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REPÚBLICA DE COLOMBIA

DIVISIÓN DE PROPIEDAD INDUSTRIAL

PCT

PATENTE DE INVENCIÓN

Industria y Comercio
SUPERINTENDENCIA

06-82842

TITULO: COMPUESTOS NOVEDOSOS COMO INHIBIDORES DE NS3 SERINA PROTEASA DEL VIRUS DE LA HEPATITIS C.

SOLICITANTE: SCHERING CORPORATION

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

APODERADO: J. IAN RAISBECK

BