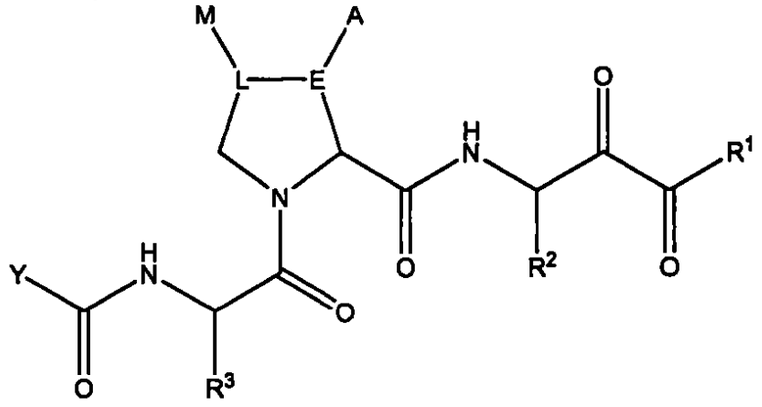
	3

Aunque la presente invención se ha descripto en conjunción con las realizaciones específicas expuestas anteriormente, muchas alternativas, modificaciones y otras variaciones de las mismas serán evidentes para aquellos con experiencia en el arte. Todas las mencionadas alternativas, modificaciones y variaciones deberán caer dentro del espíritu y alcance de la presente invención

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REIVINDICACIONES

1. Un compuesto, o enantiómeros, estereoisómeros, rotámeros, tautómeros y racematos de dicho compuesto, o una sal o solvato o éster aceptables desde el punto de vista farmacéutico de dicho compuesto, teniendo dicho compuesto la estructura general que se muestra en la Fórmula I:



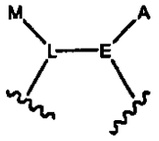
Fórmula I

en la cual:

R^1 es H, OR^8, NR^9R^{10}, o CHR^9R^{10}, en los cuales R^8, R^9 y R^{10} pueden ser iguales o diferentes, seleccionándose cada uno en forma independiente del grupo formado por H, alquilo-, alquenilo-, alquinilo-, arilo-, heteroalquilo-, heteroarilo-, cicloalquilo-, heterociclilo-, arilalquilo- y heteroarilalquilo;

A y M pueden ser iguales o diferentes, seleccionándose cada uno en forma independiente de R, OR, NHR, NRR', SR, SO_2R y halo;

o A y M están conectados uno al otro de modo tal que el resto:



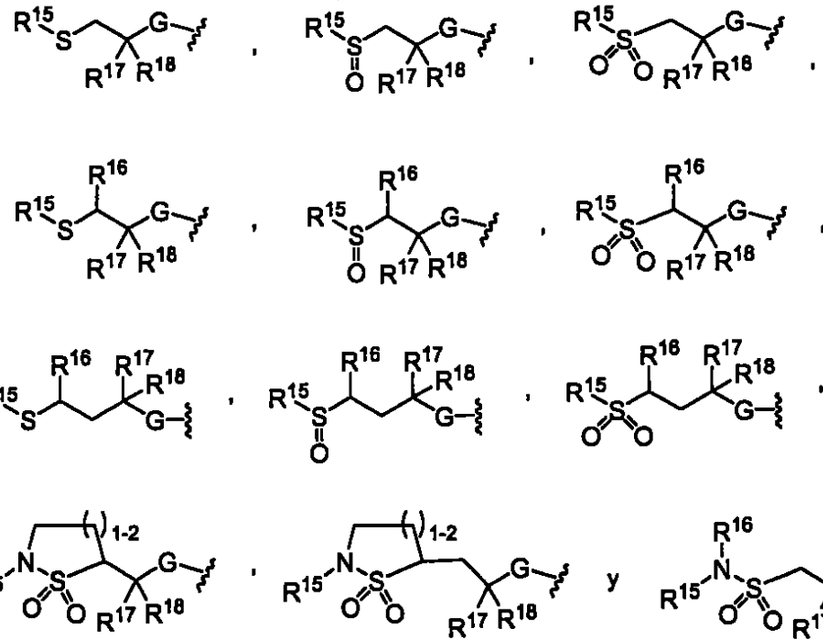
que se mostró anteriormente en la Fórmula I forma tanto un cicloalquilo de tres, cuatro, seis, siete y ocho miembros, un heterociclilo de cuatro a ocho miembros, un arilo de seis a diez miembros, o un heteroarilo de cinco a diez miembros;

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, seleccionándose cada uno en forma independiente del grupo formado por H, alquilo, heteroalquilo, alquenilo, heteroalquenilo, alquinilo, heteroalquinilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, o alternativamente R y R' en NRR' están conectados uno al otro de manera tal que NRR' forma un heterociclilo de cuatro a ocho miembros;

e Y se selecciona de los siguientes restos:



en los cuales G es NH u O; y R^{15}, R^{16}, R^{17} y R^{18} pueden ser iguales o diferentes, seleccionándose cada uno en forma independiente del grupo formado por H, alquilo, heteroalquilo, alquenilo, heteroalquenilo, alquinilo, heteroalquinilo, cicloalquilo, heterociclilo, arilo, y heteroarilo, o alternativamente, (i) R^{15} y R^{16} están conectados entre sí para formar una estructura cíclica de cuatro a ocho

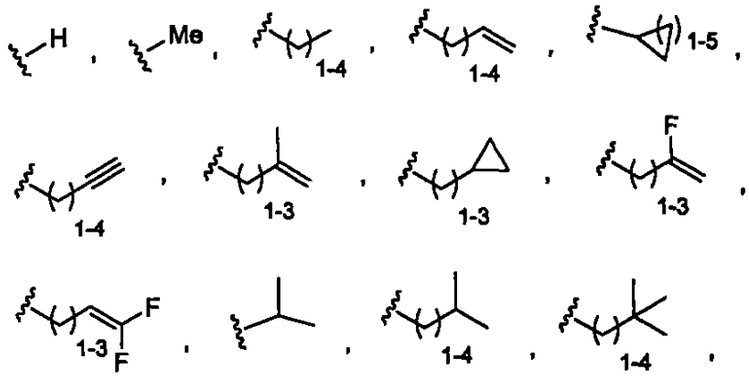
1356

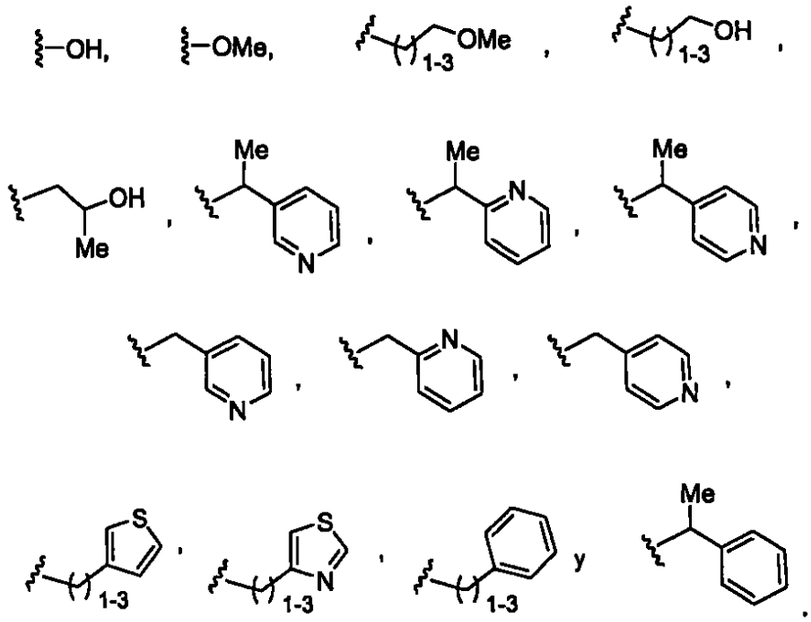
miembros, y (ii) del mismo modo, en forma independiente R^{17} y R^{18} están conectados uno al otro para formar un cicloalquilo o heterociclilo de tres a ocho miembros;

donde cada uno de dichos alquilo, arilo, heteroarilo, cicloalquilo o heterociclilo pueden no estar sustituidos o estar sustituidos en forma opcional e independiente con uno o más restos seleccionados del grupo formado por: hidroxi, alcoxi, ariloxi, tio, alquiltio, ariltio, amino, amido, alquilamino, arilamino, alquilosulfonilo, arilsulfonilo, sulfonamido, alquilosulfonamido, arilsulfonamido, alquilo, arilo, heteroarilo, ceto, carboxi, carbalcoxi, carboxamido, alcoxicarbonilamino, alcoxicarboniloxi, alquilureido, arilureido, halo, ciano y nitro.

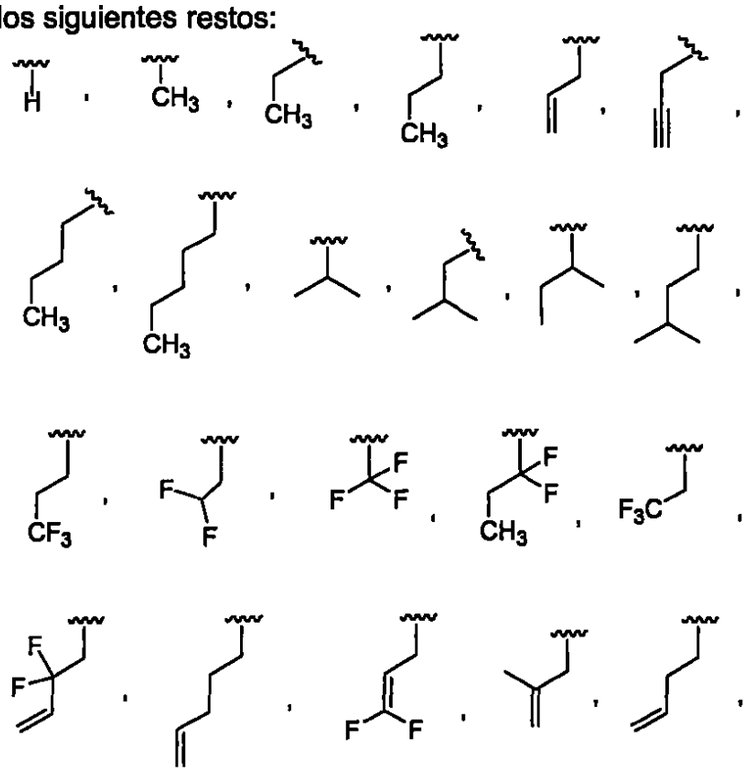
2. El compuesto de la reivindicación 1, en el cual R^1 es NR^9R^{10}, y R^9 es H, R^{10} es H, o R^{14} en los cuales R^{14} es H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, alquil-arilo, alquil-heteroarilo, aril-alquilo, alquenilo, alquinilo o heteroaril-alquilo.

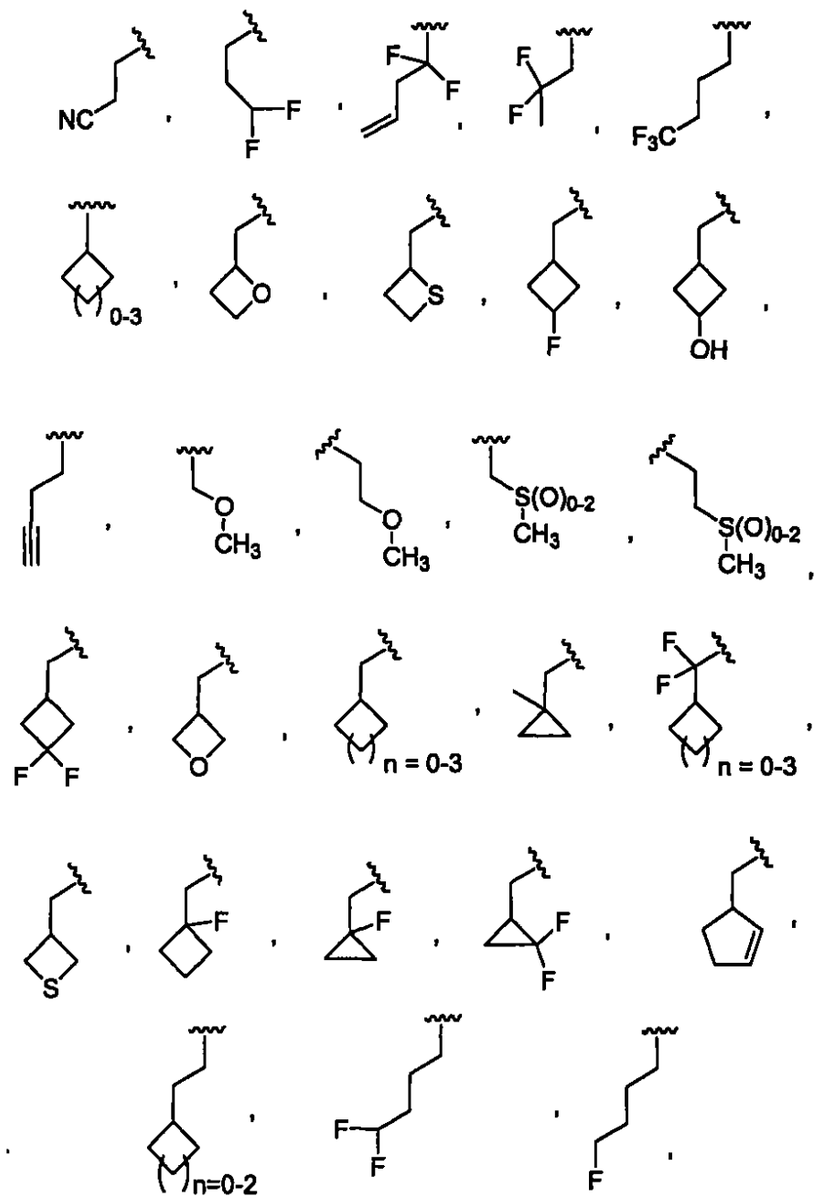
3. El compuesto de la reivindicación 2, en el cual R^{14} se selecciona del grupo formado por:





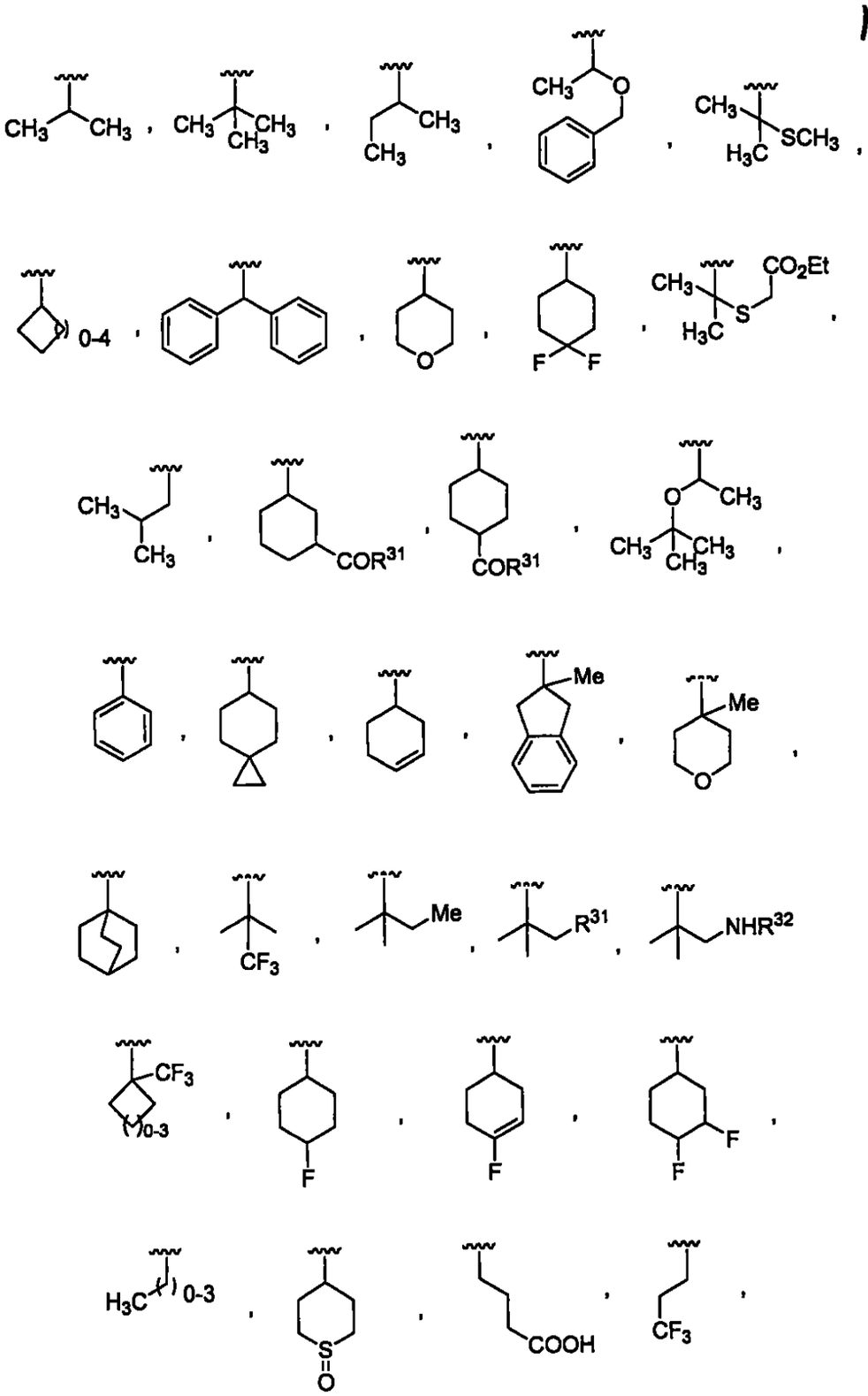
4. El compuesto de la reivindicación 1, en el cual R^2 se selecciona del grupo formado por los siguientes restos:

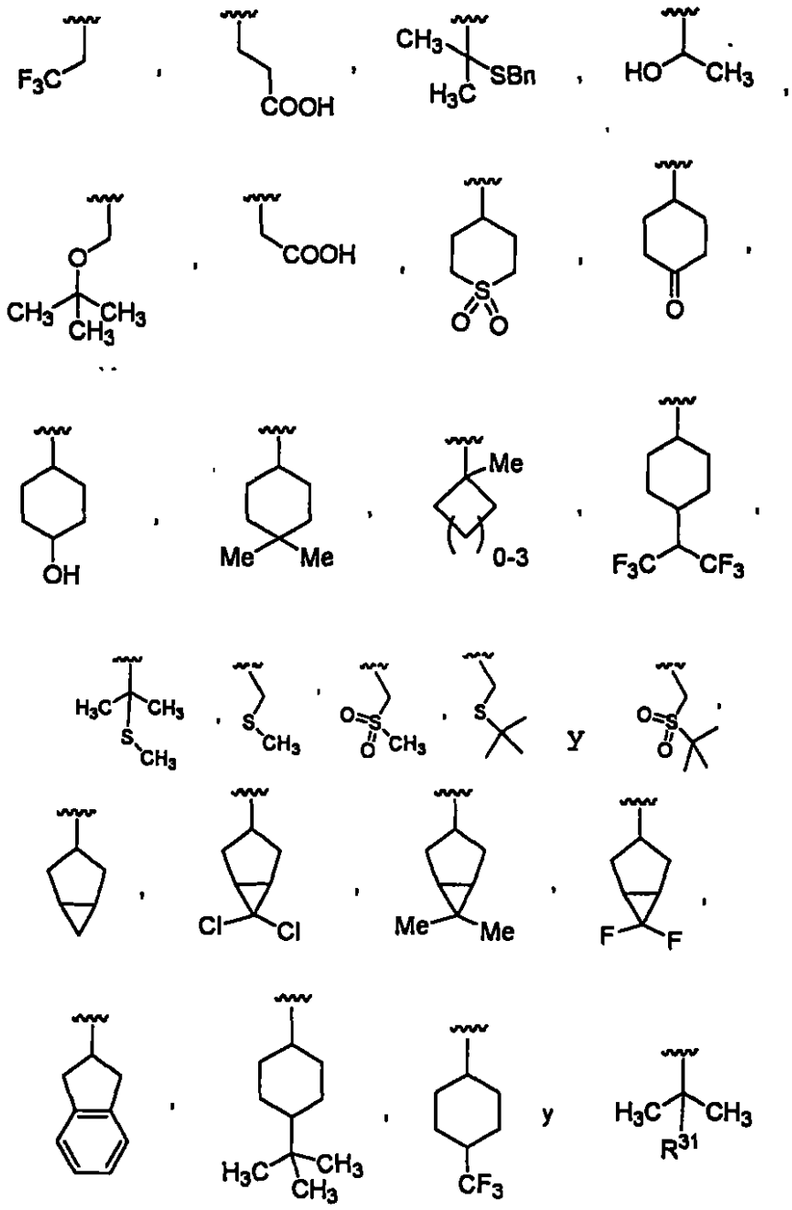




5. El compuesto de la reivindicación 1, en el cual R^3 se selecciona del grupo formado por:

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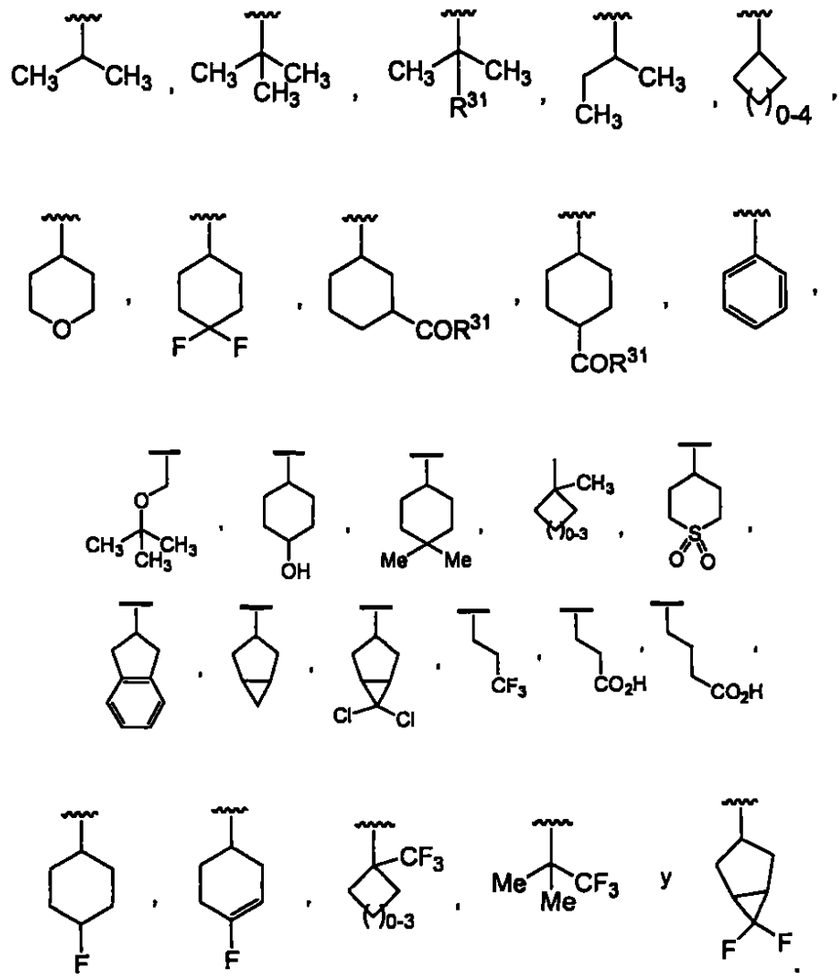

CH3
CH3
CH3
CH3
CH3
CH3
CH3
CH3
O
CH3
H3C
SCH3
0-4
O
F
F
CH3
S
CO2Et
H3C
CH3
CH3
COR31
COR31
O
CH3
CH3
CH3
Me
Me
O
CF3
Me
R31
NHR32
CF3
0-3
F
F
F
F
H3C
0-3
S
O
COOH
CF3



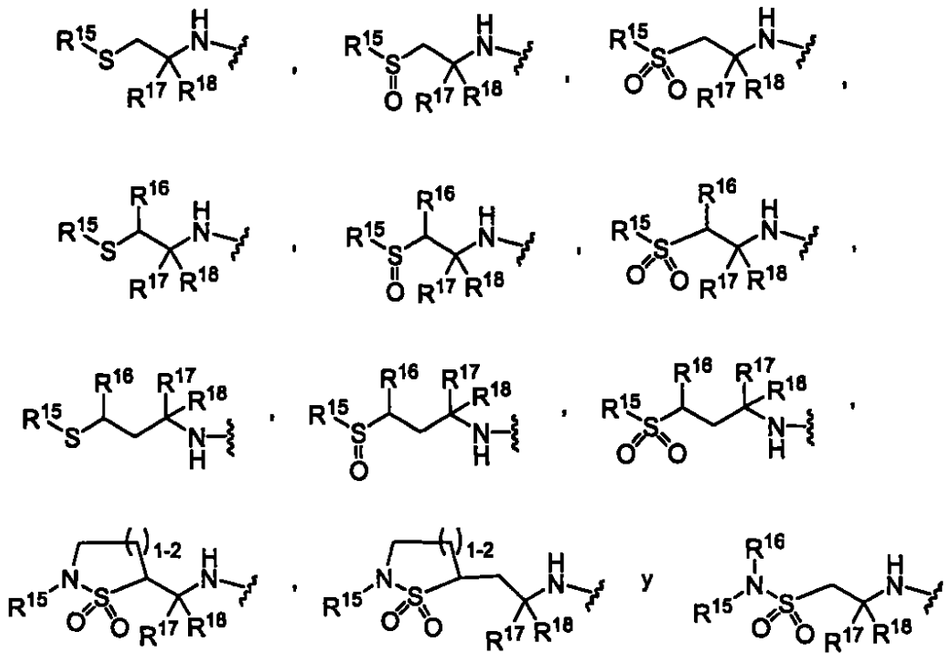
en los cuales R^{31} es OH u O-alquilo; y

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 se selecciona del grupo formado por los siguientes restos:

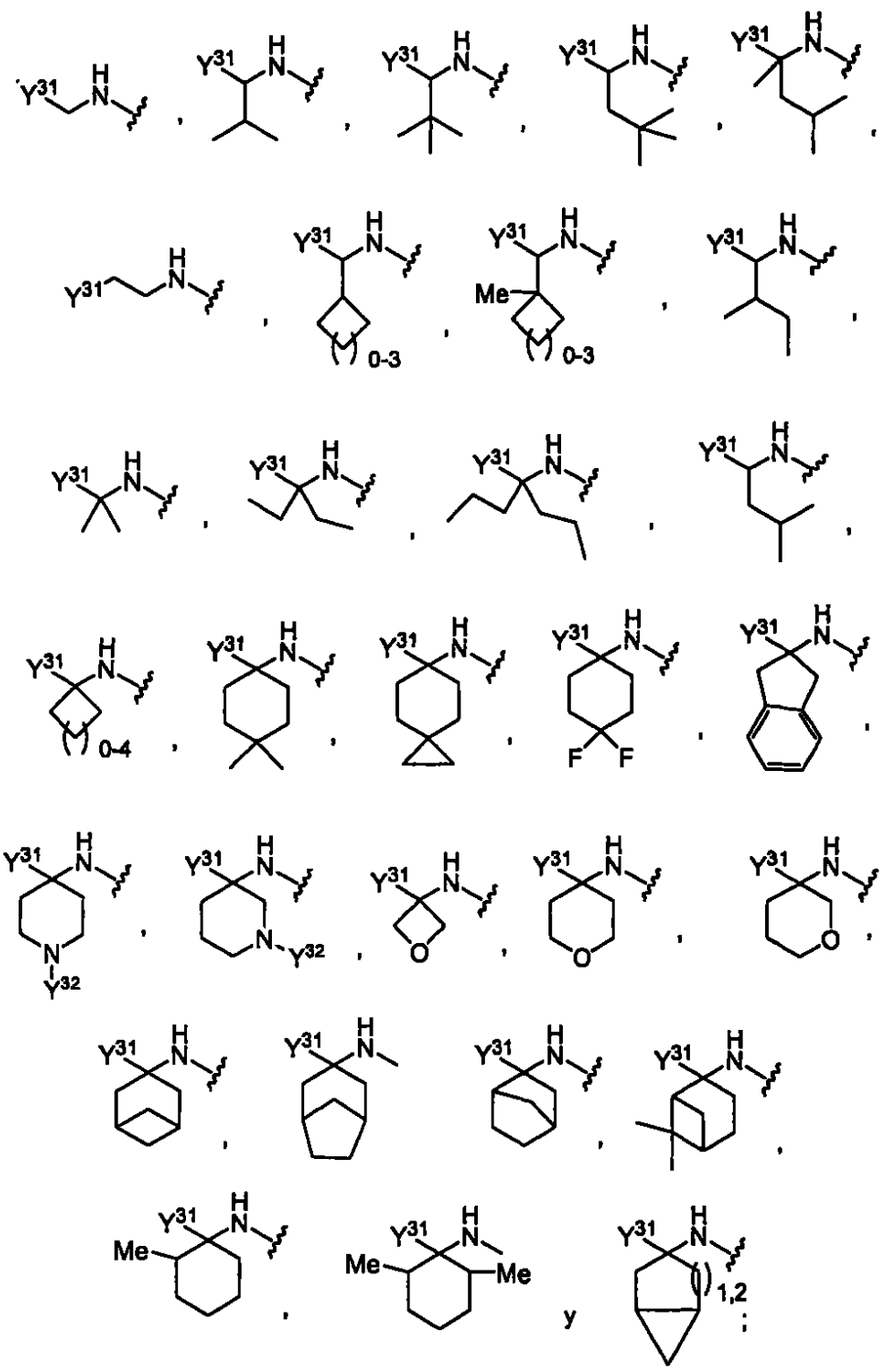


7. El compuesto de la reivindicación 1, en el cual Y se selecciona de los siguientes restos:

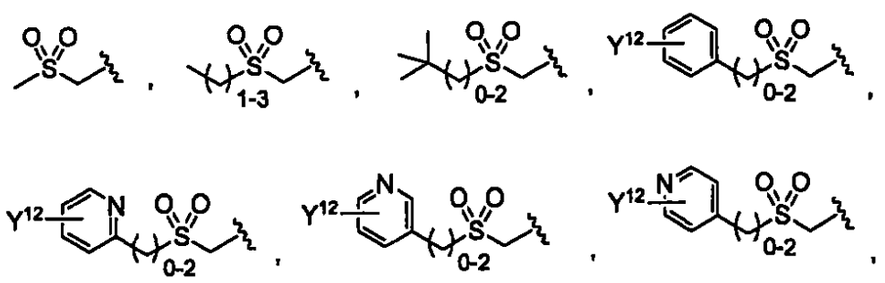


en los cuales R^{15}, R^{16}, R^{17} y R^{18} pueden ser iguales o diferentes, seleccionándose cada uno en forma independiente del grupo formado por H, alquilo, heteroalquilo, alquenilo, heteroalquenilo, alquinilo, heteroalquinilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, o alternativamente, R^{15} y R^{16} están conectados uno al otro para formar una estructura cicloalquílica o heterocíclica de cuatro a ocho miembros; R^{17} y R^{18} están conectados uno al otro para formar un cicloalquilo o heterociclilo de tres a ocho miembros, en el cual cada uno de dichos arilo, heteroarilo, cicloalquilo o heterociclilo pueden no estar sustituidos o estar sustituidos en forma opcional e independiente con uno o más restos seleccionados del grupo formado por: hidroxi, alcoxi, ariloxi, tio, alquiltio, ariltio, amino, amido, alquilamino, arilamino, alquilosulfonilo, arilsulfonilo, sulfonamido, alquilosulfonamido, arilsulfonamido, alquilo, arilo, heteroarilo, carboxi, carbalcoxi, carboxamido, alcoxicarbonilamino, alcoxicarboniloxi, alquilureido, arilureido, halo, ciano y nitro.

8. El compuesto de la reivindicación 7, Y se selecciona del grupo formado por:

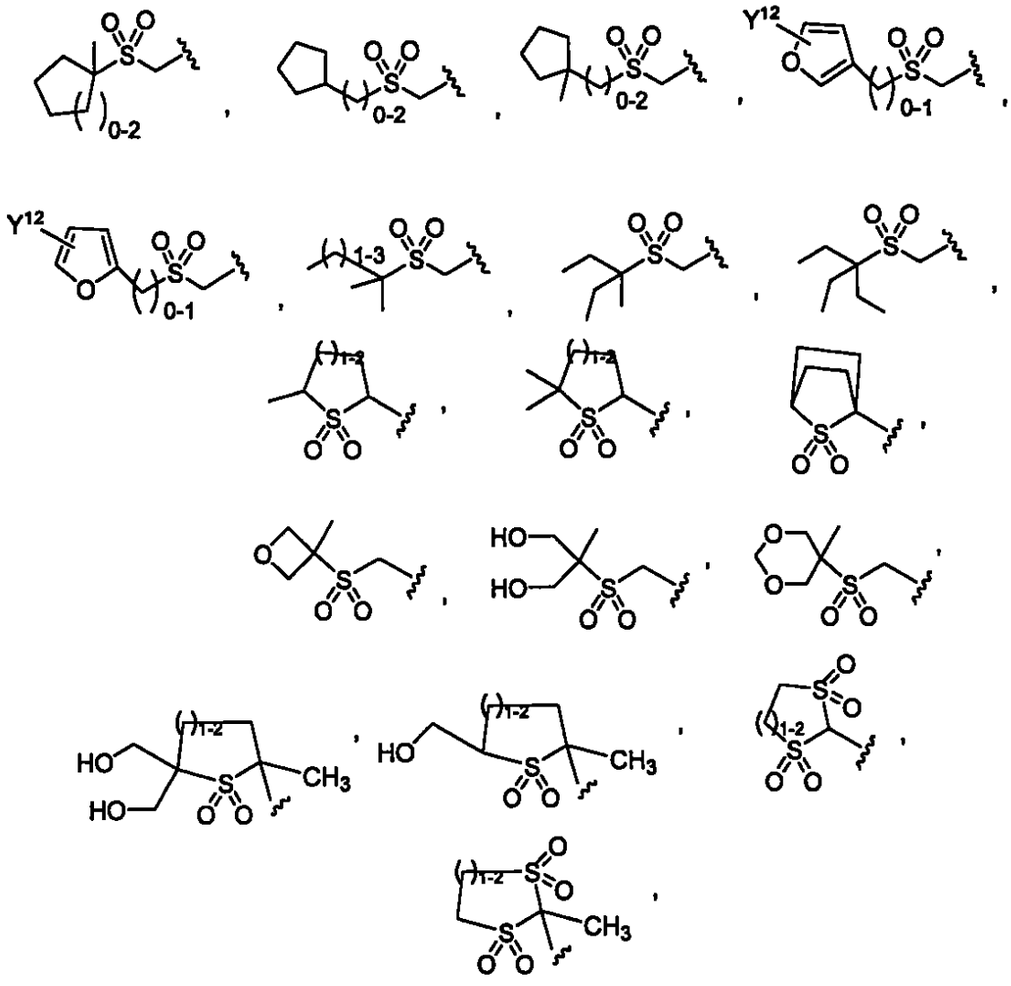


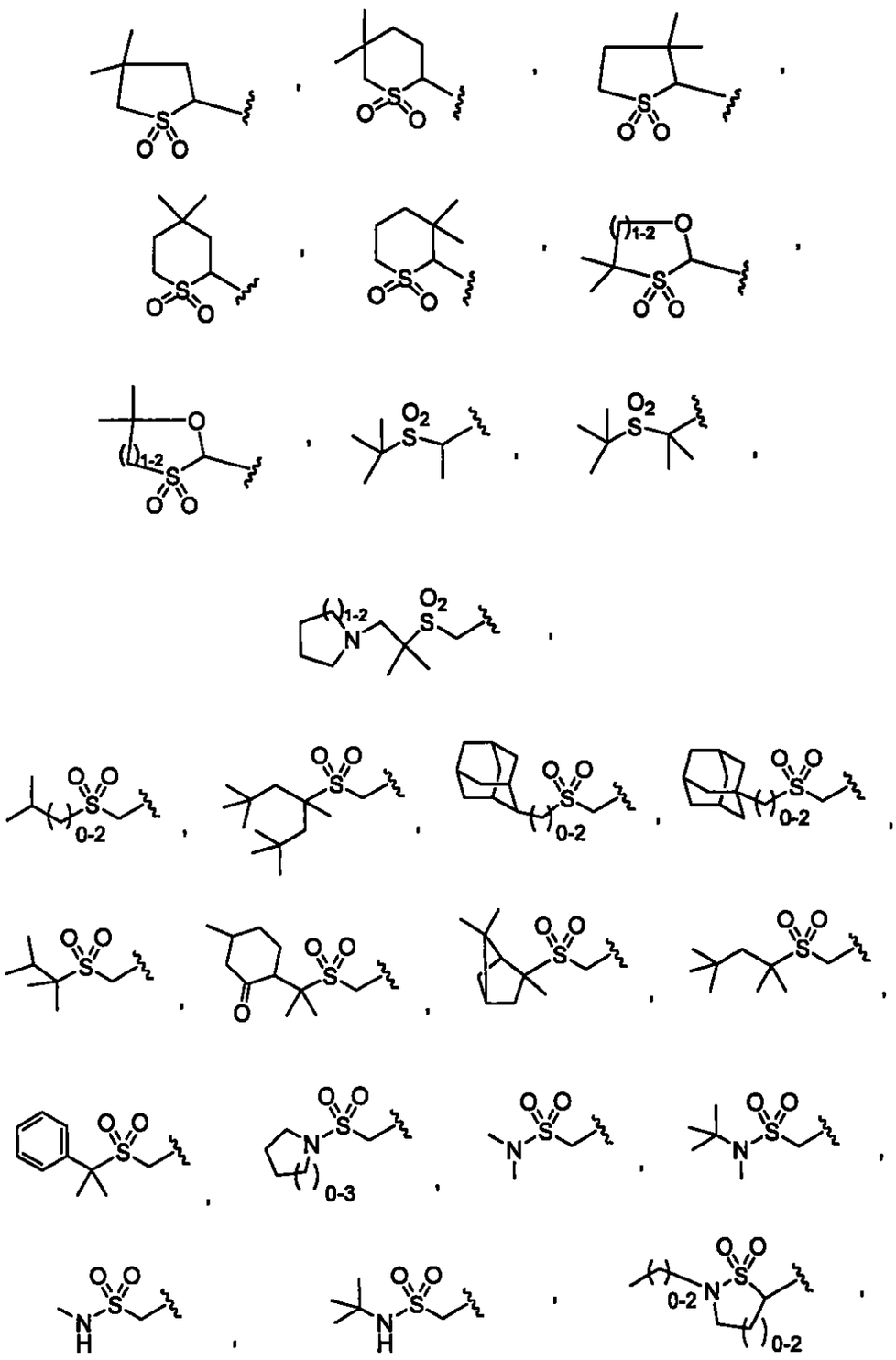
en los cuales Y^{31} se selecciona del grupo formado por:

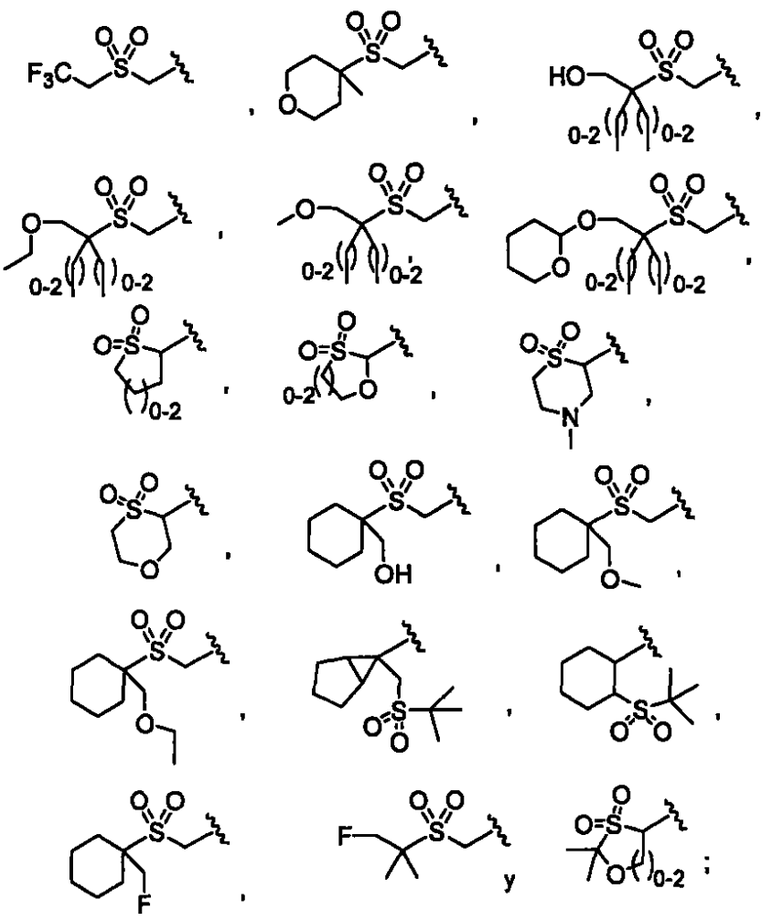


1384

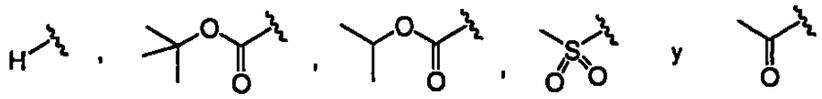
1364





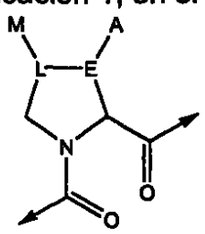


Y^{32} se selecciona del grupo formado por:



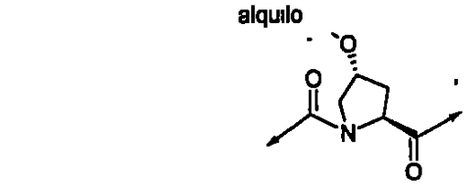
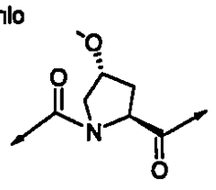
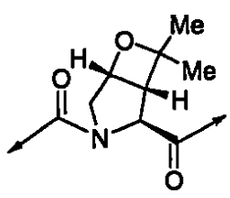
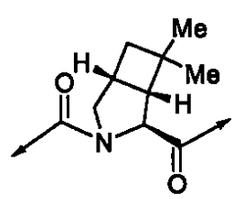
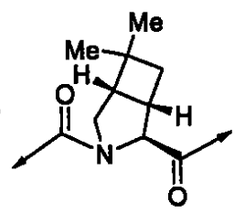
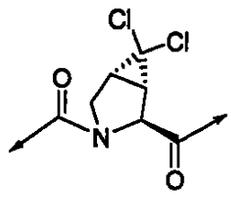
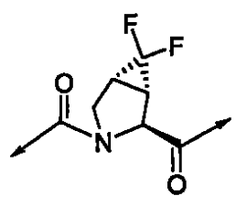
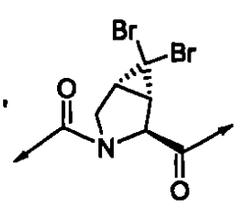
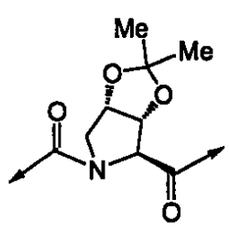
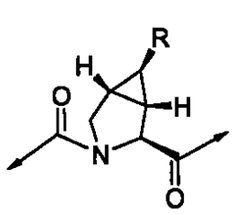
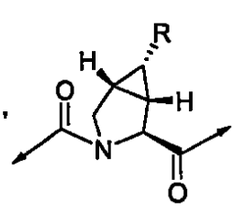
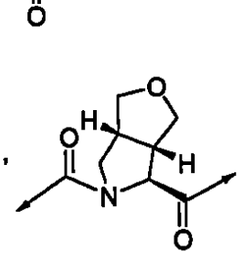
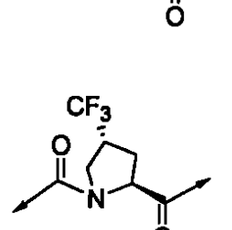
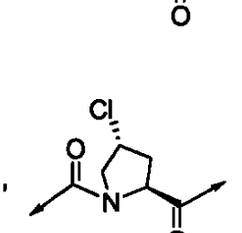
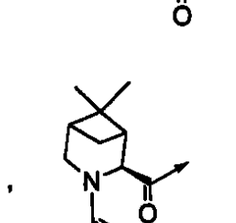
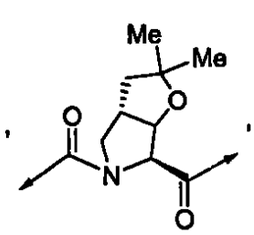
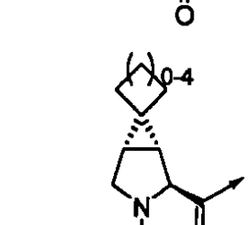
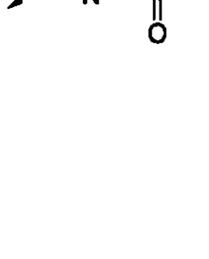
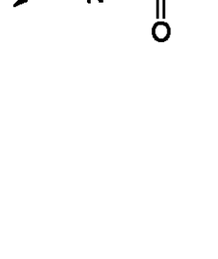
e Y^{12} se selecciona del grupo formado por H, CO_2H, CO_2Me, OMe, F, Cl, Br, NH_2, $N(H)S(O_2)CH_3$, $N(H)C(O)CH_3$, NO_2, $S(O_2)NH_2$, CF_3, Me, OH, OCF_3 y $C(O)NH_2$.

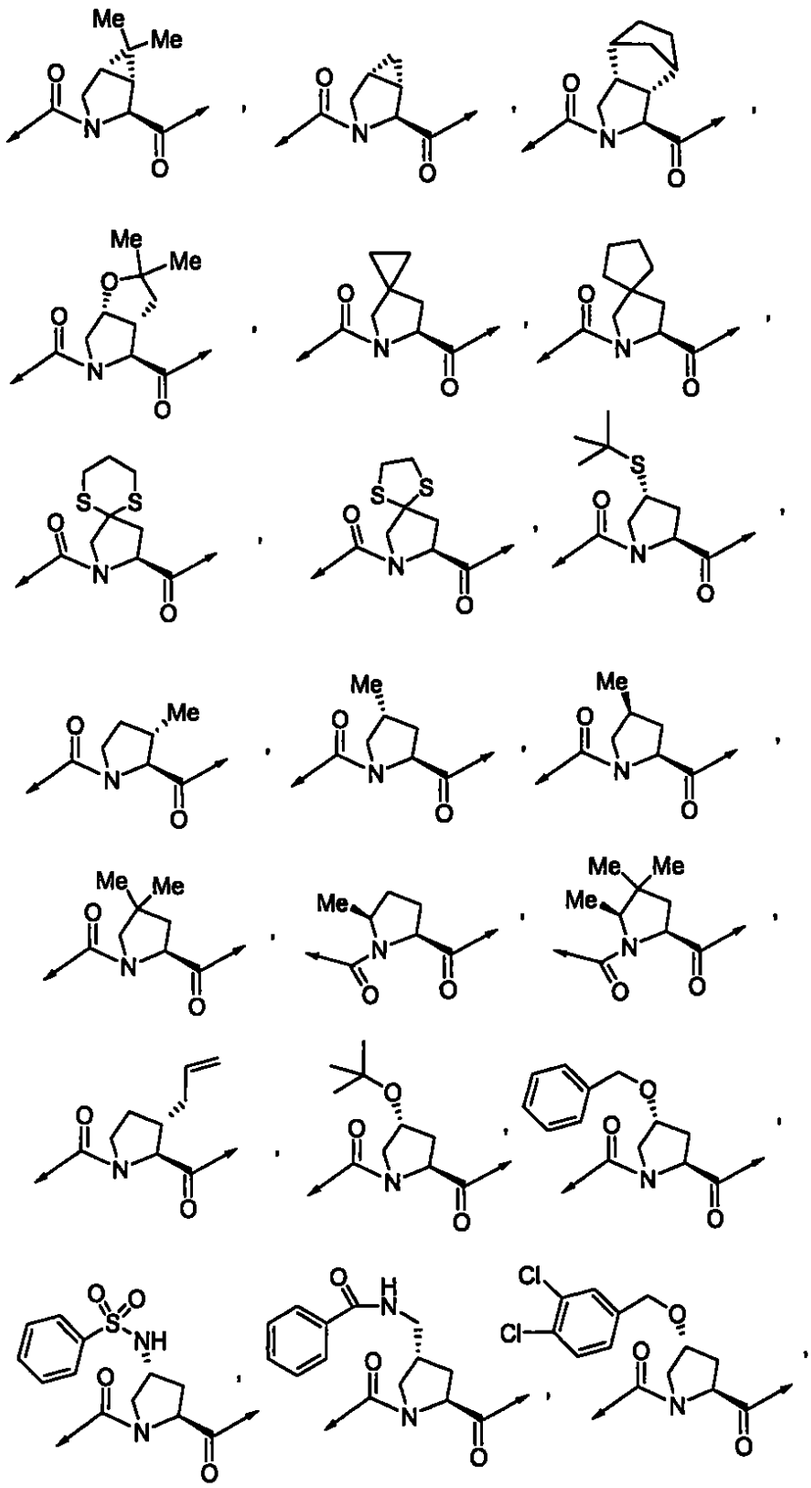
9. El compuesto de la reivindicación 1, en el cual el resto:

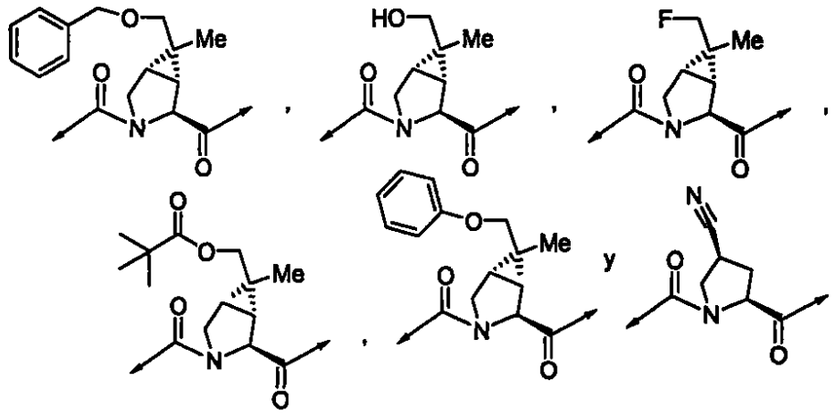


se selecciona de las siguientes estructuras:

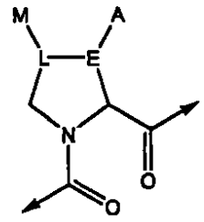
alquilo anilo

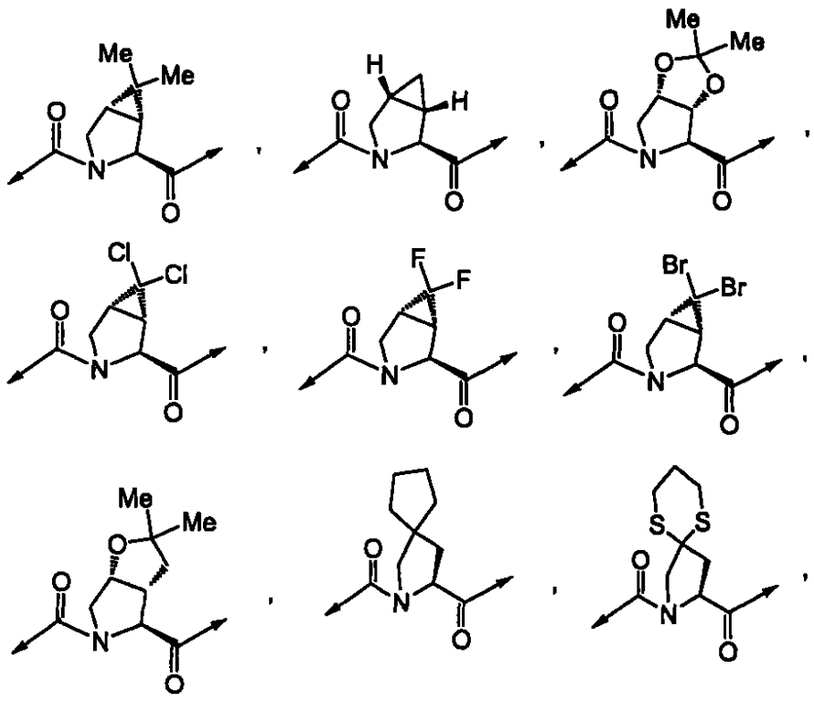


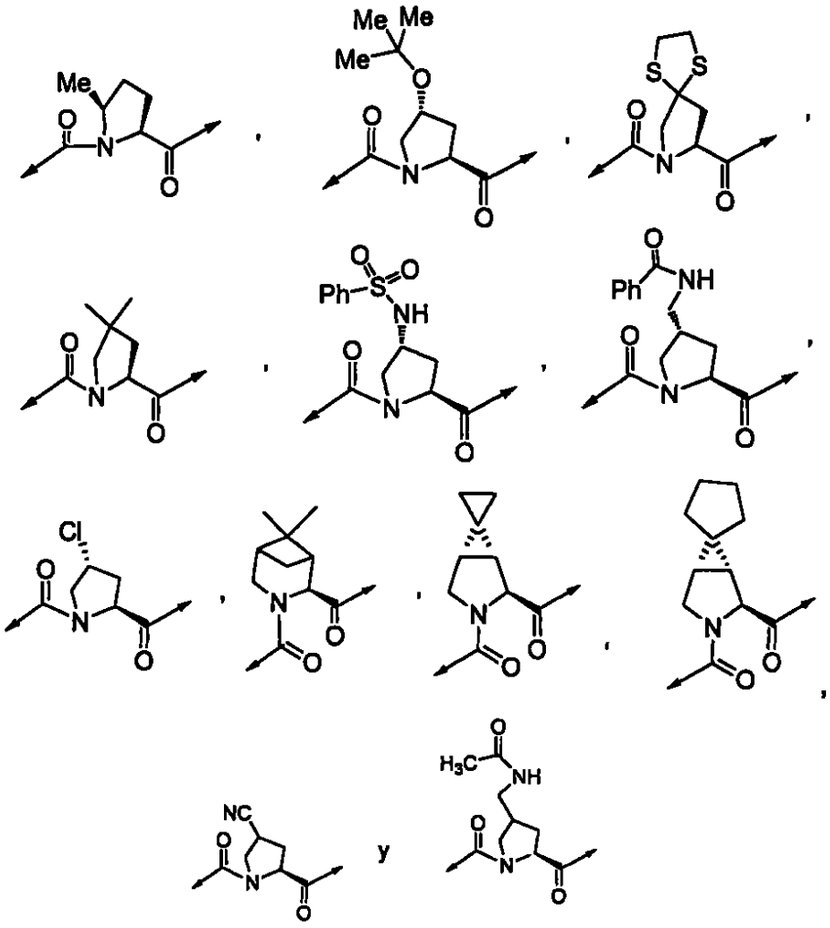


10. El compuesto de la reivindicación 9, en el cual el resto:



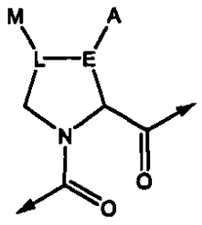
se selecciona de las siguientes estructuras:



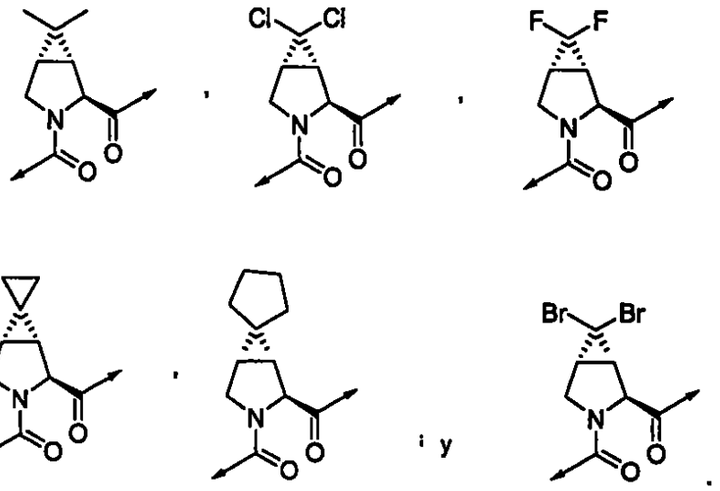


y

11. El compuesto de la reivindicación 10, en el cual el resto:



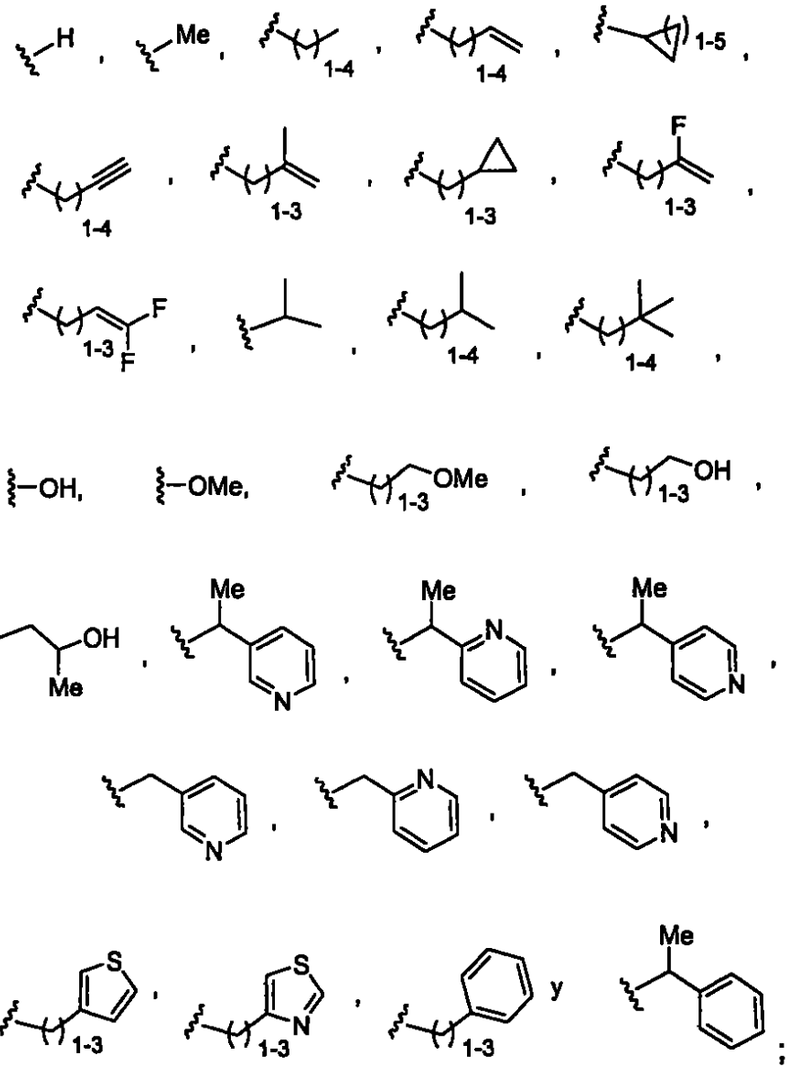
se selecciona de las siguientes estructuras:



; y

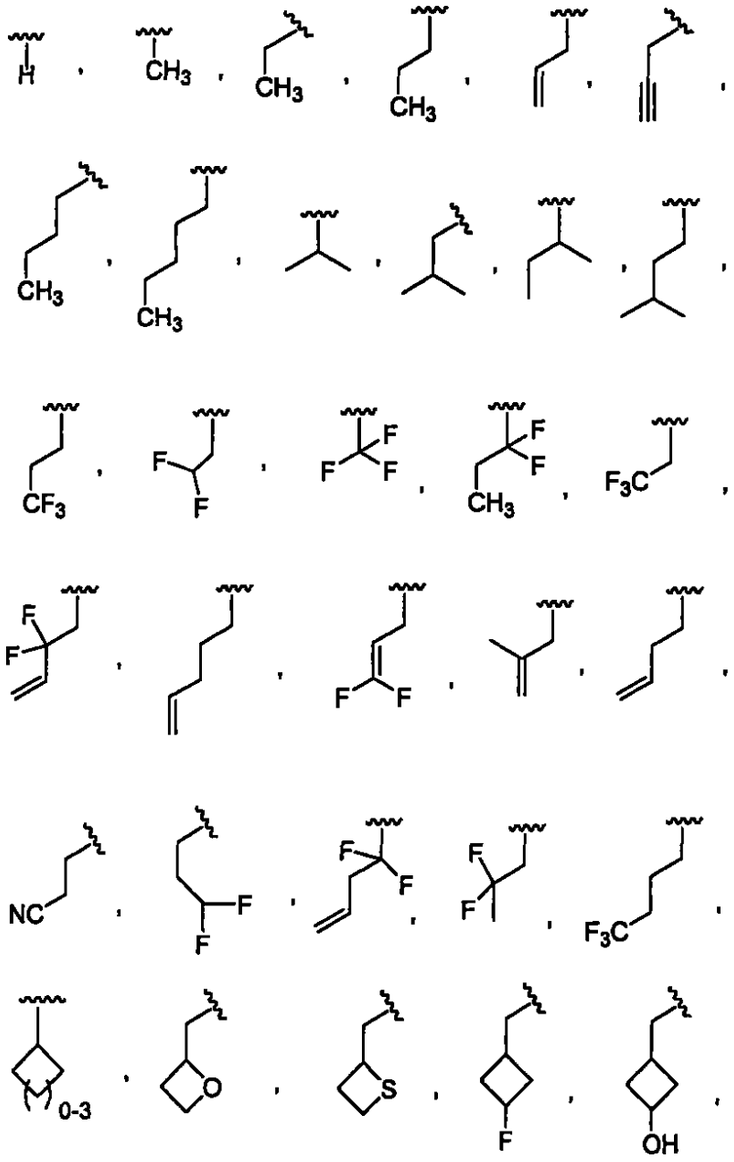
12. El compuesto de la reivindicación 1, en el cual:

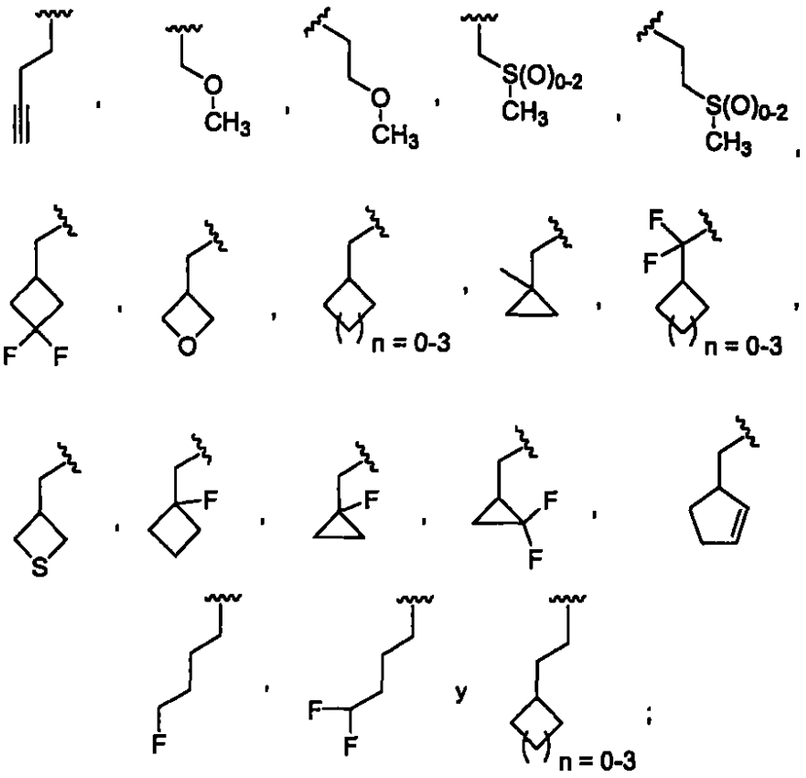
R^1 es NHR^{14}, donde R^{14} se selecciona del grupo formado por:



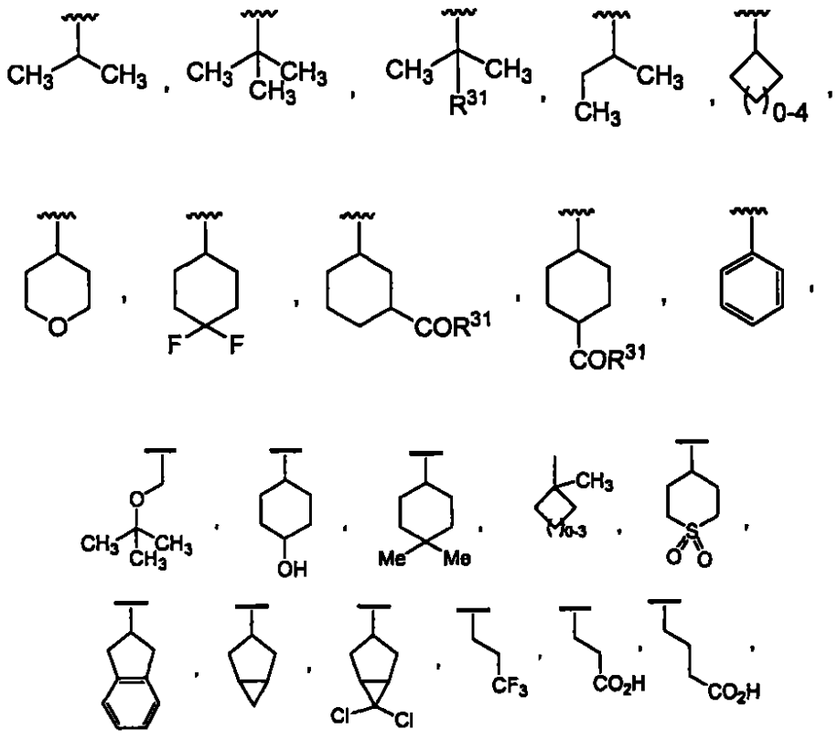
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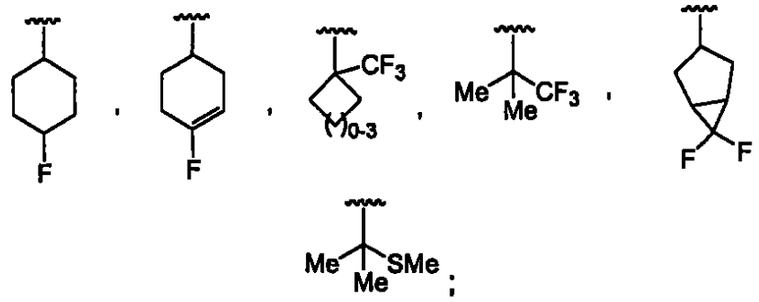
R^2 se selecciona del grupo formado por los siguientes restos:



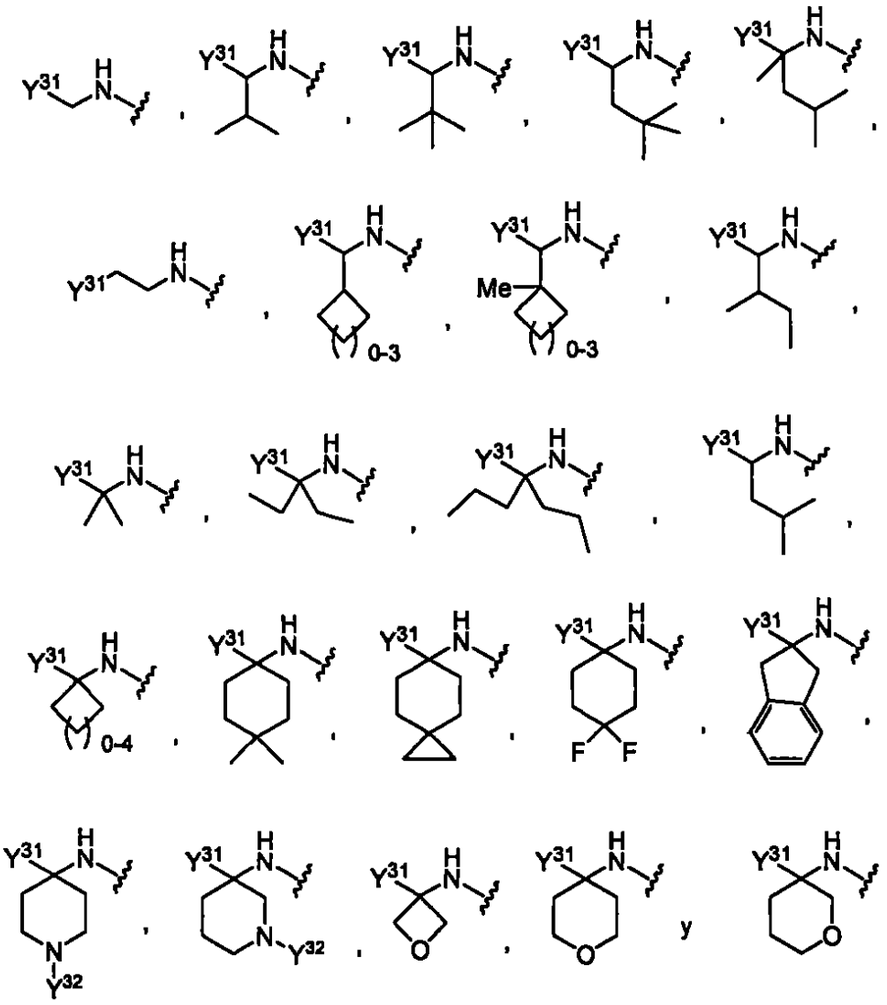


R^3 se selecciona del grupo formado por los siguientes restos:

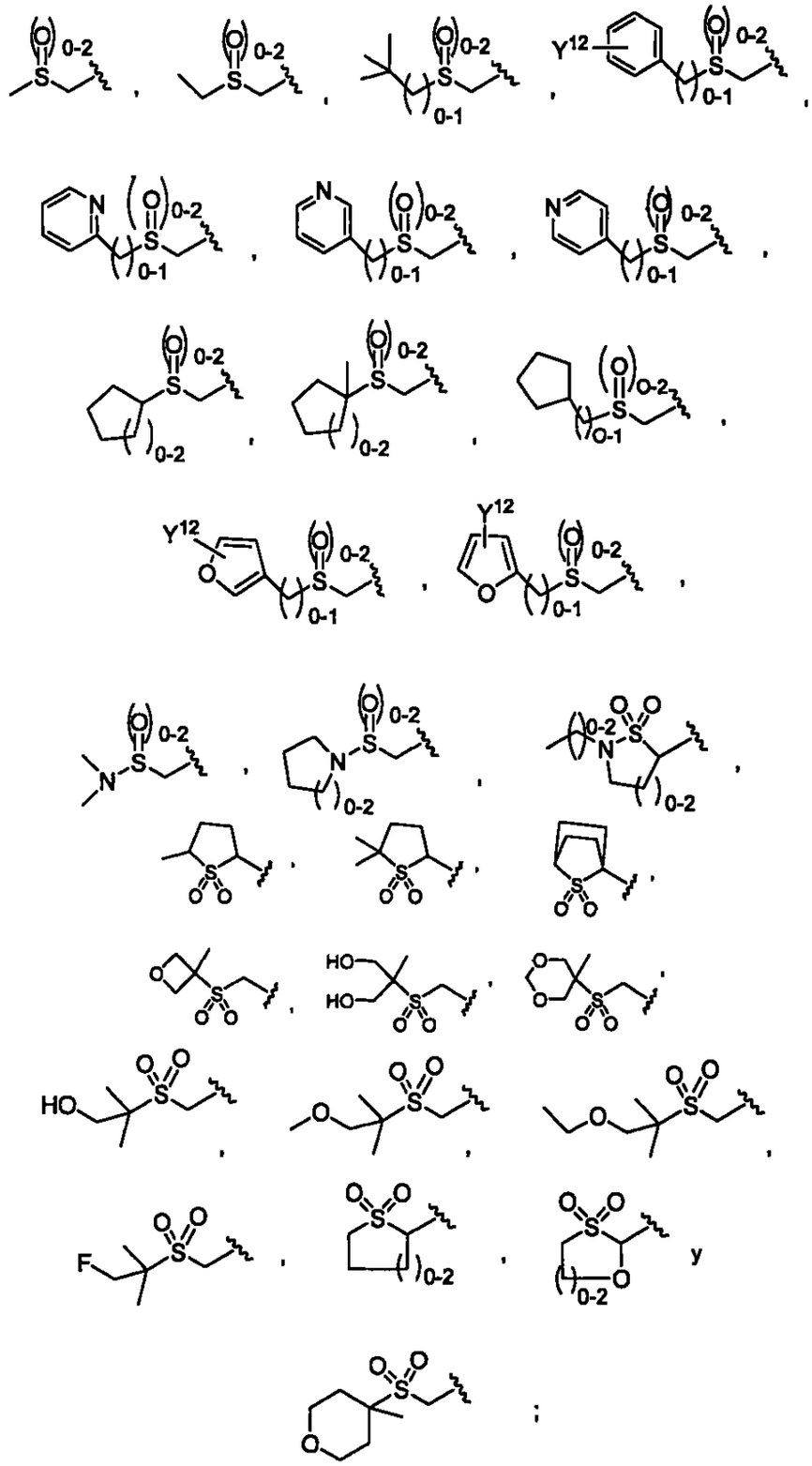




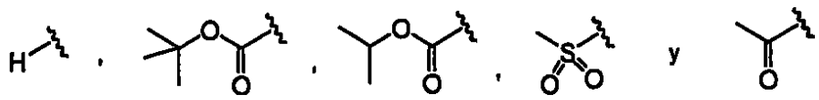
Y se selecciona del grupo formado por:



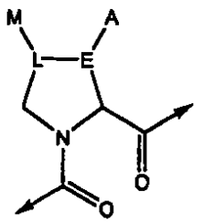
en los cuales Y^{31} se selecciona del grupo formado por:



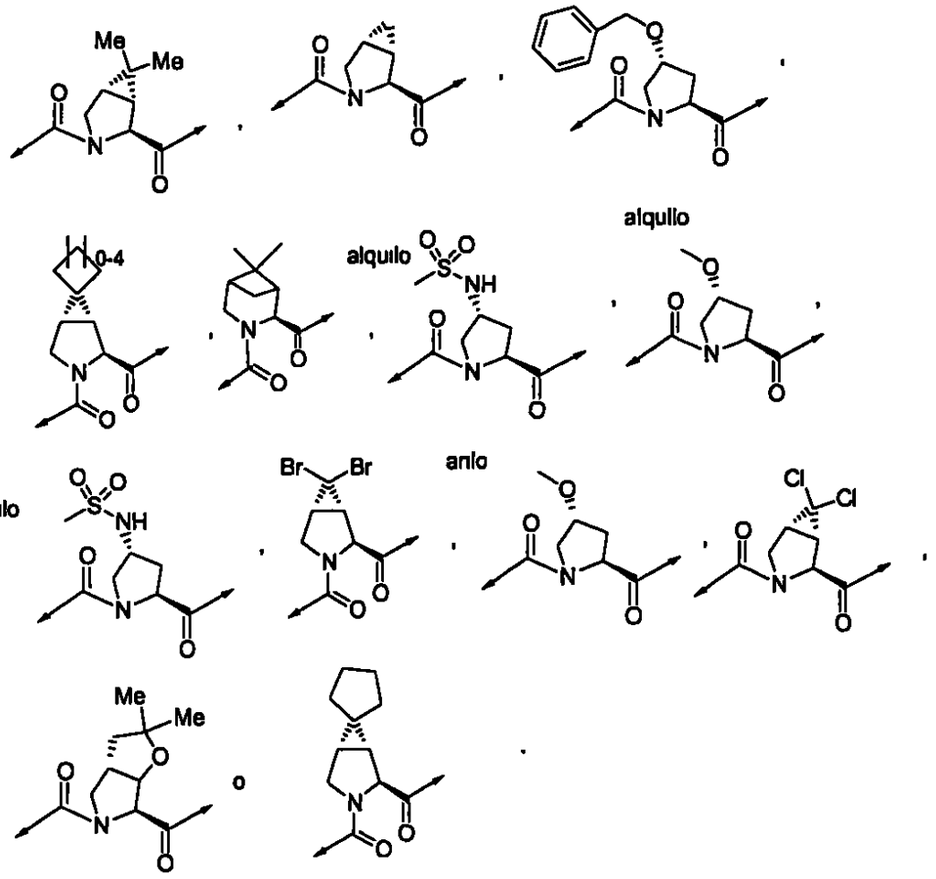
Y^{32} se selecciona del grupo formado por:



e Y^{12} se selecciona del grupo formado por H, CO_2H, CO_2Me, OMe, F, Cl, Br, NH_2, $N(H)S(O_2)CH_3$, $N(H)C(O)CH_3$, NO_2, $S(O_2)NH_2$, CF_3, Me, OH, OCF_3 y $C(O)NH_2$; y el resto:



es:



13. Una composición farmacéutica que comprende como componente activo por lo menos un compuesto de la reivindicación 1.

14. La composición farmacéutica de la reivindicación 13 para usar en el tratamiento de trastornos asociados con el VHC.

15. La composición farmacéutica de la reivindicación 13 que comprende en forma adicional por lo menos un vehículo aceptable desde el punto de vista farmacéutico.

16. La composición farmacéutica de la reivindicación 15, que contiene en forma adicional por lo menos un agente antiviral.

17. La composición farmacéutica de la reivindicación 16, que inclusive contiene en forma adicional por lo menos un interferón.

18. La composición farmacéutica de la reivindicación 17, en la cual dicho por lo menos un agente antiviral es ribavirin y dicho por lo menos un interferón es α-interferón o interferón pegilado.

19. Un método para tratar trastornos asociados con el VHC, comprendiendo dicho método administrar a un paciente que necesita de dicho tratamiento una composición farmacéutica que comprende cantidades terapéuticamente efectivas de por lo menos un compuesto de la reivindicación 1.

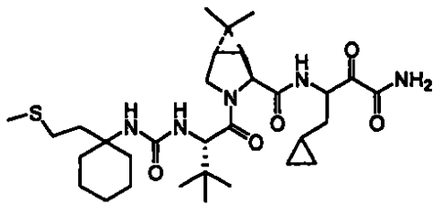
20. El método de la reivindicación19, en el cual dicha administración es oral o subcutánea.

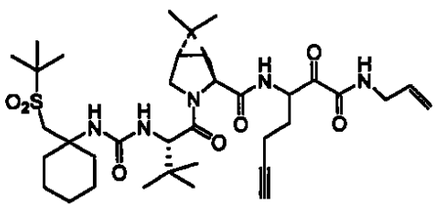
21. Un método para preparar una composición farmacéutica para tratar los trastornos asociados con el VHC, comprendiendo dicho método llevar a contacto íntimo por lo menos un compuesto de la reivindicación 1 y por lo menos un vehículo aceptable desde el punto de vista farmacéutico.

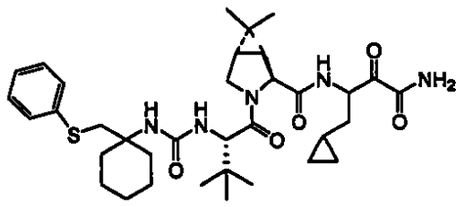
22. Un compuesto que presenta actividad inhibidora de la proteasa del VHC, o enantiómeros, estereoisómeros, rotámeros, tautómeros y racematos de dicho compuesto, o una sal o solvato o éster aceptables desde el punto de vista farmacéutico de dicho compuesto, seleccionándose dicho compuesto de los compuestos de las estructuras agrupadas a continuación:

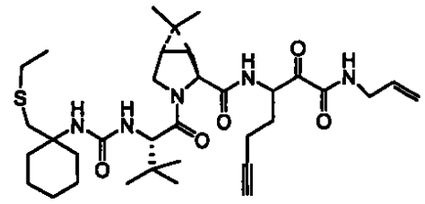
1395

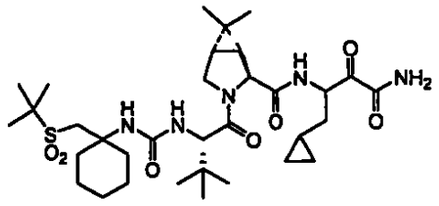
1378

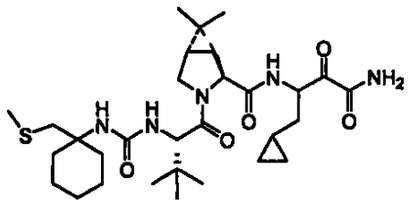


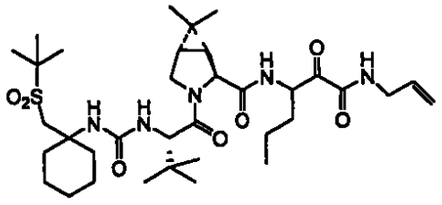


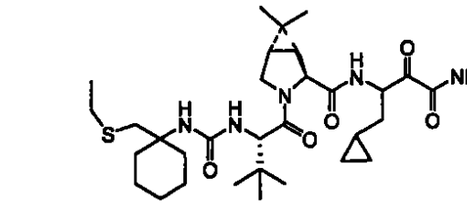


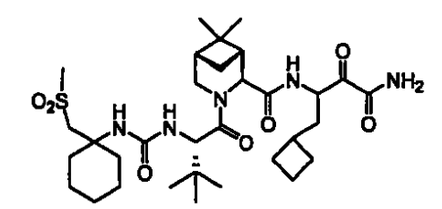


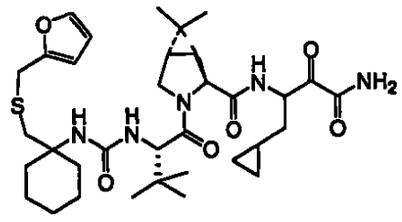


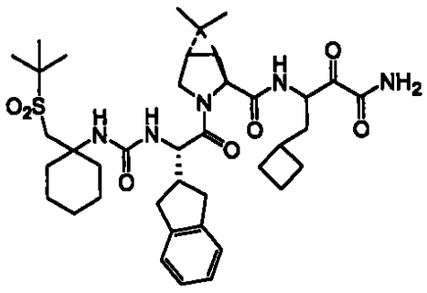


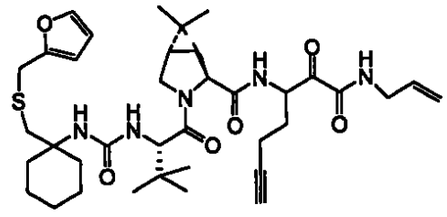


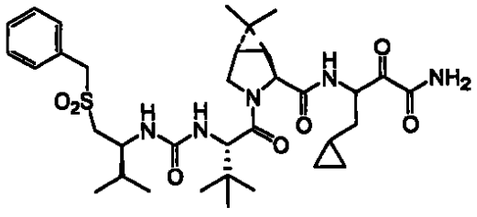


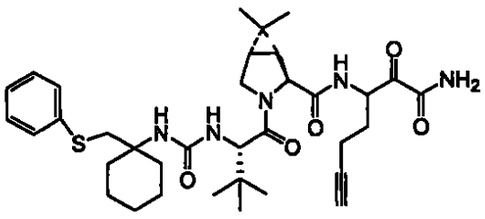


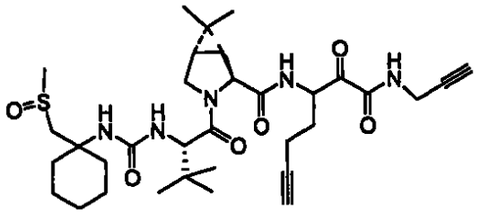


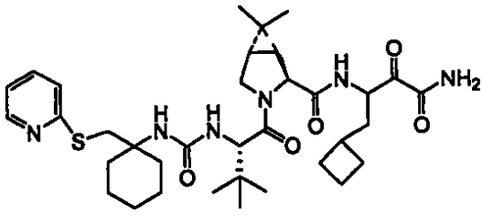


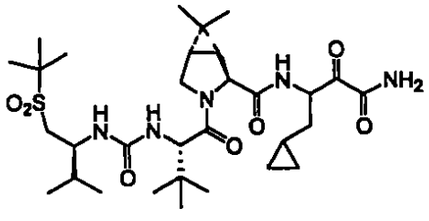


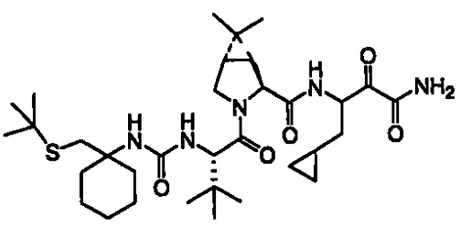


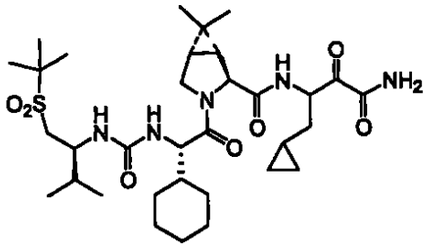


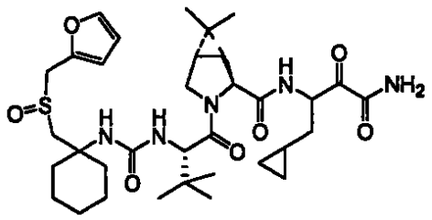


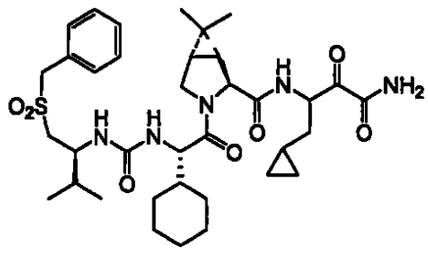


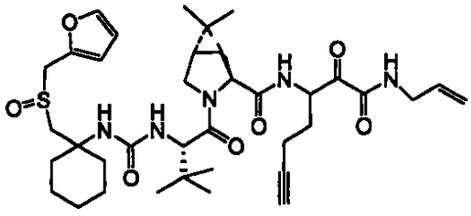


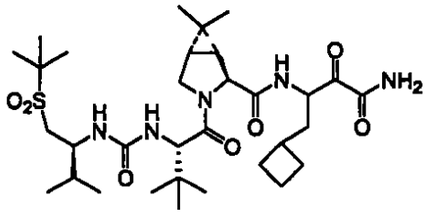


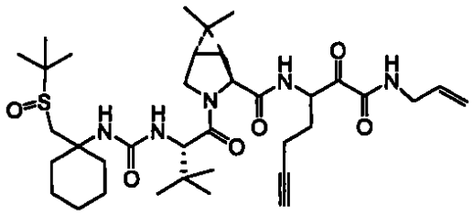


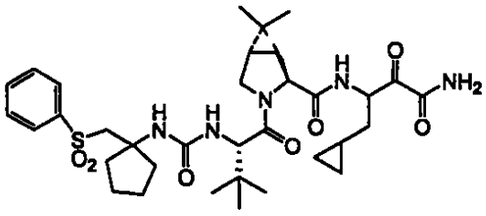


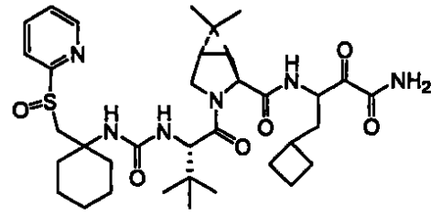


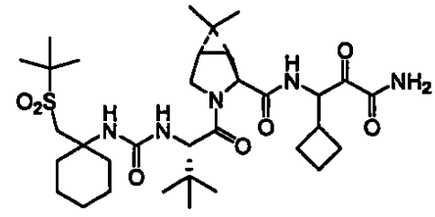


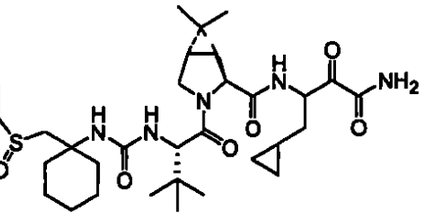


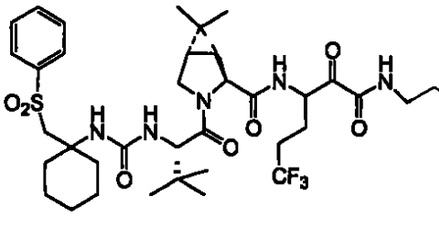


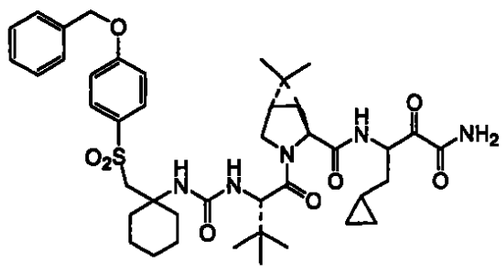


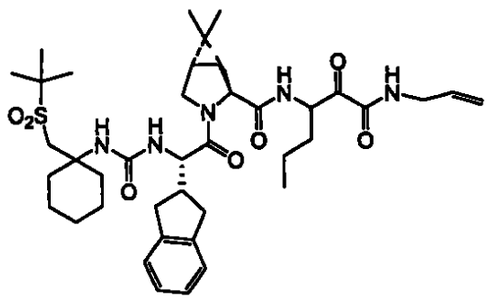


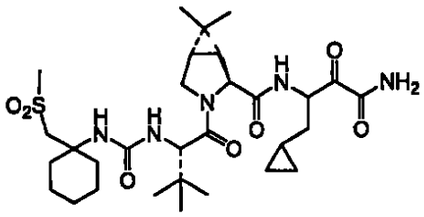


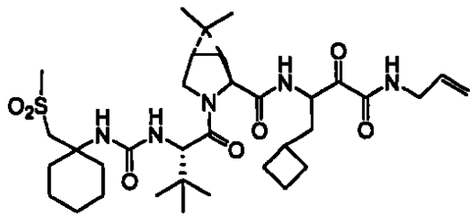


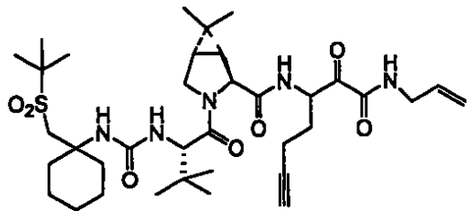


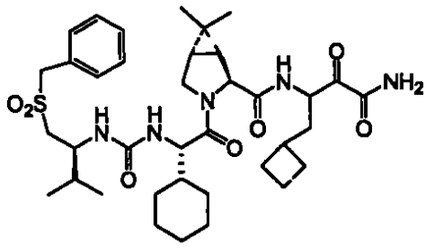


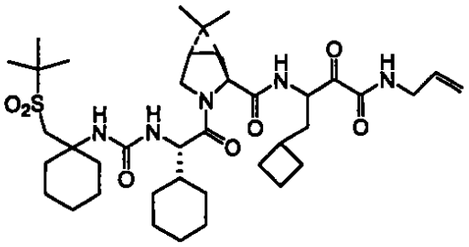


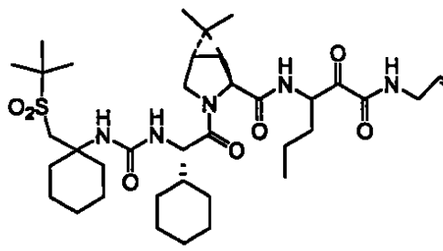


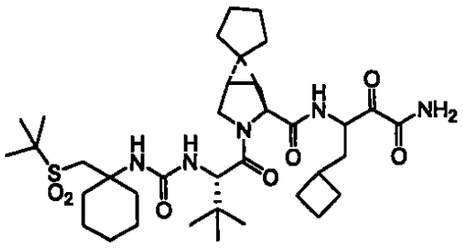


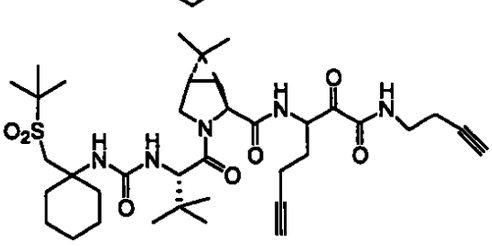


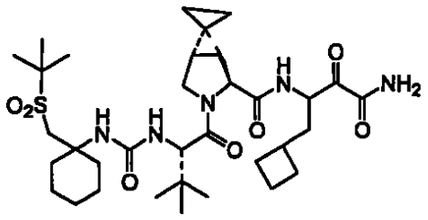


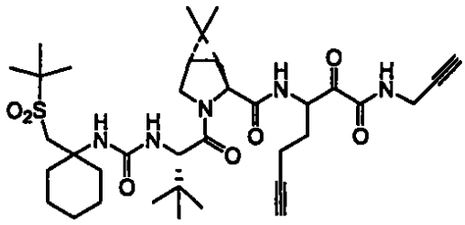


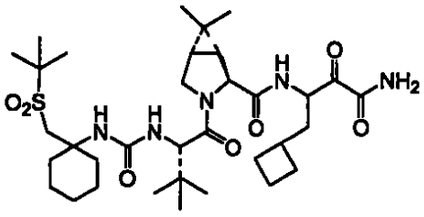


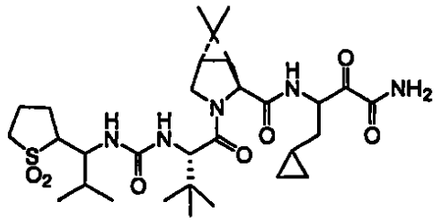


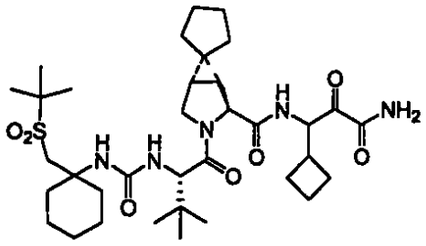


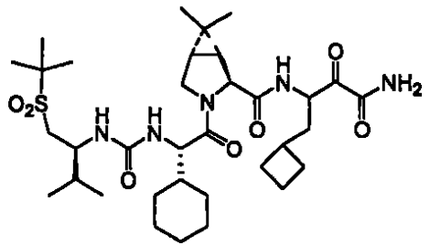


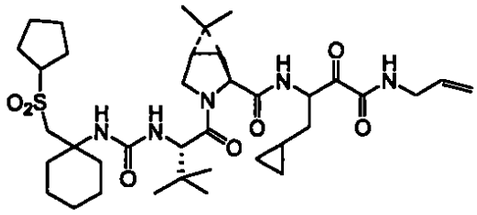


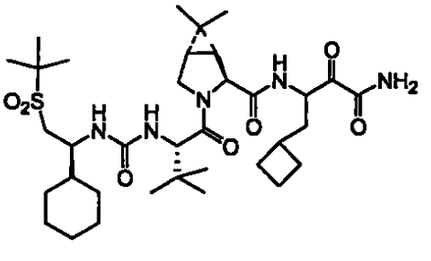


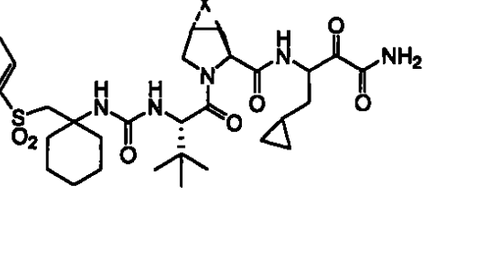


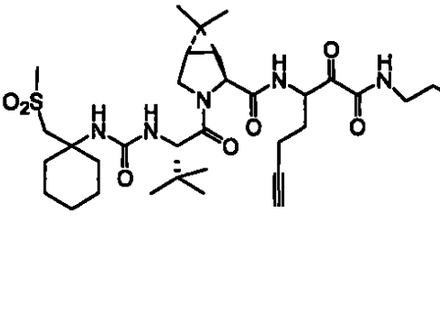


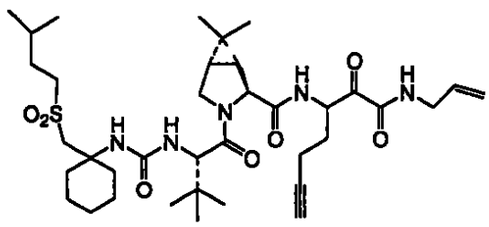


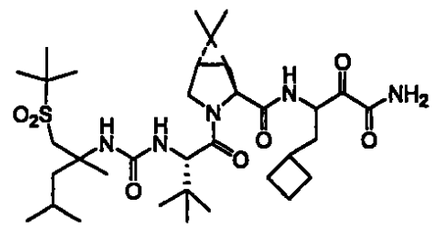


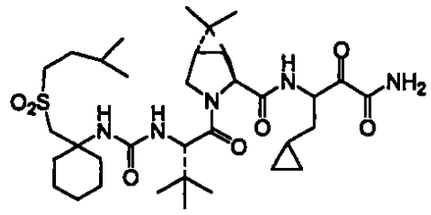


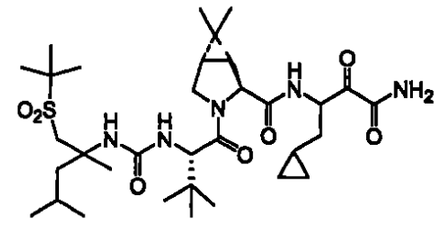


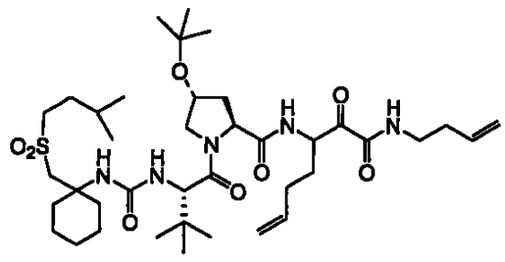


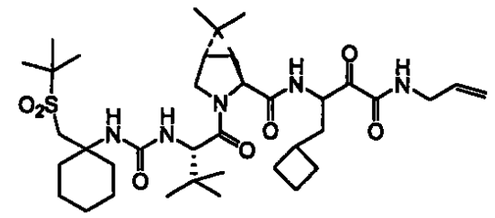


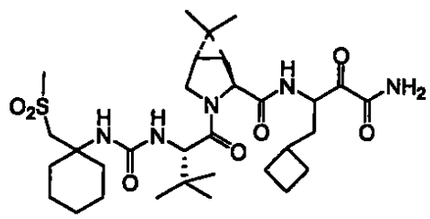


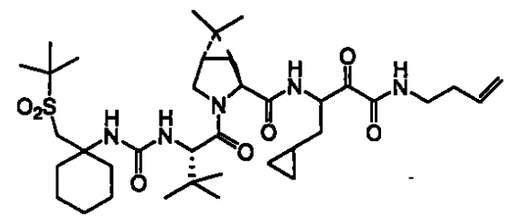


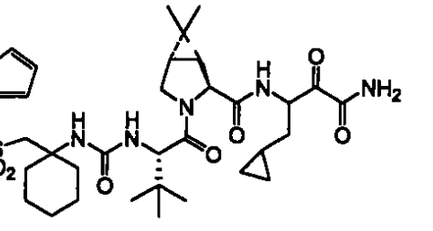


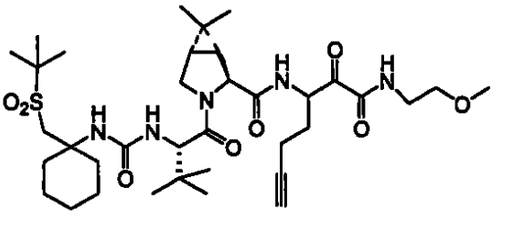


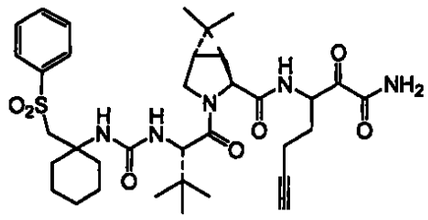


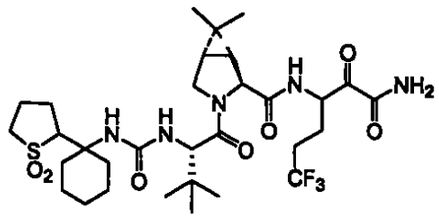


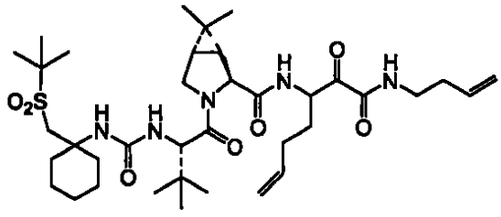


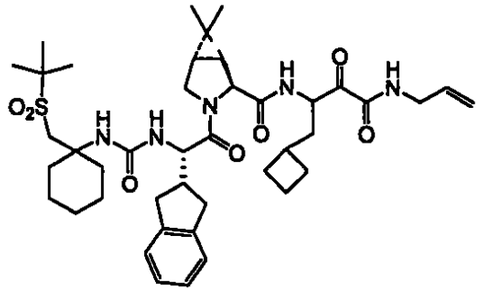


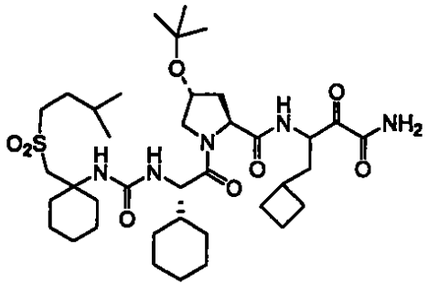


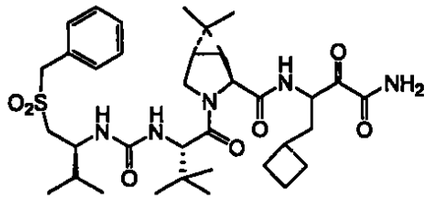


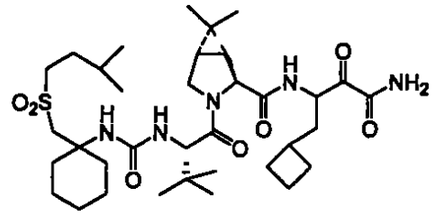


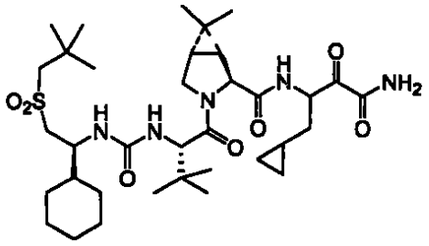


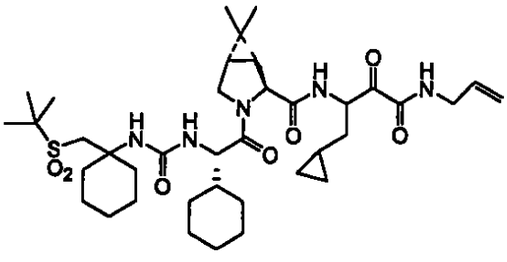


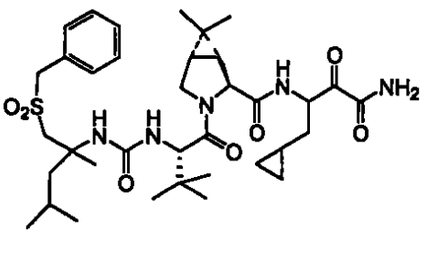


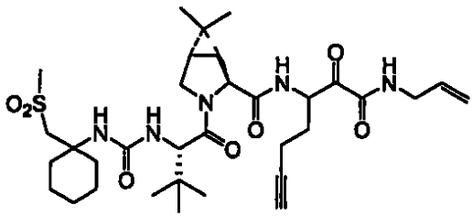


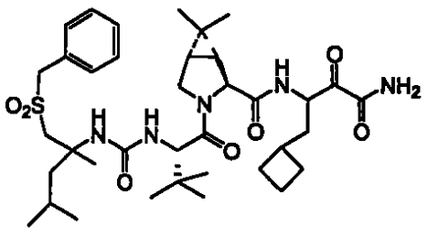


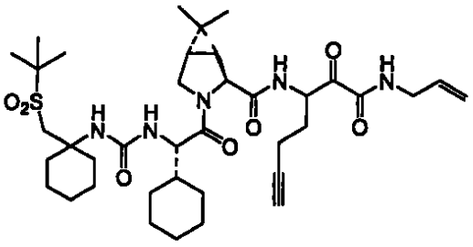


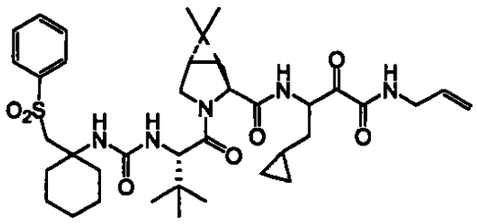


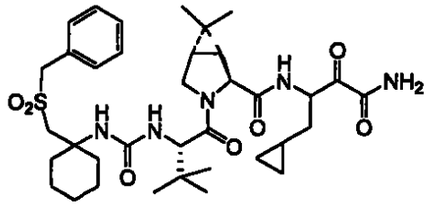


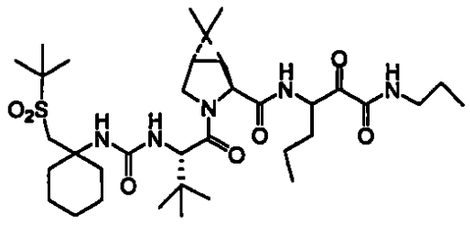


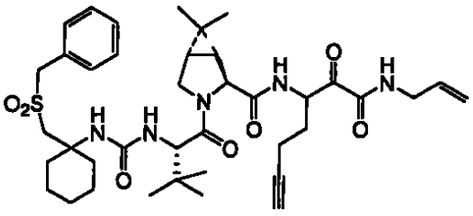


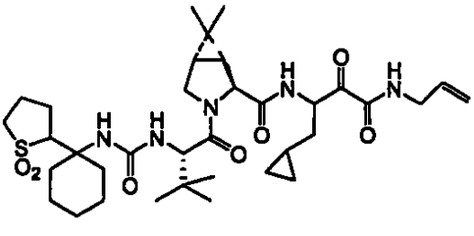


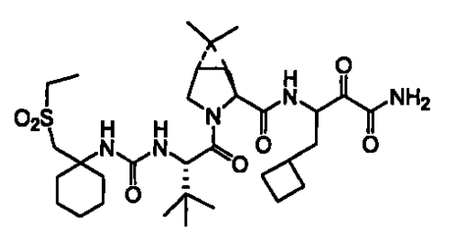


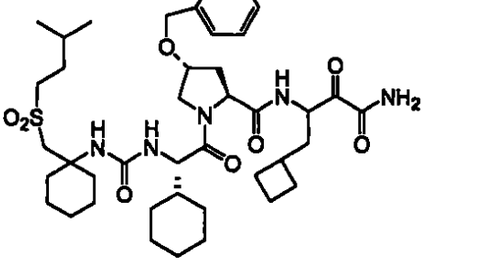


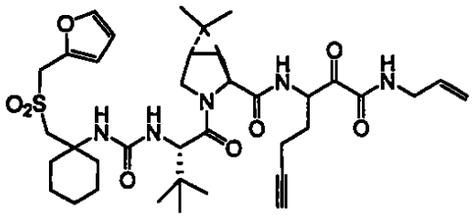


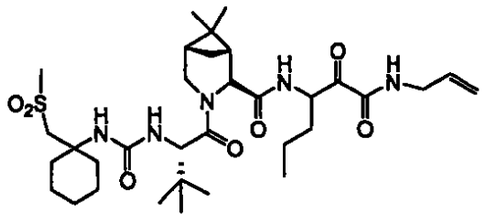


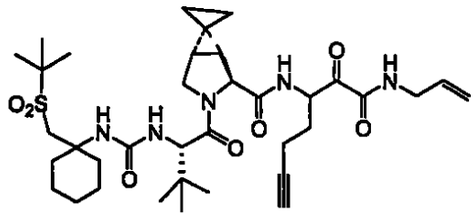


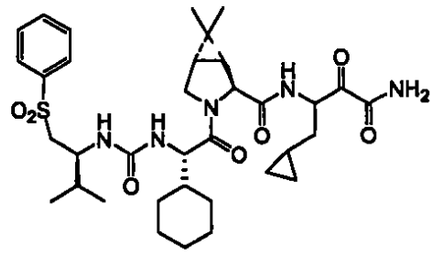


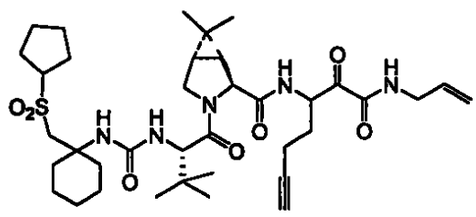


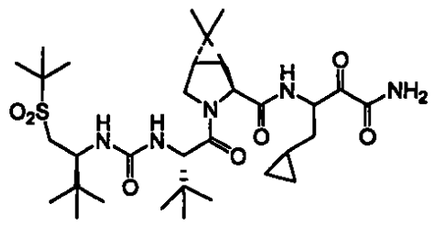


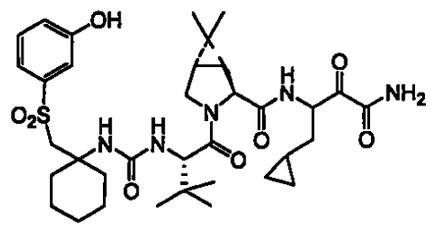


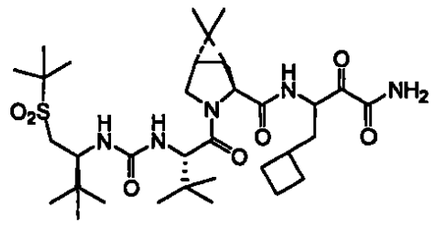


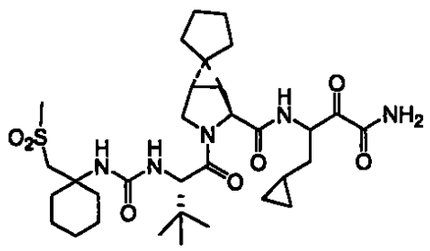


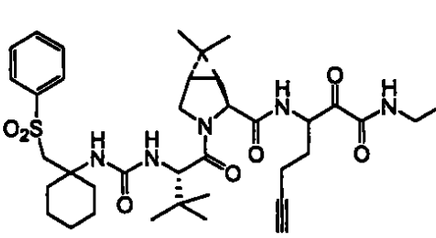


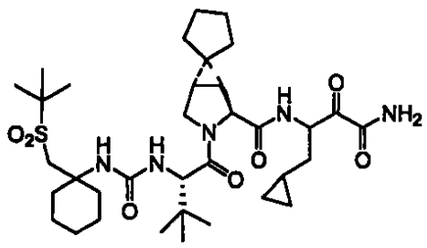


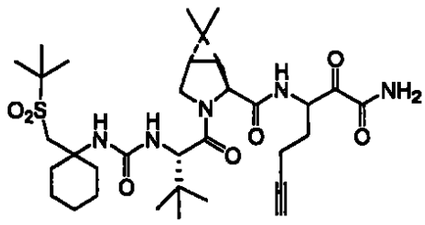


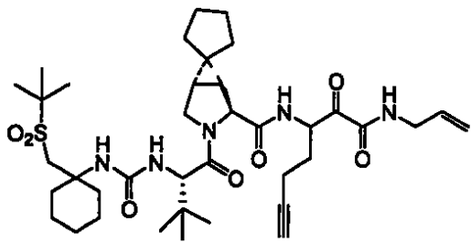


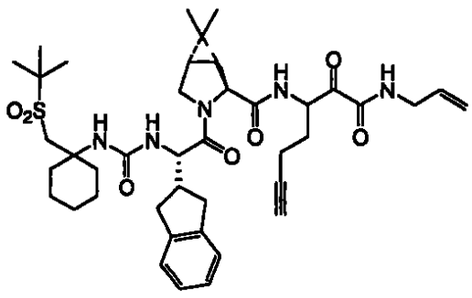


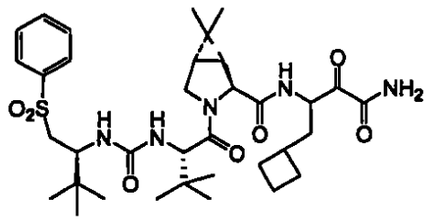


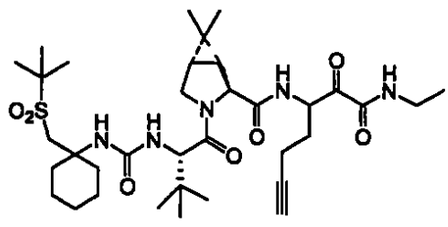


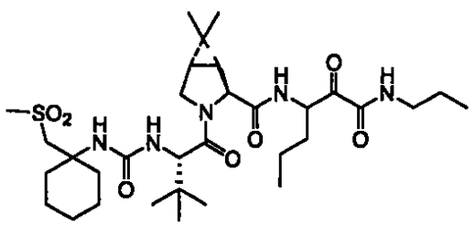


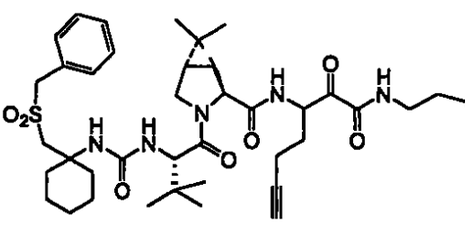


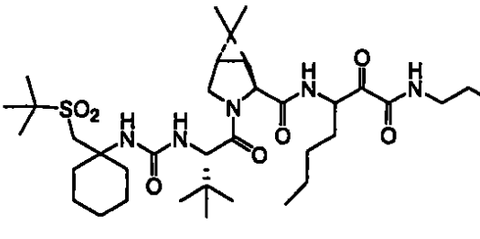


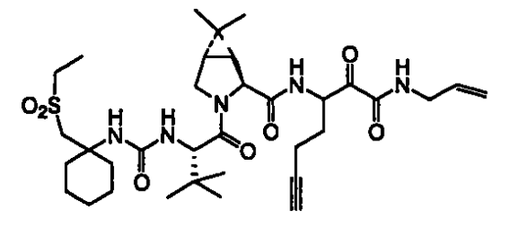


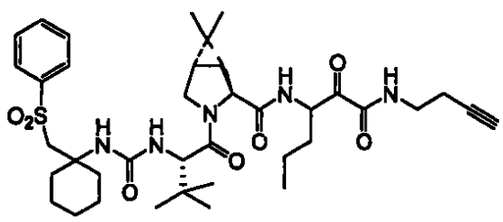


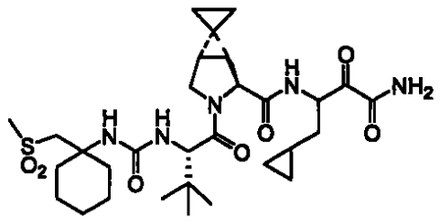


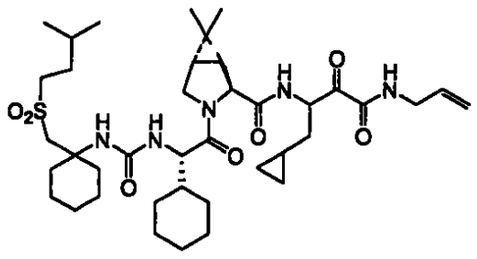


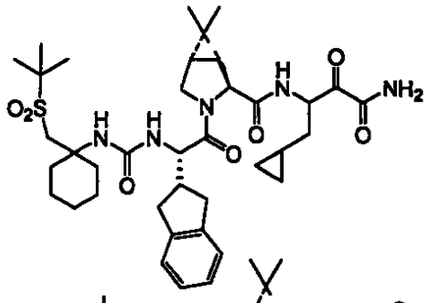


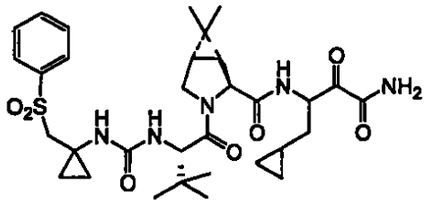


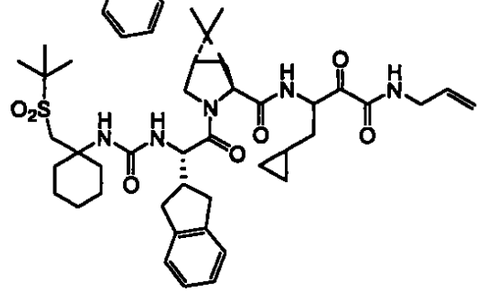


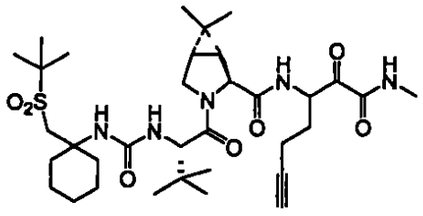


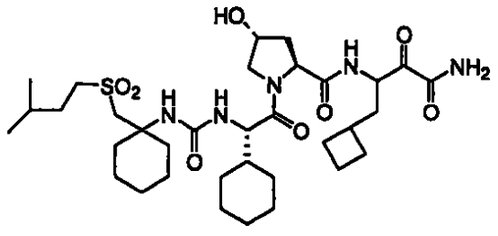


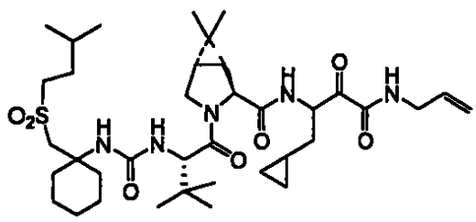


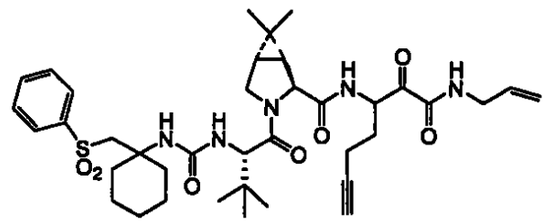


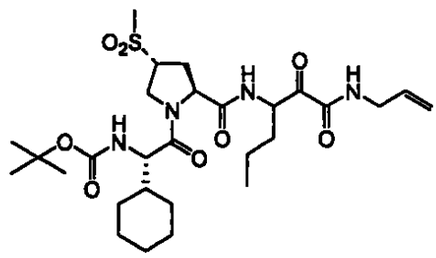


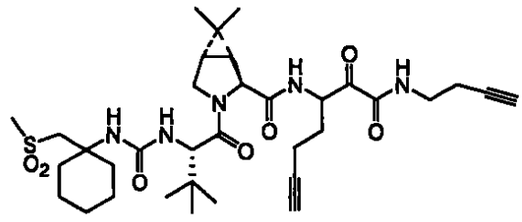


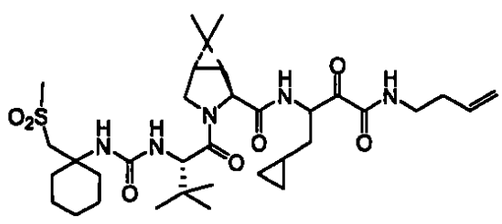


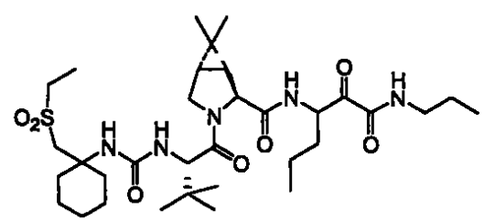


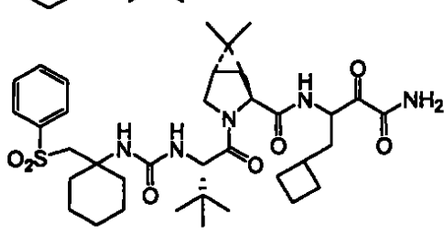


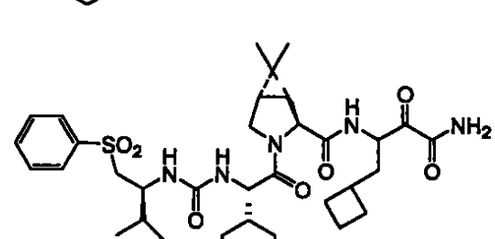


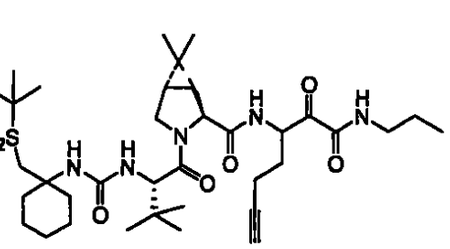


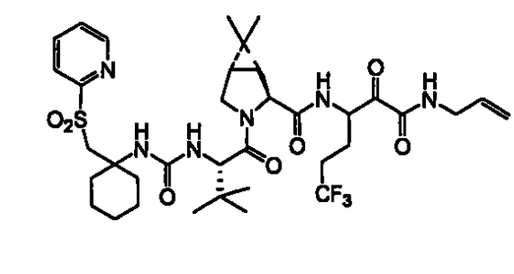


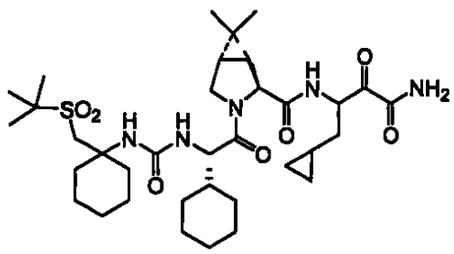


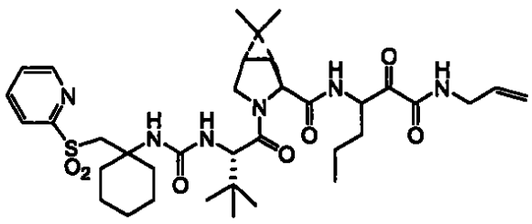


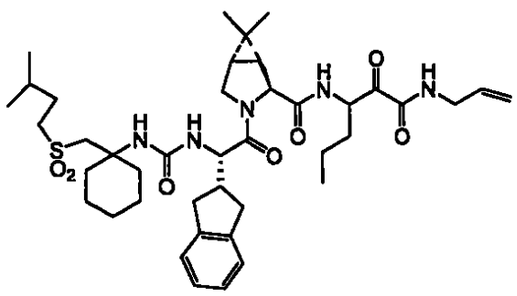


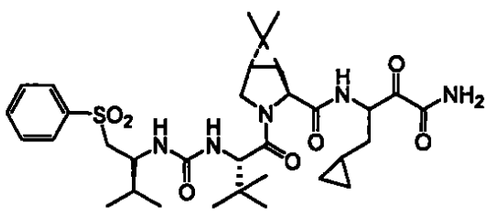


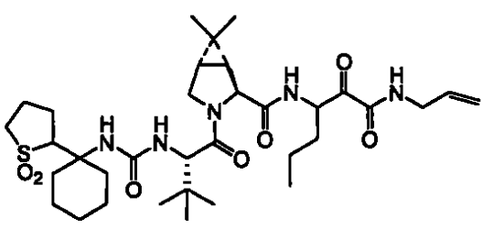


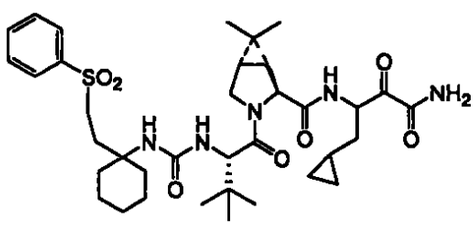


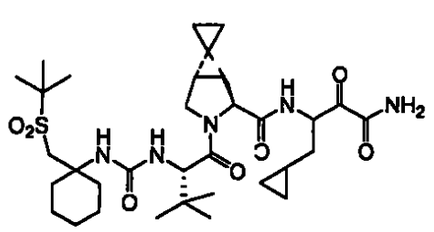


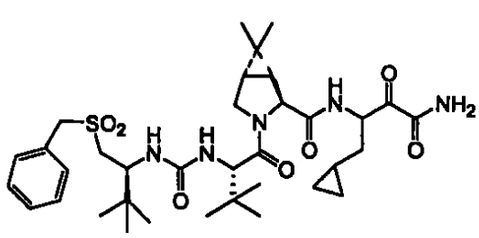


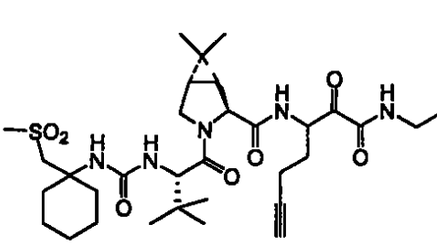


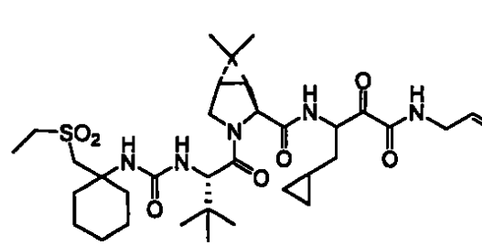


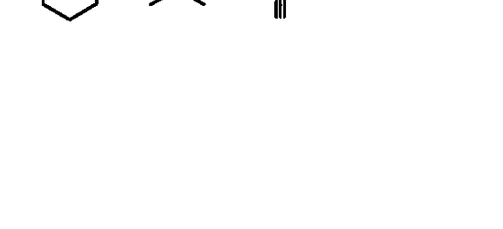


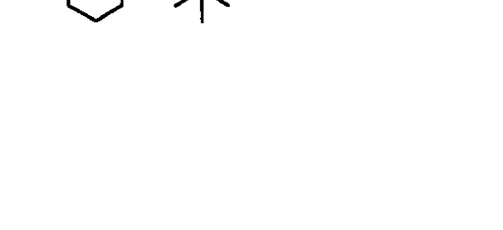


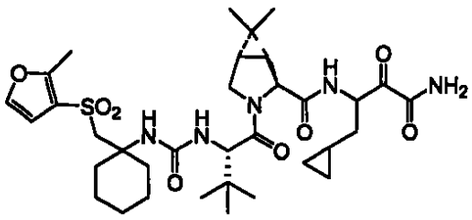


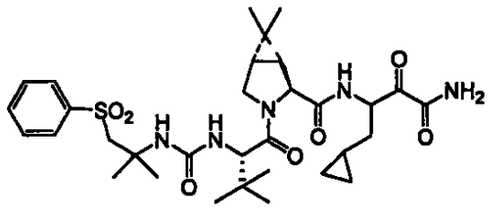


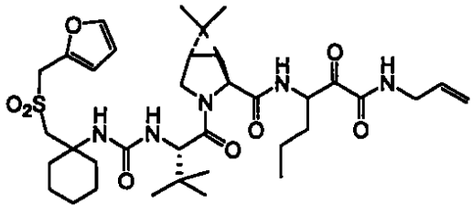


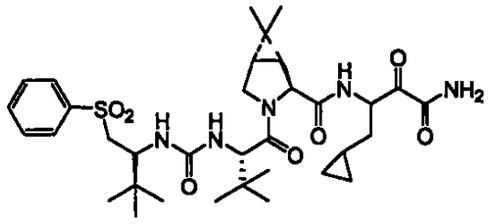


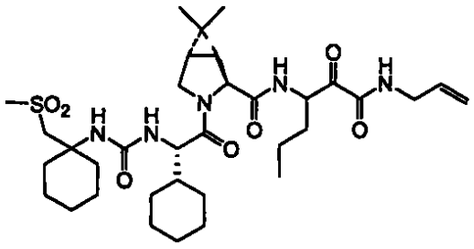


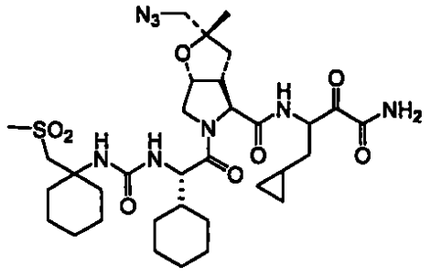


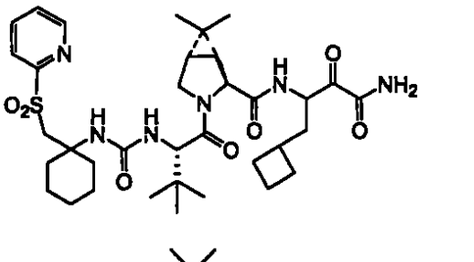


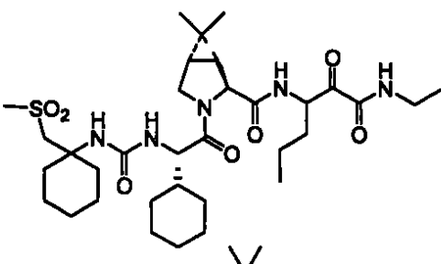


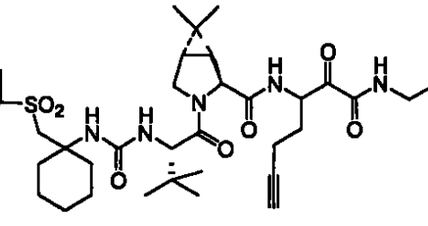


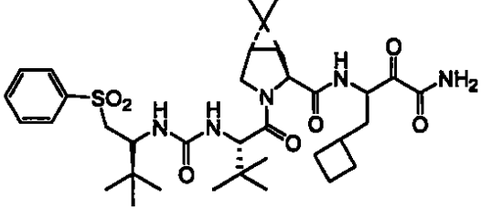


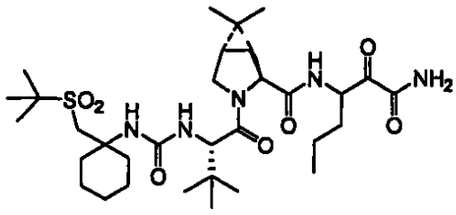


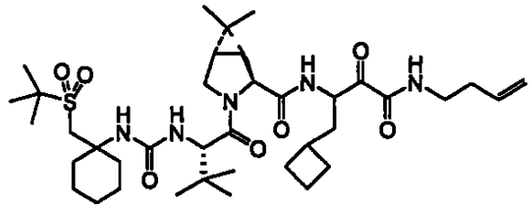


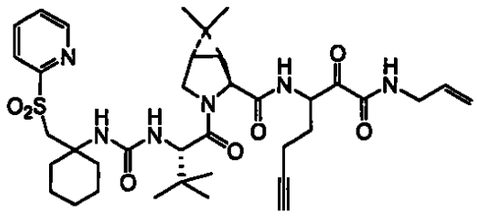


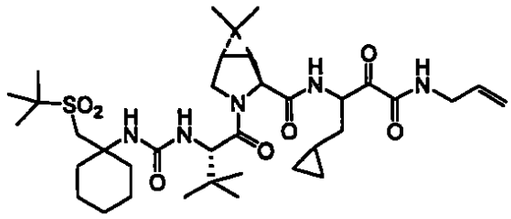


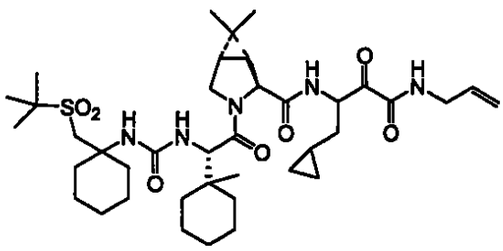


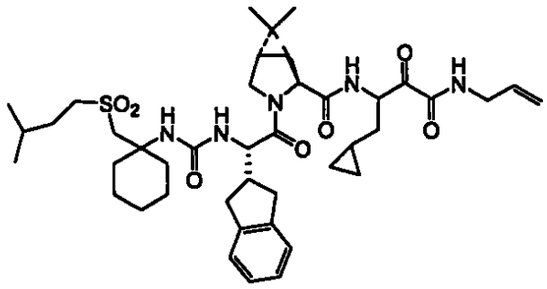


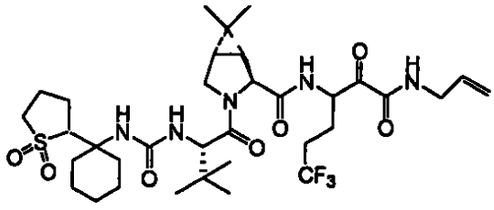


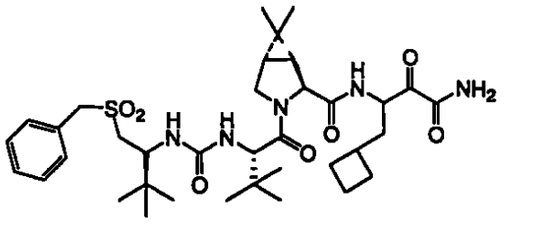


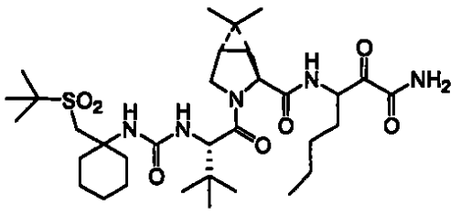


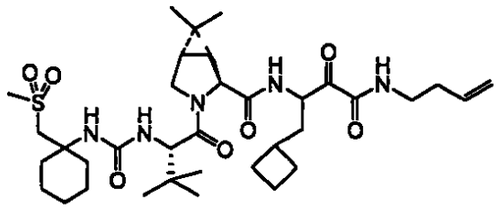


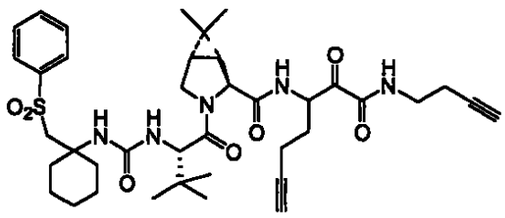


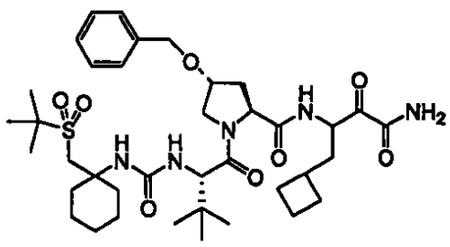


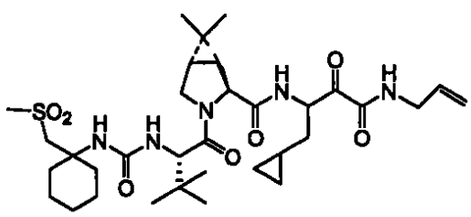


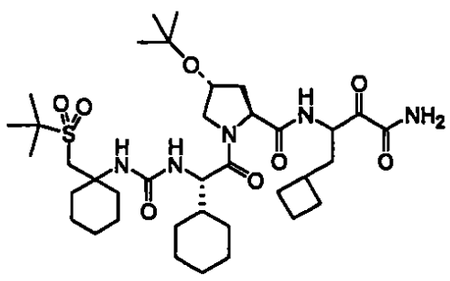


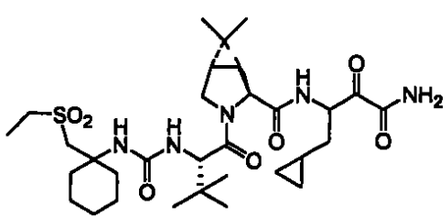


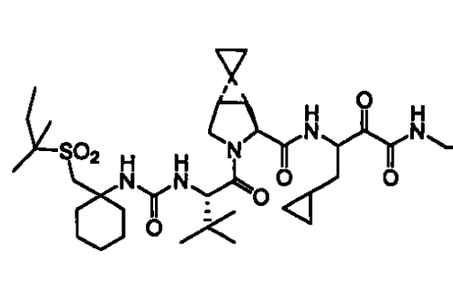


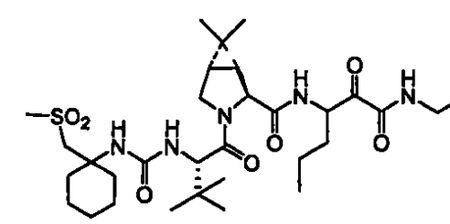


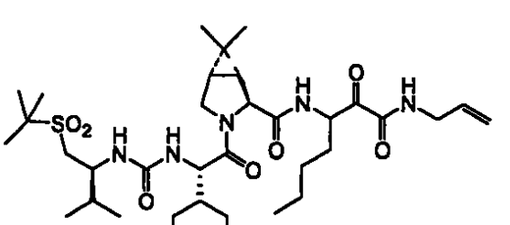


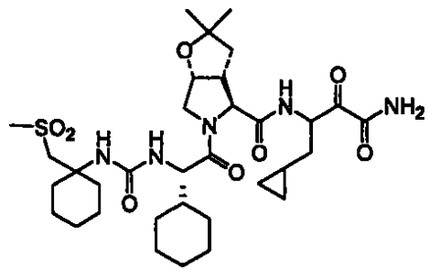


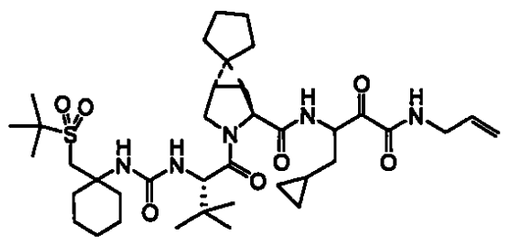


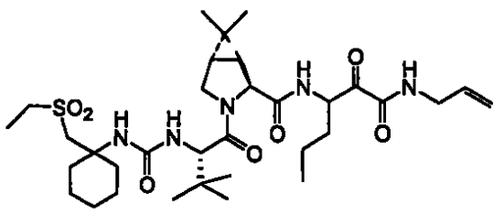


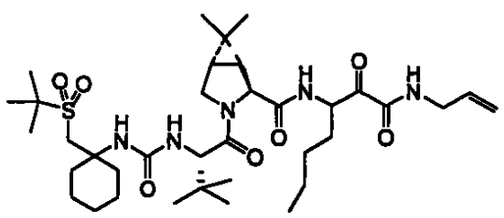


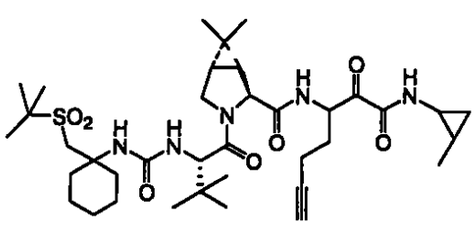


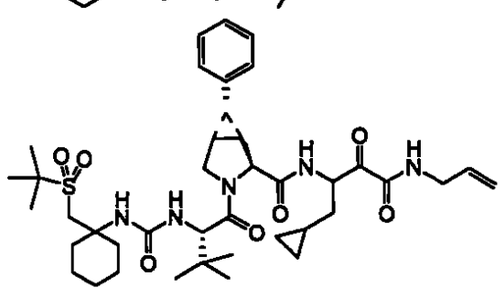


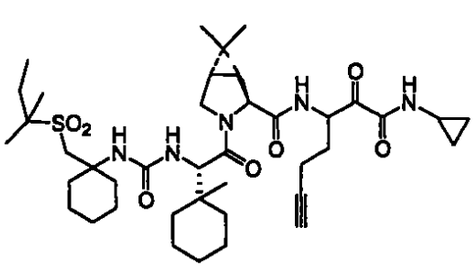


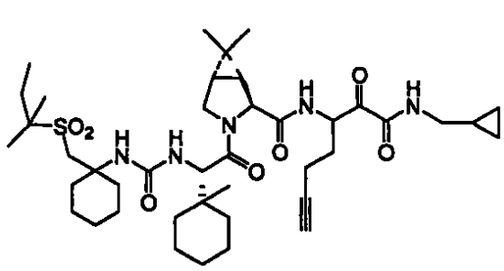


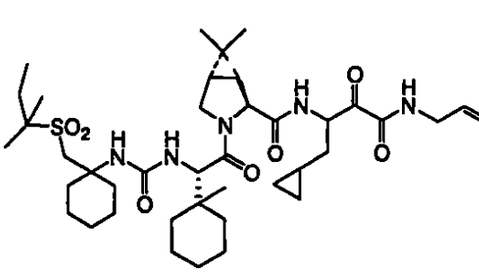


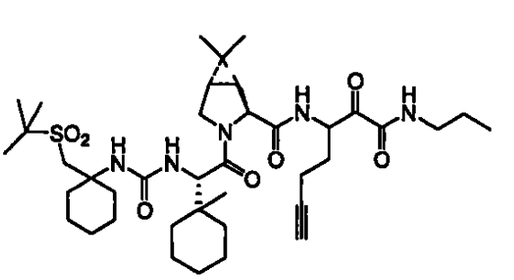


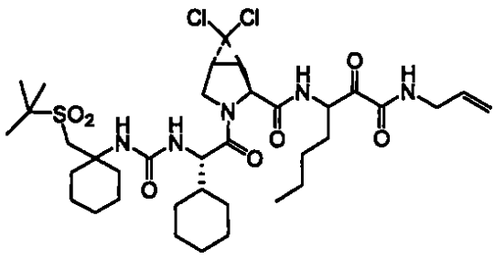


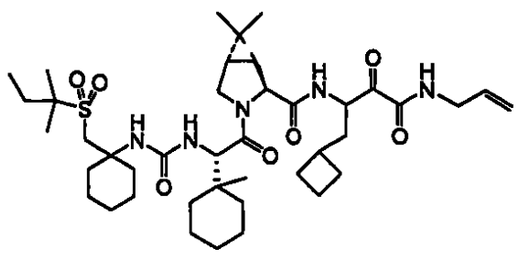


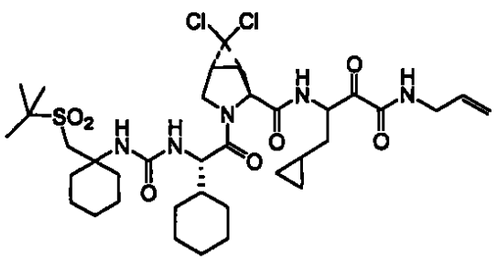


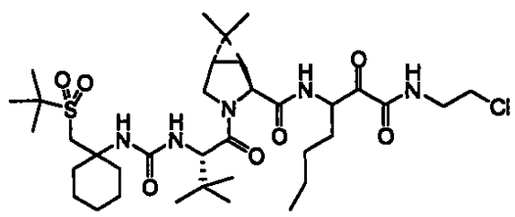


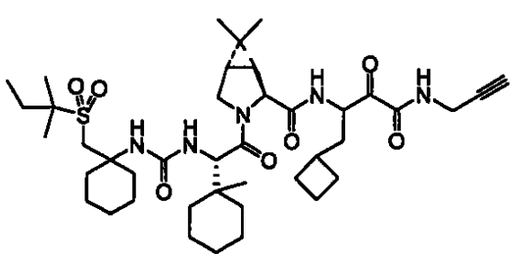


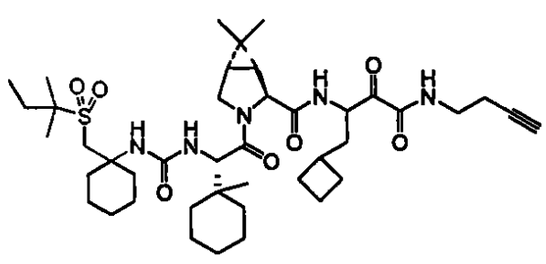


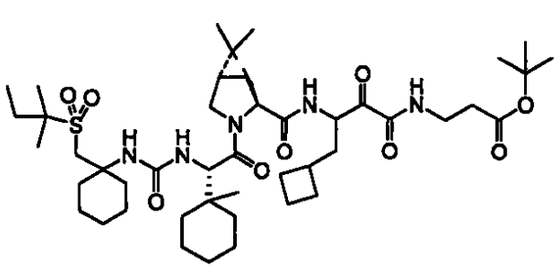


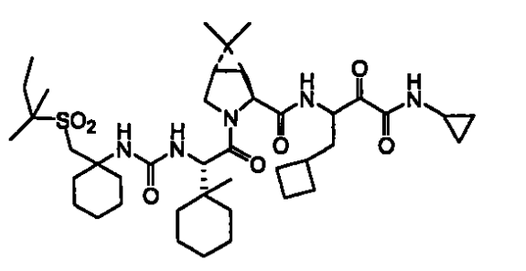


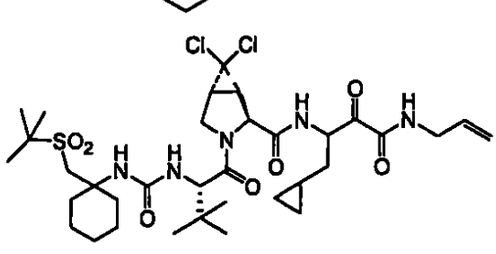


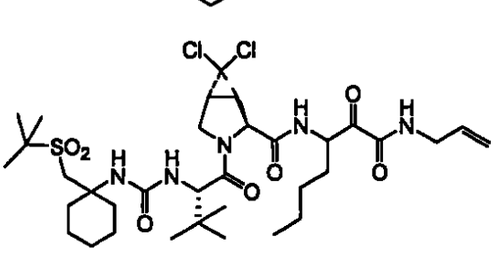






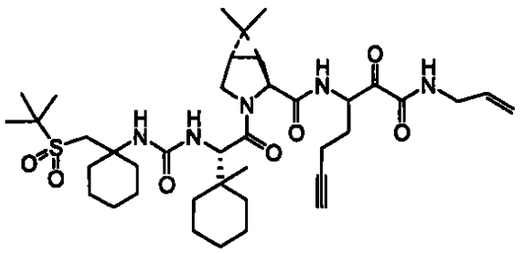


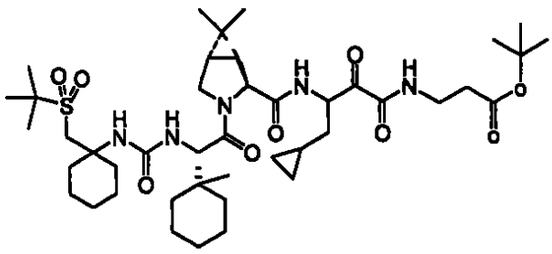


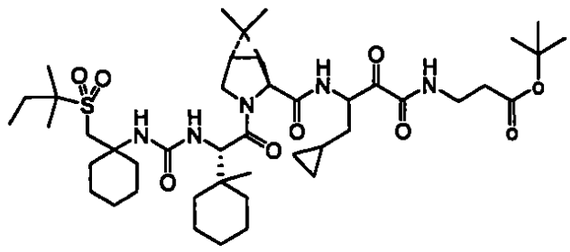


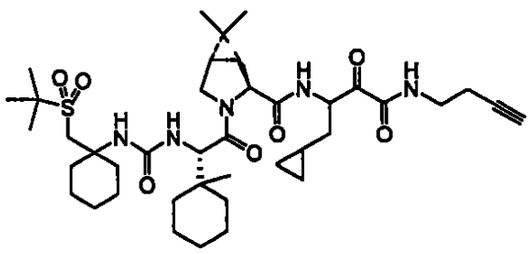
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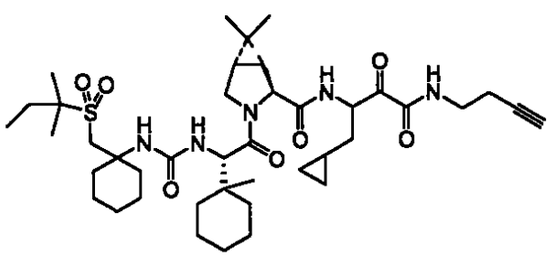
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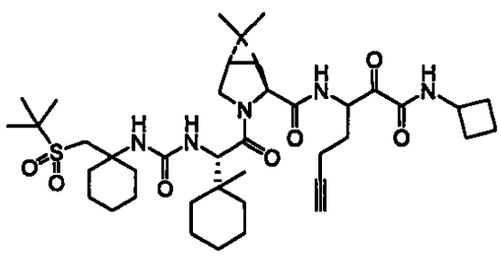


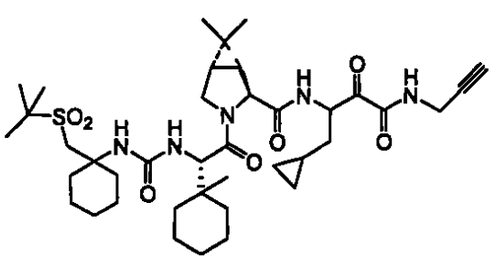


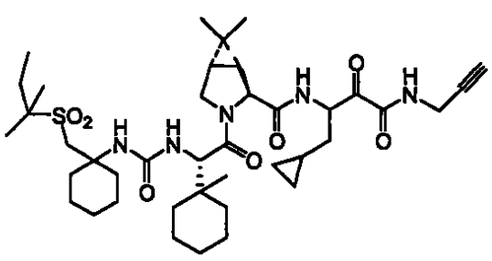


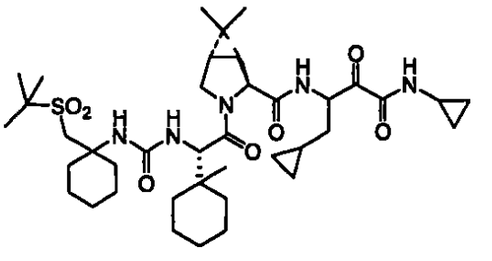


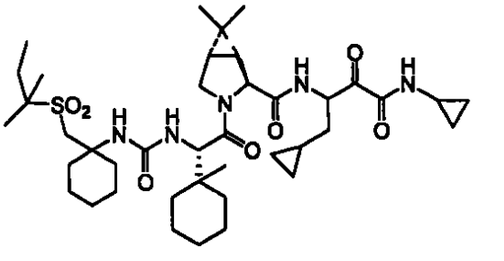


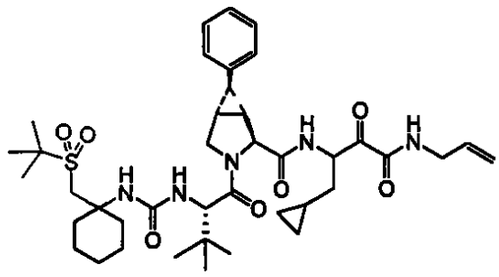


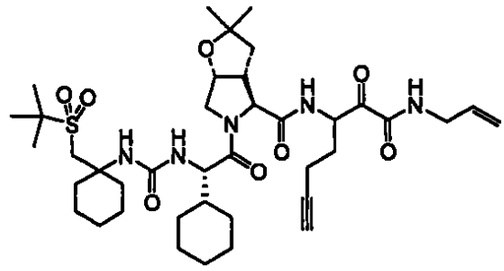


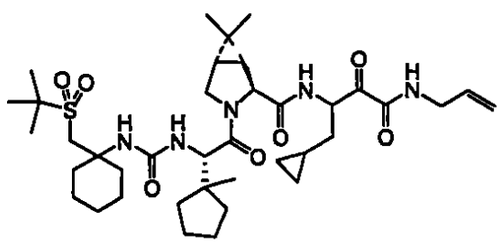


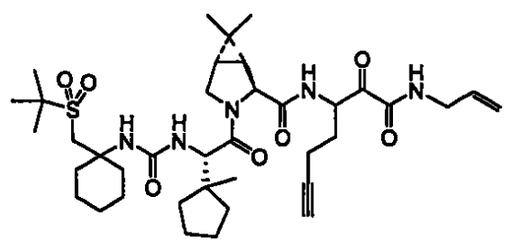


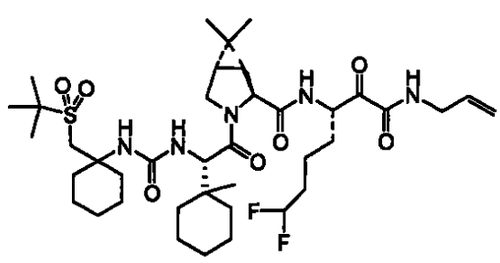


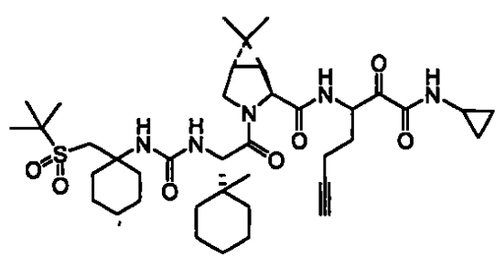


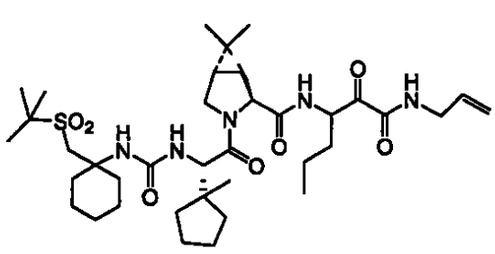


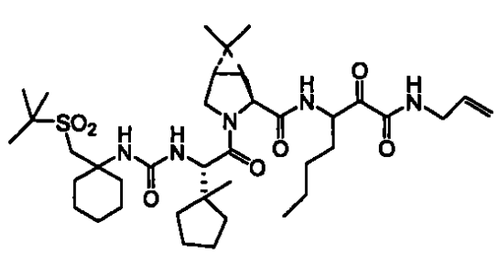


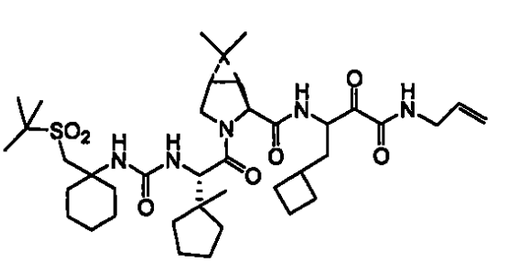


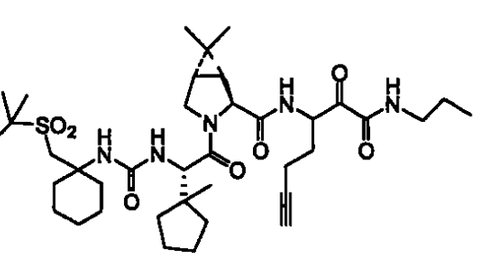




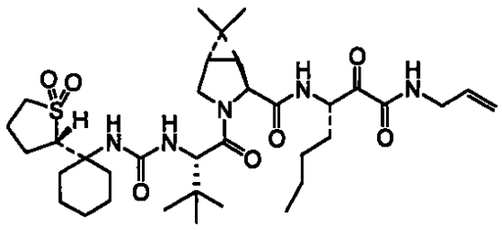


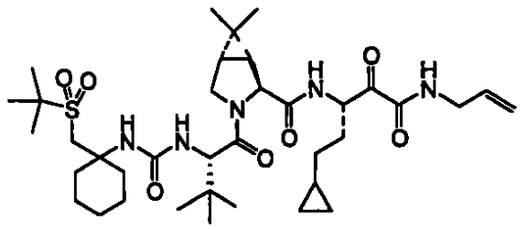


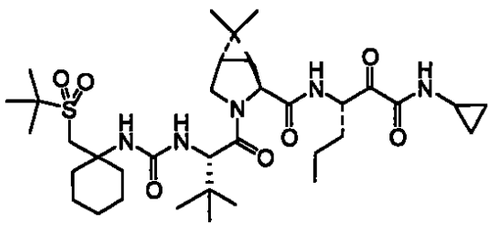


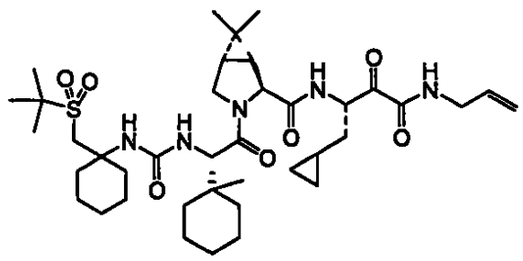


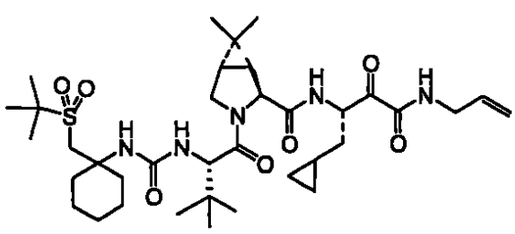
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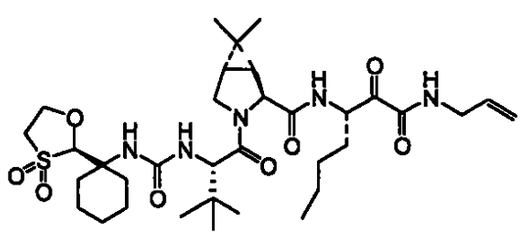


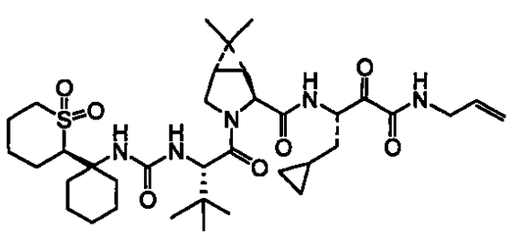


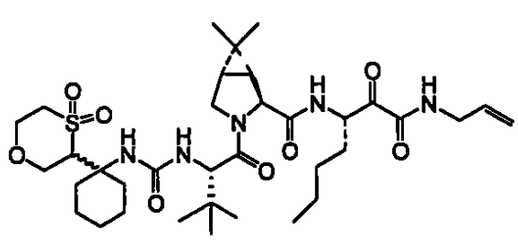


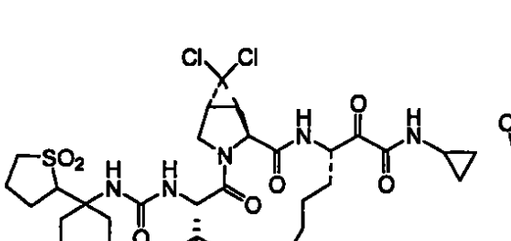


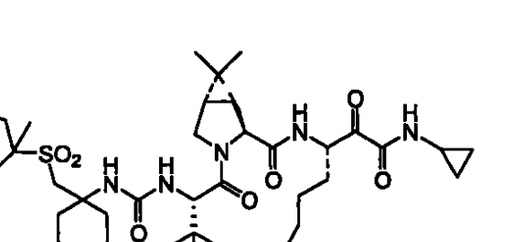


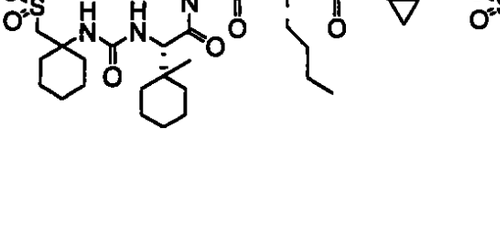


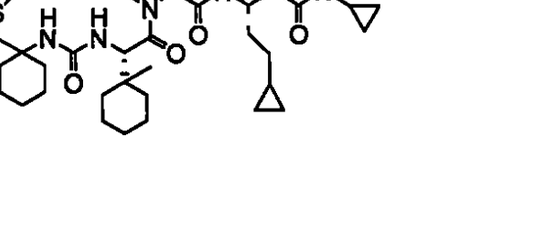


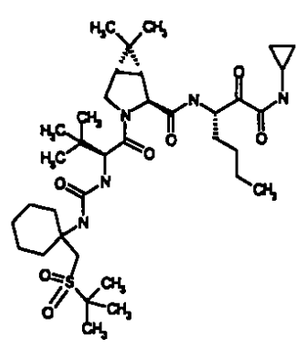


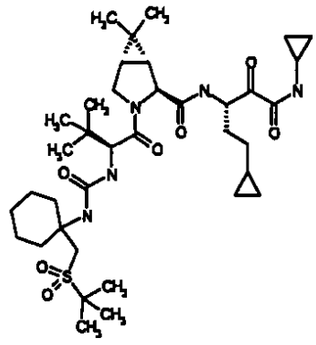




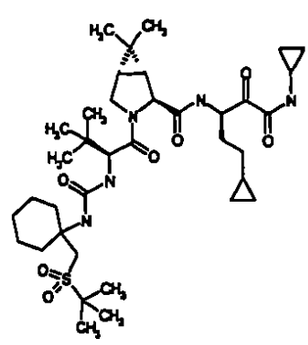








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23. Una composición farmacéutica para tratar trastornos asociados con el VHC, comprendiendo dicha composición una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 22 y un vehículo aceptable desde el punto de vista farmacéutico.

24. La composición farmacéutica de la reivindicación 23, que contiene, en forma adicional, por lo menos un agente antiviral.

25. La composición farmacéutica de la reivindicación 24, que contiene inclusive, en forma adicional, por lo menos un interferón o conjugado PEG-interferón alfa.

26. La composición farmacéutica de la reivindicación 25, en la cual dicho por lo menos un agente antiviral es ribavirin y dicho por lo menos un interferón es α-interferón o interferón pegilado.

27. Un método de tratamiento de un trastorno asociado con el virus de la hepatitis C, que comprende administrar una cantidad efectiva de uno o más compuestos de la reivindicación 22.

28. Un método para modular la actividad de la proteasa del virus de la hepatitis C (VHC), que comprende contactar la proteasa del VHC con uno o más compuestos de la reivindicación 22.

29. Un método de tratamiento, prevención o atenuación de uno o más síntomas de la hepatitis C, que comprende administrar una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 22.

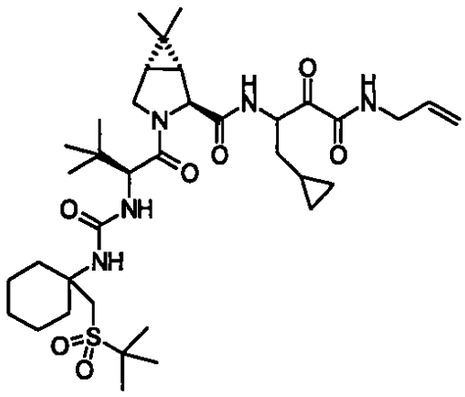
30. El método de la reivindicación 29, en el cual la proteasa del VHC es la proteasa NS3/NS4a.

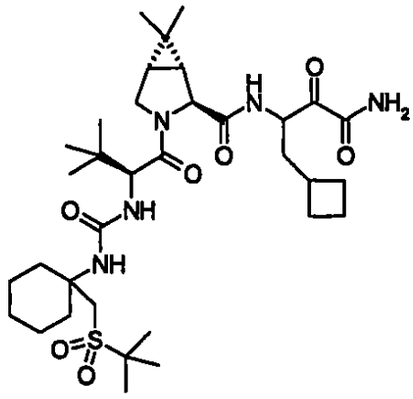
31. El método de la reivindicación 30, en el cual el compuesto o los compuestos inhiben la proteasa NS3/NS4a del VHC.

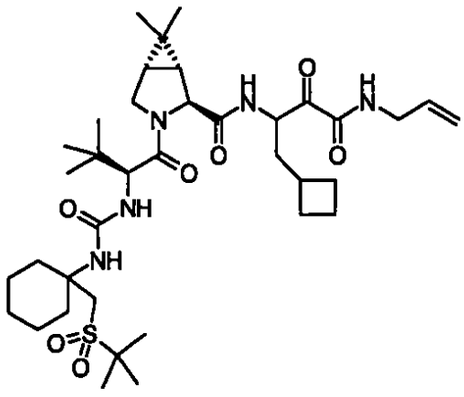
32. Un método para modular el procesamiento del polipéptido del virus de la hepatitis C (VHC), que comprende contactar una composición que contiene el polipéptido del VHC en condiciones en las cuales dicho polipéptido se procesa con uno o más compuestos de la reivindicación 22.

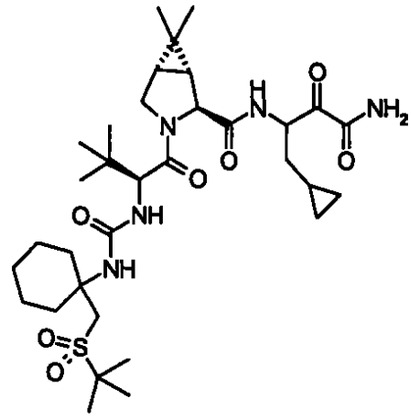
33. Un método de tratamiento de trastornos asociados con el VHC, comprendiendo dicho método administrar a un paciente que necesita de dicho tratamiento, una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de por lo menos un compuesto, o enantiómeros, estereoisómeros, rotámeros, tautómeros y racematos de dicho compuesto, o una sal o solvato o éster aceptables desde el punto de vista farmacéutico de dicho compuesto, seleccionándose dicho compuesto de los siguientes:

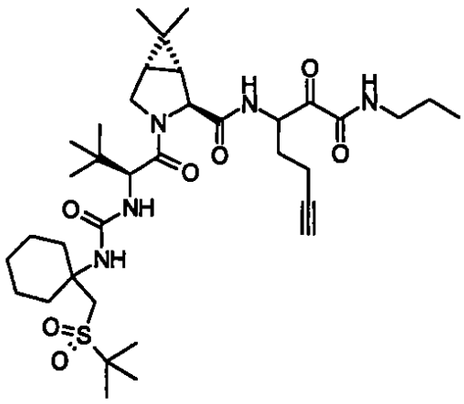
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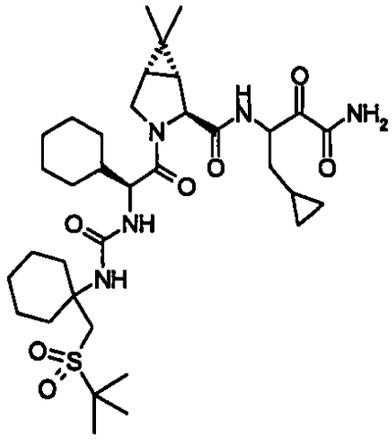


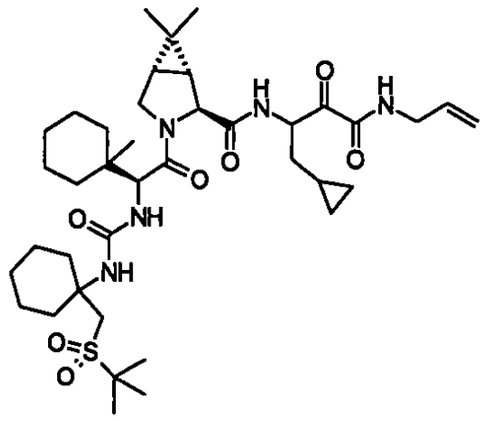


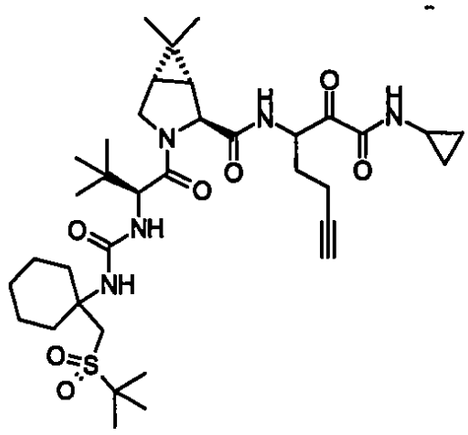


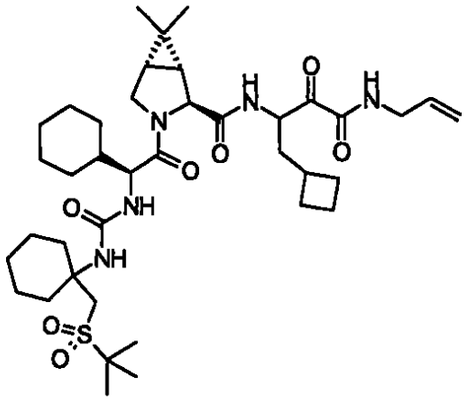


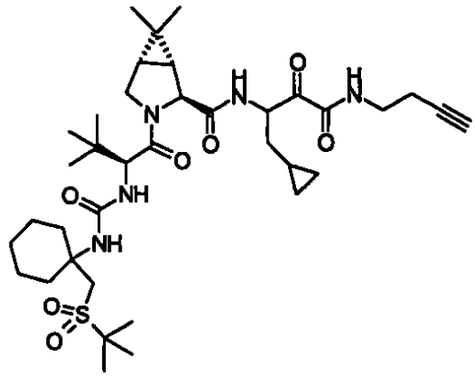


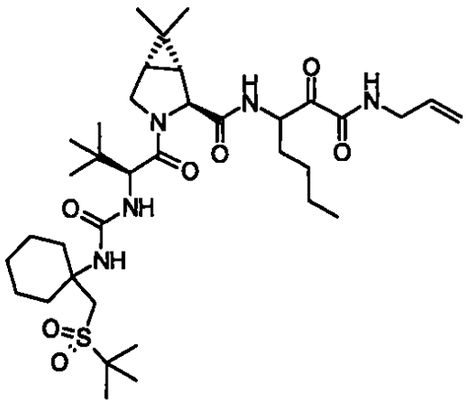


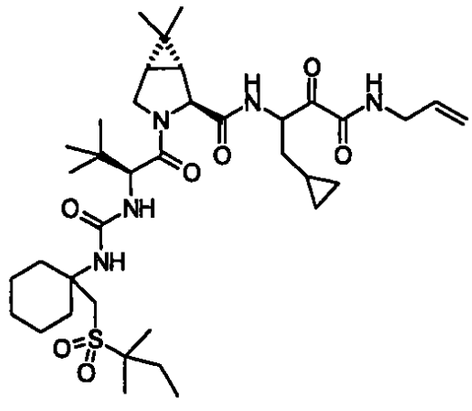




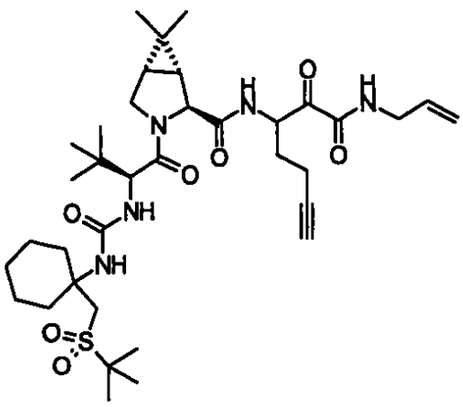


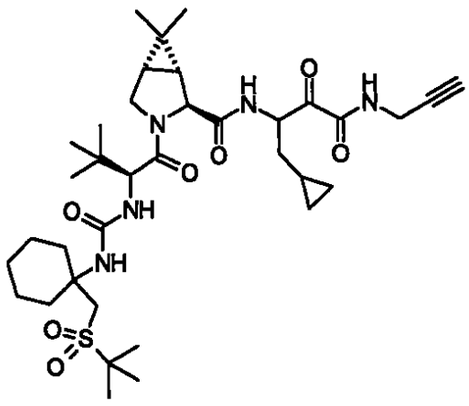


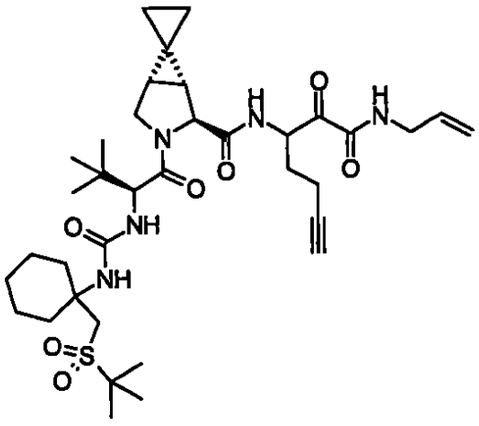




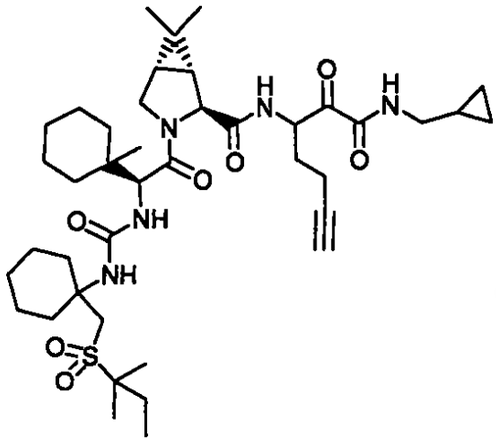
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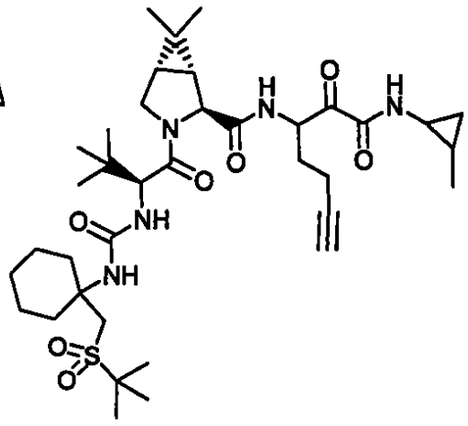


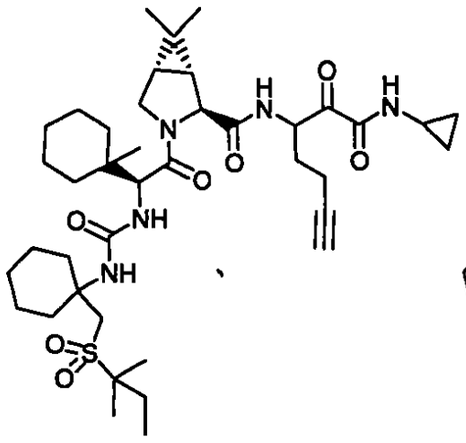


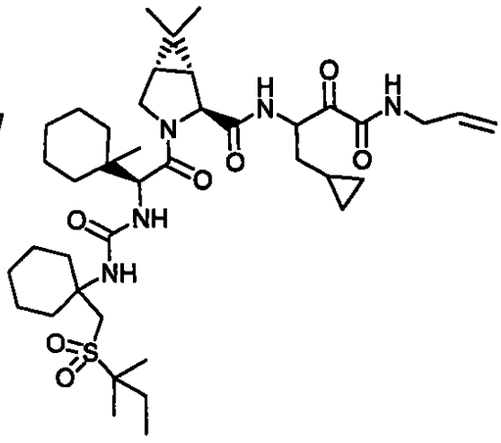


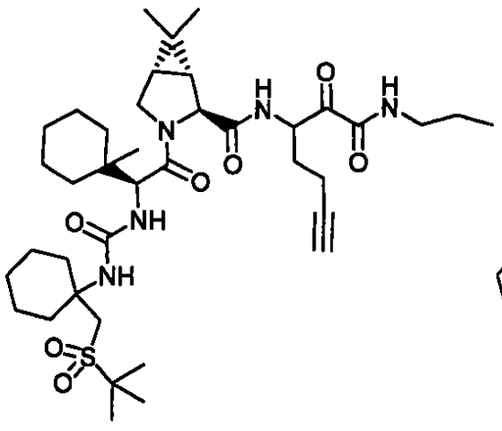
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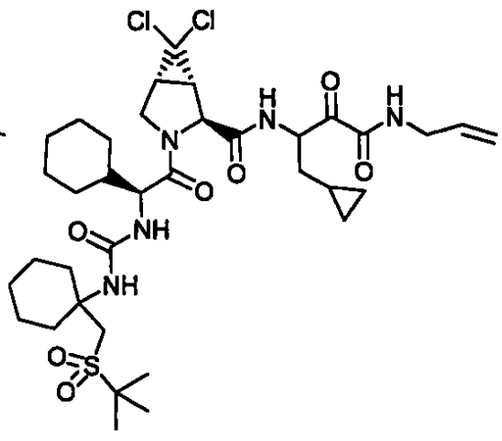






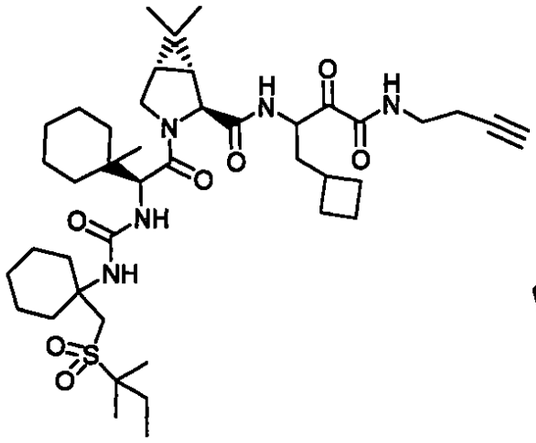


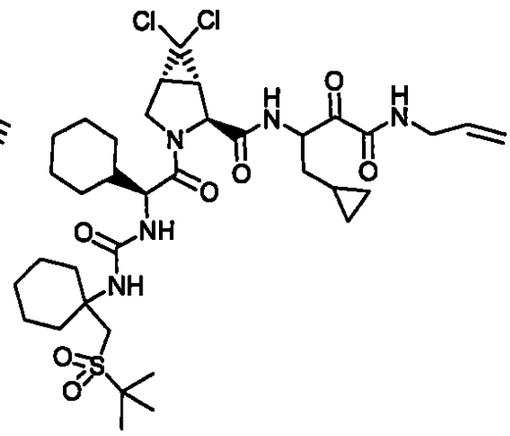


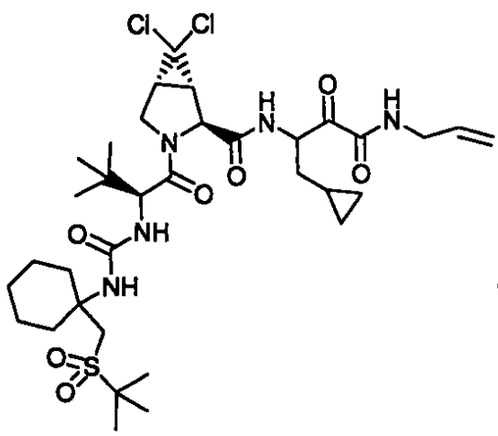


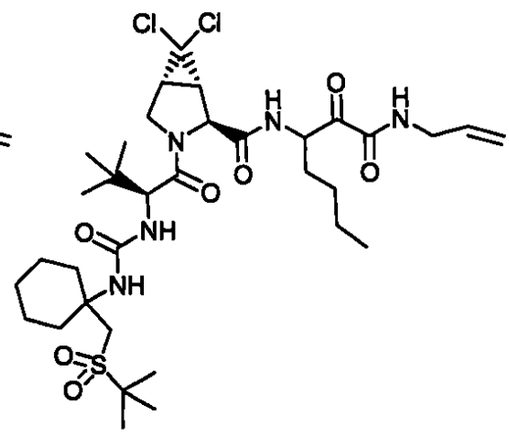
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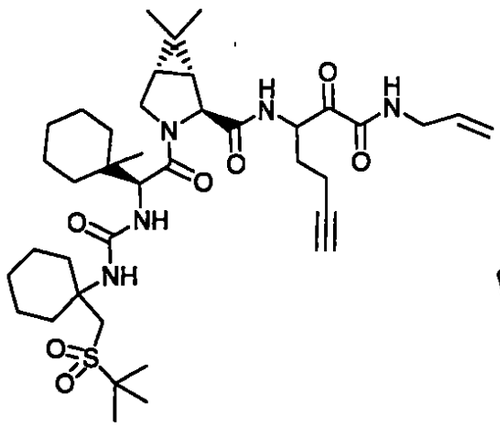
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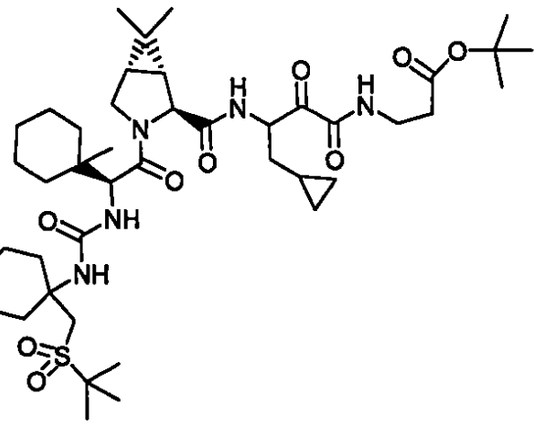




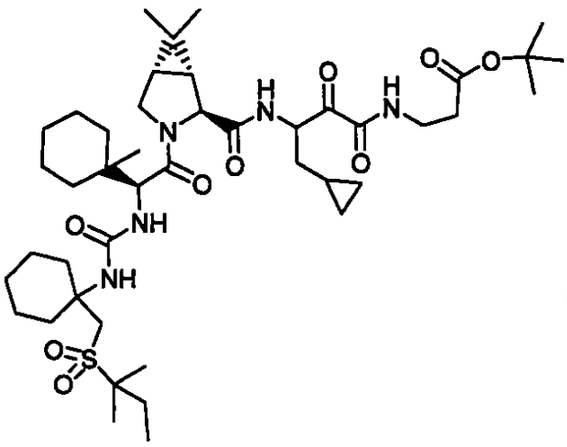


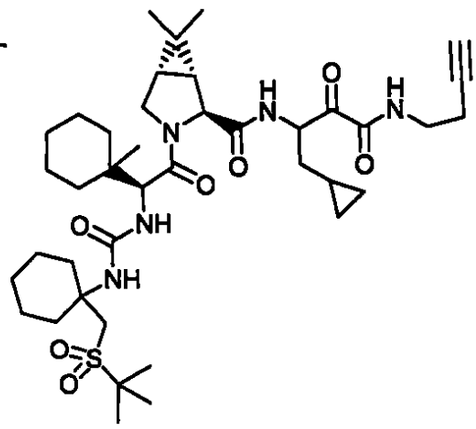


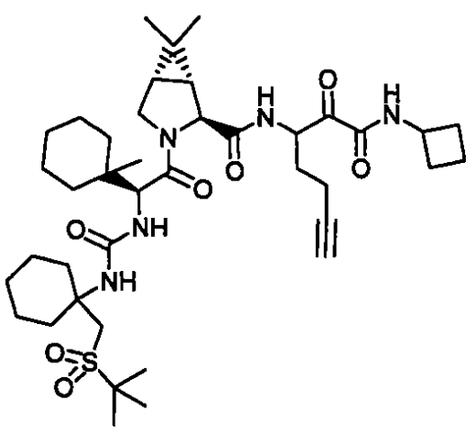


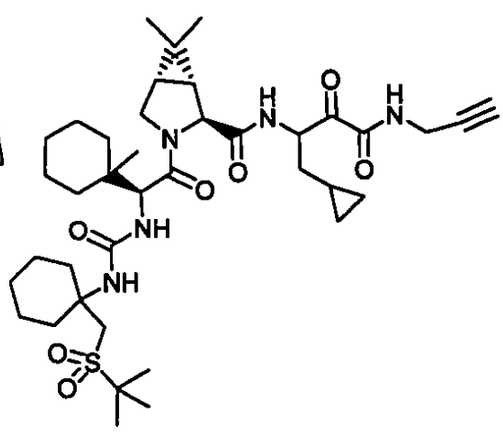


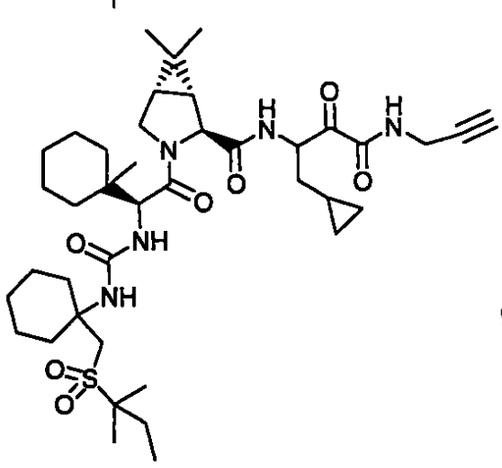
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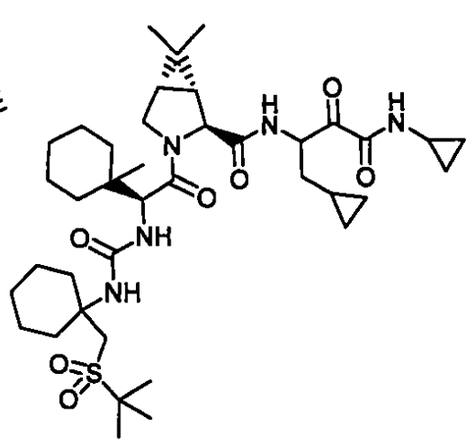






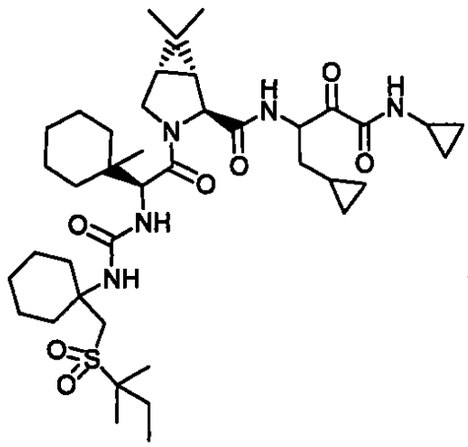


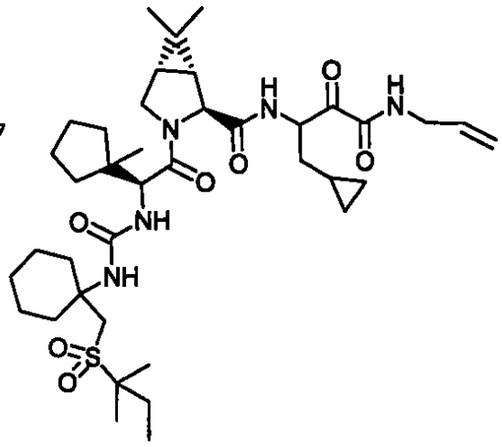


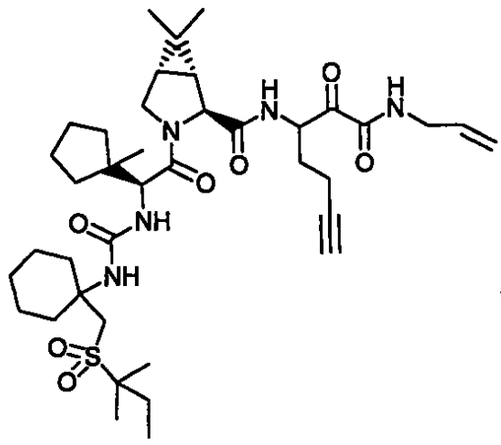


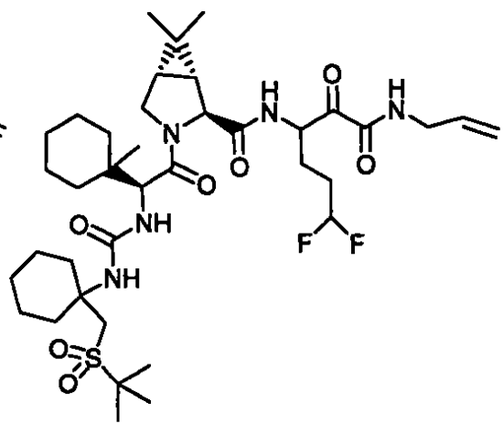
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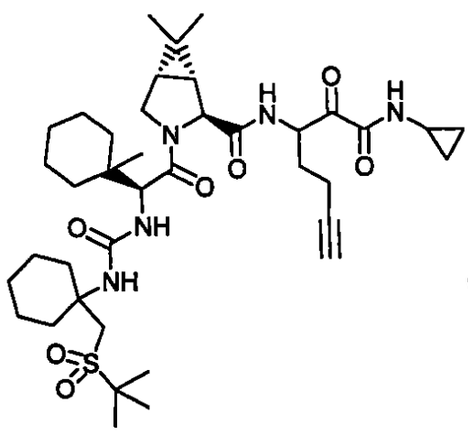
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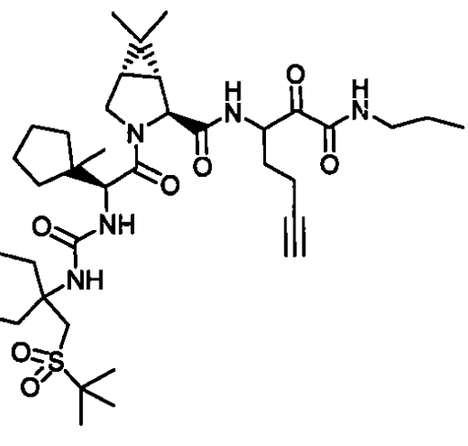




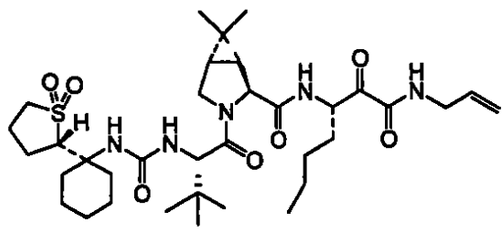


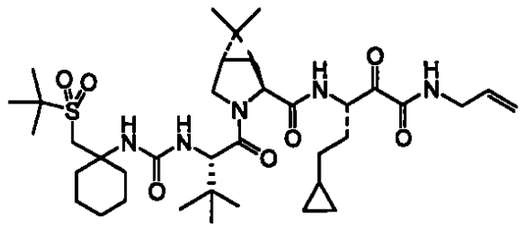


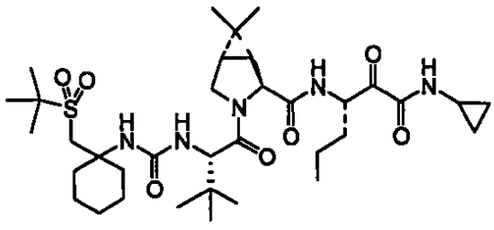


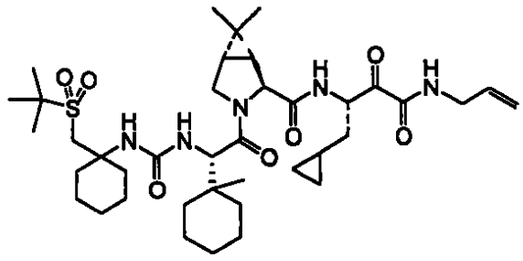


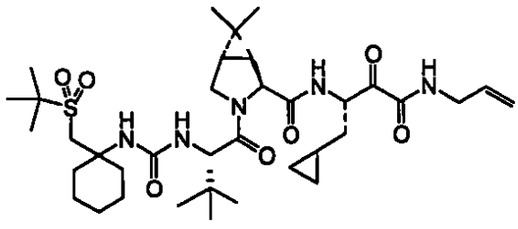
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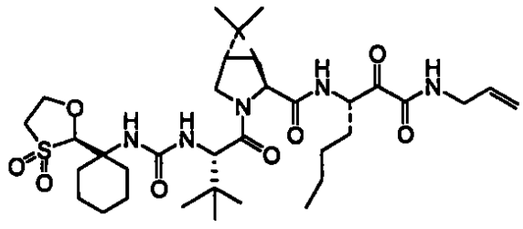


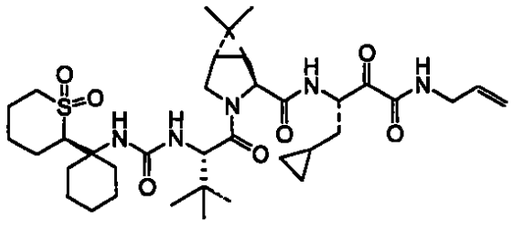


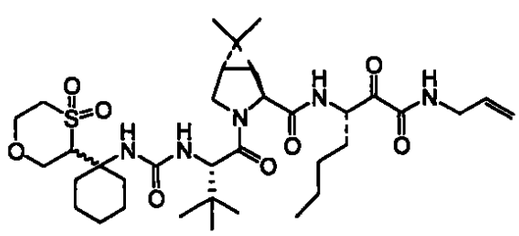


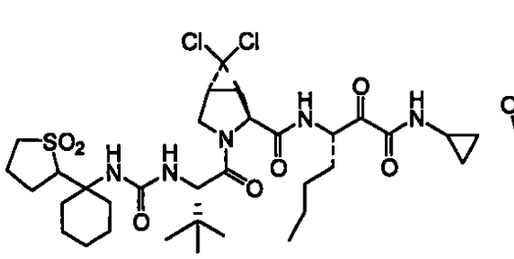


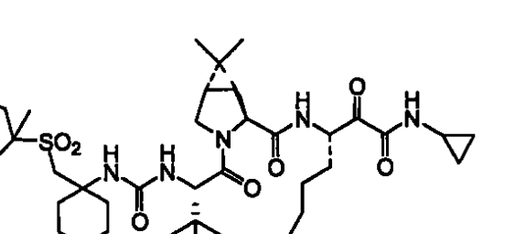




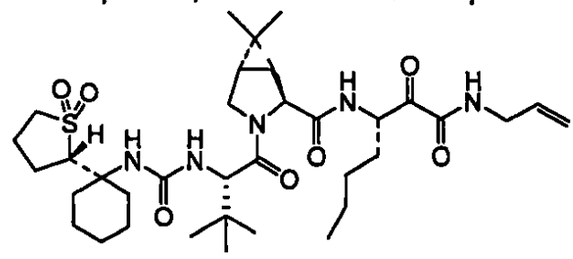




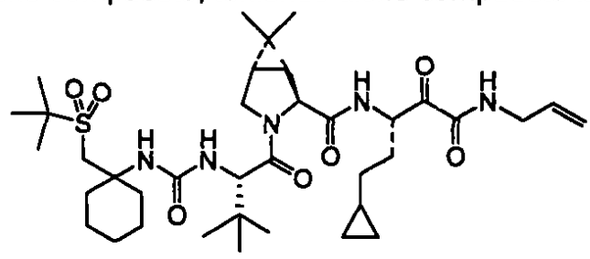




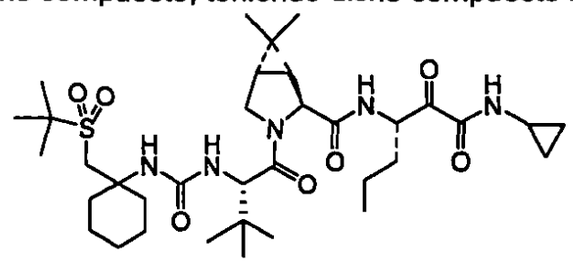
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35. Un compuesto que presenta actividad inhibidora de la proteasa del VHC, o enantiómeros, estereoisómeros, rotámeros, tautómeros y racematos de dicho compuesto, o una sal o solvato o éster aceptables desde el punto de vista farmacéutico de dicho compuesto, teniendo dicho compuesto la estructura:

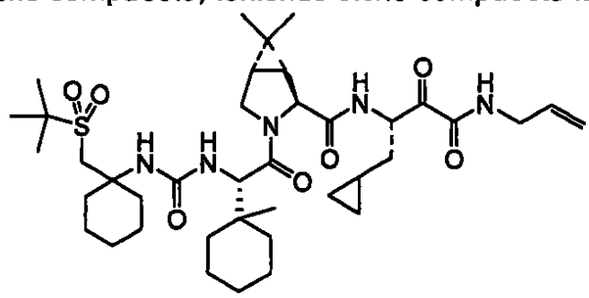


36. Un compuesto que presenta actividad inhibidora de la proteasa del VHC, o enantiómeros, estereoisómeros, rotámeros, tautómeros y racematos de dicho compuesto, o una sal o solvato o éster aceptables desde el punto de vista farmacéutico de dicho compuesto, teniendo dicho compuesto la estructura:

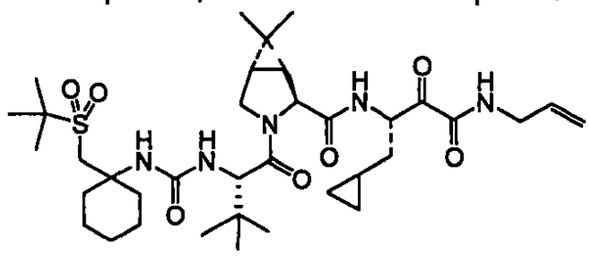


37. Un compuesto que presenta actividad inhibidora de la proteasa del VHC, o enantiómeros, estereoisómeros, rotámeros, tautómeros y racematos de dicho

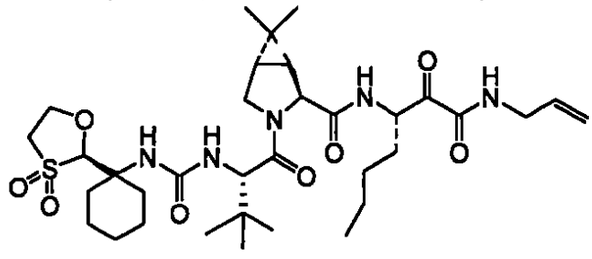
compuesto, o una sal o solvato o éster aceptables desde el punto de vista farmacéutico de dicho compuesto, teniendo dicho compuesto la estructura:



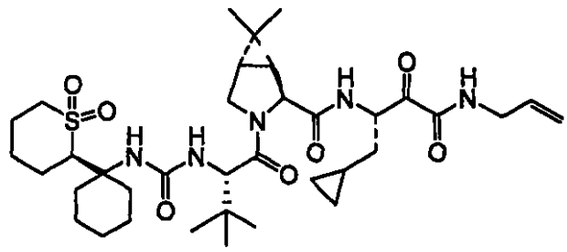
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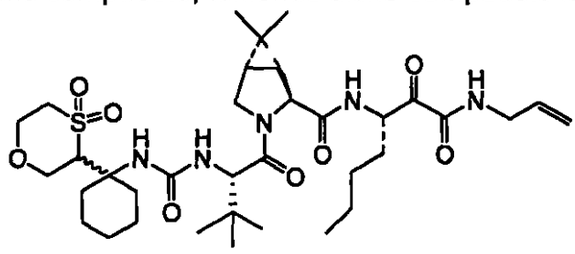
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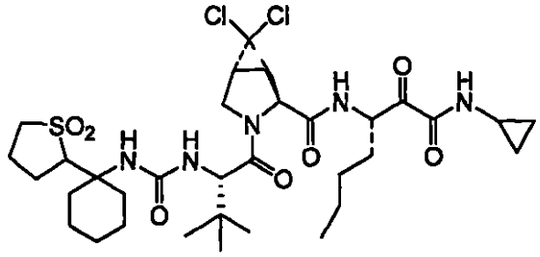
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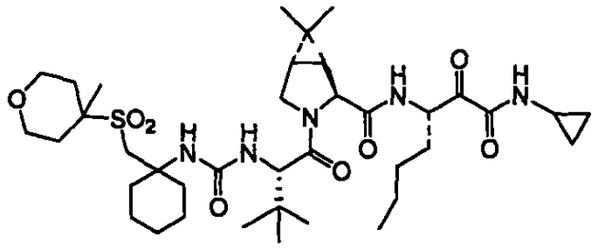
41. Un compuesto que presenta actividad inhibidora de la proteasa del VHC, o enantiómeros, estereoisómeros, rotámeros, tautómeros y racematos de dicho compuesto, o una sal o solvato o éster aceptables desde el punto de vista farmacéutico de dicho compuesto, teniendo dicho compuesto la estructura:



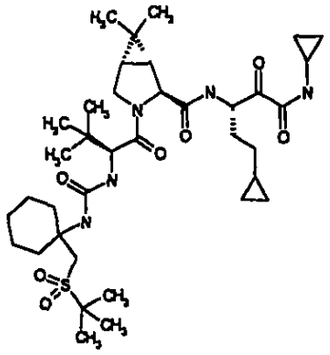
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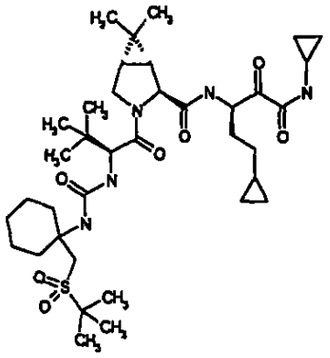
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44. Un compuesto que presenta actividad inhibidora de la proteasa del VHC, o enantiómeros, estereoisómeros, rotámeros, tautómeros y racematos de dicho compuesto, o una sal o solvato o éster aceptables desde el punto de vista farmacéutico de dicho compuesto, teniendo dicho compuesto la estructura:

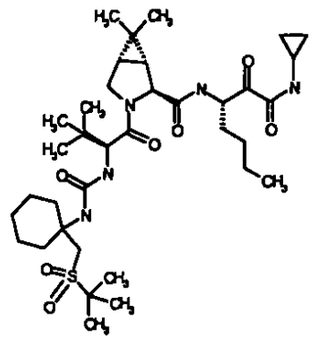


45. Un compuesto que presenta actividad inhibidora de la proteasa del VHC, o enantiómeros, estereoisómeros, rotámeros, tautómeros y racematos de dicho compuesto, o una sal o solvato o éster aceptables desde el punto de vista farmacéutico de dicho compuesto, teniendo dicho compuesto la estructura:

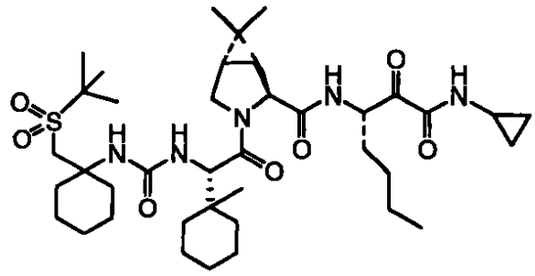


46. Un compuesto que presenta actividad inhibidora de la proteasa del VHC, o enantiómeros, estereoisómeros, rotámeros, tautómeros y racematos de dicho

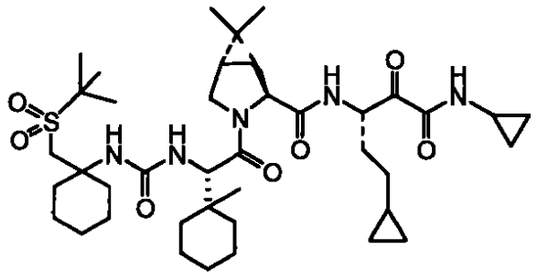
compuesto, o una sal o solvato o éster aceptables desde el punto de vista farmacéutico de dicho compuesto, teniendo dicho compuesto la estructura:



47. Un compuesto que presenta actividad inhibidora de la proteasa del VHC, o enantiómeros, estereoisómeros, rotámeros, tautómeros y racematos de dicho compuesto, o una sal o solvato o éster aceptables desde el punto de vista farmacéutico de dicho compuesto, teniendo dicho compuesto la estructura:



48. Un compuesto que presenta actividad inhibidora de la proteasa del VHC, o enantiómeros, estereoisómeros, rotámeros, tautómeros y racematos de dicho compuesto, o una sal o solvato o éster aceptables desde el punto de vista farmacéutico de dicho compuesto, teniendo dicho compuesto la estructura:



49. Un compuesto de la reivindicación 1 en forma purificada.

p.: SCHERING CORPORATION

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RESUMEN DE LA INVENCIÓN

La presente invención revela nuevos compuestos que tienen actividad inhibidora de la proteasa del VHC como así también métodos para preparar tales compuestos. En otra realización, la invención revela composiciones farmacéuticas que comprenden tales compuestos como así también métodos para usarlos para tratar trastornos asociados con la proteasa del VHC.

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06

From the INTERNATIONAL BUREAU

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NOTIFICATION OF THE RECORDING OF A CHANGE

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(PCT Rule 92bis 1 and Administrative Instructions, Section 422)

To

KALYANARAMAN, Palaiyur, S.
Schering-Plough Corporation
2000 Galloping Hill Road
Mail Stop K-6-1 1990
Kenilworth, New Jersey 07033-0530
United States of America

Date of mailing (day/month/year) 10 May 2006 (10.05.2006)	
Applicant's or agent's file reference IN06135	**IMPORTANT NOTIFICATION**
International application No. PCT/US2005/005795 ✓	**International filing date** (day/month/year) 24 February 2005 (24.02.2005) ✓

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No	
	Facsimile No	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning

[X] the person [ ] the name [X] the address [X] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
NAIR, Latha 560 Darwin Boulevard Edison, NJ 08820 United States of America	IN	
	Telephone No	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary

The person identified in Box 2 is now recorded as applicant for the United States of America only and inventor for all designated States.

4. A copy of this notification has been sent to

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Rodolfo CLEMENTE
Facsimile No +41 22 338 7090	Telephone No (41-22) 338 8456

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Fve 379 FASENACIONALII
Act 411 PRESENTACION Folios 1a 32

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL

1416
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	

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2005/005795 Fecha Febrero 24, 2005

Publicación Internacional No. WO 2005/087731 Fecha Septiembre 22, 2005

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

Clasificación Internacional (51) C07D 209/52, 206/56, 491/04, C07K 5/08, 7/02, A61K 31/403, 31/407, A61P 31/12 //(C07D 491/04, 307:00, 209:00.

Prioridad SI [X] N [ ]

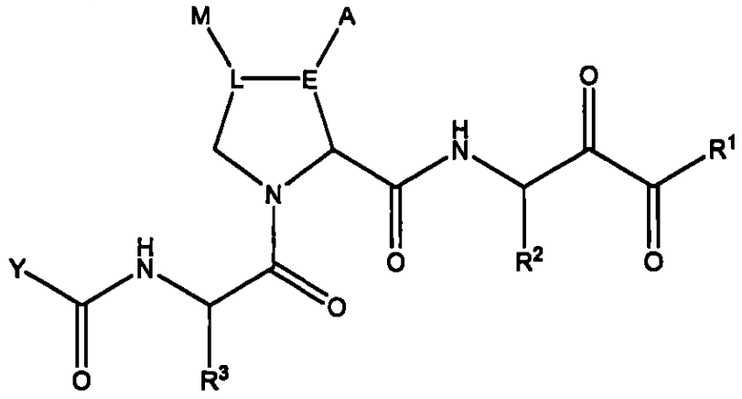
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Febrero 27, 2004	60/548,670

(9) **Comprobante de pago No.** 06-63.712 **Fecha** Agosto 22, 2006

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REIVINDICACIONES

1. Un compuesto, o enantiómeros, estereoisómeros, rotámeros, tautómeros y racematos de dicho compuesto, o una sal o solvato o éster aceptables desde el punto de vista farmacéutico de dicho compuesto, teniendo dicho compuesto la estructura general que se muestra en la Fórmula I:



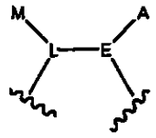
Fórmula I

en la cual:

R^1 es H, OR^8, NR^9R^{10}, o CHR^9R^{10}, en los cuales R^8, R^9 y R^{10} pueden ser iguales o diferentes, seleccionándose cada uno en forma independiente del grupo formado por H, alquilo-, alquenilo-, alquinilo-, arilo-, heteroalquilo-, heteroarilo-, cicloalquilo-, heterociclilo-, arilalquilo- y heteroarilalquilo;

A y M pueden ser iguales o diferentes, seleccionándose cada uno en forma independiente de R, OR, NHR, NRR', SR, SO_2R y halo;

o A y M están conectados uno al otro de modo tal que el resto:



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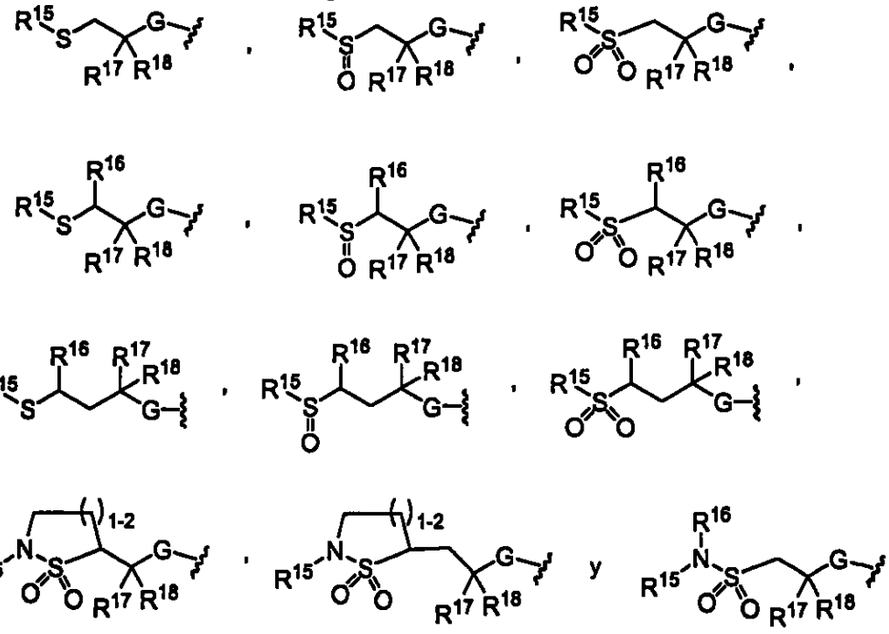
que se mostró anteriormente en la Fórmula I forma tanto un cicloalquilo de tres, cuatro, seis, siete y ocho miembros, un heterociclilo de cuatro a ocho miembros, un arilo de seis a diez miembros, o un heteroarilo de cinco a diez miembros;

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, seleccionándose cada uno en forma independiente del grupo formado por H, alquilo, heteroalquilo, alquenilo, heteroalquenilo, alquinilo, heteroalquinilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, o alternativamente R y R' en NRR' están conectados uno al otro de manera tal que NRR' forma un heterociclilo de cuatro a ocho miembros;

e Y se selecciona de los siguientes restos:



en los cuales G es NH u O; y R^{15}, R^{16}, R^{17} y R^{18} pueden ser iguales o diferentes, seleccionándose cada uno en forma independiente del grupo formado por H, alquilo, heteroalquilo, alquenilo, heteroalquenilo, alquinilo, heteroalquinilo, cicloalquilo, heterociclilo, arilo, y heteroarilo, o alternativamente, (i) R^{15} y R^{16} están conectados entre sí para formar una estructura cíclica de cuatro a ocho

LISTA DE INVENTORES PCT/US2005/005795

1419

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[redacted]

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-082859 -00000-0000
Fec 2006-08-22 13 09 15 Dep 2020 NUECREACIONES
Tra 11 PATENTEIYII
Exe 379 FASENACIONALII
Act 411 PRESENTACION Folios 1432

Industria y Comercio
SUPERINTENDENCIA

1421

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [X]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [X] 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 [ ]

Fdo B
Firma Responsable

Fecha 22-AG-6

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador. 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D C , Colombia

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Copy for the designated Office (DO/EP) PCT/US2005/005795

PATENT COOPERATION TREATY 31

1422

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

KALYANARAMAN, Palaiyur, S.
Schering-Plough Corporation
2000 Galloping Hill Road
Mail Stop K-6-1 1990
Kenilworth, New Jersey 07033-0530
United States of America

Date of mailing (day/month/year)	
10 May 2006 (10.05 2006)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
IN06135	
International application No.	**International filing date** (day/month/year)
PCT/US2005/005795	24 February 2005 (24.02.2005)

1. The following indications appeared on record concerning:
[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:
[X] the person [ ] the name [X] the address [X] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
NAIR, Latha 560 Darwin Boulevard Edison, NJ 08820 United States of America	IN	
	Telephone No	
	Facsimile No.	
	Teleprinter No.	

PCT-DG 1
19. 05. 2006
TEAM 14

3. Further observations, if necessary:
The person identified in Box 2 is now recorded as applicant for the United States of America only and inventor for all designated States.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Rodolfo CLEMENTE

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Expediente 4 30629

ASIGNACION DE NUMERO DE CERTIFICADO

Certificado No. 287680

DATOS DEL SIGNO

Marca nominativa	GEO-PILOT
PARA DISTINGUIR	HERRAMIENTAS DE FONDO DE POZO UTILIZADAS EN LA PERFORACION DE POZOS DE PETROLEO Y GAS, TALES COMO LOS COMPRENDIDOS POR UN MOTOR DE FONDO DE POZO, BROCA Y SENSORES DE DIAMETRO UTILIZADOS PARA PERFORACION CON ROTARIA DIRIGIBLE
	Productos comprendidos en la clase 7 de la Octava Edición de la Clasificación Internacional de Niza
Vigencia	Desde 08/10/2004 Hasta 08/10/2014
Titular	HALLIBURTON ENERGY SERVICES, INC
Domicilio	CARROLLTON TEXAS ESTADOS UNIDOS 2601 BELTLINE ROAD, 1-B-121, 75006

SECRETARIA GENERAL AD HOC
20/10/2004 (dd/mm/yyyy)F973F797

El presente documento corresponde a una información sobre la asignación de número de certificado del signo respectivo Por lo anterior, a efectos de establecer su titularidad y vigencia, deberá estarse a lo dispuesto en los actos administrativos que hayan concedido el derecho, notificados de conformidad con la ley, y en las certificaciones expedidas por la Superintendencia de Industria y Comercio

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REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

1423

Bogotá,
2020

Doctor(a)
RAISBECK J. IAN
Apoderado(a) y/o Representante de
SCHERING CORPORATION

REFERENCIA	Radicación No.	06 82859
	Solicitud internacional	US2005/005795
	Fecha inicio fase nacional	27/09/2006
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	11916

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. Si fuere el caso, el solicitante debe adjuntar la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT.

2. 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.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única 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 20 OCT. 2006
aalvarado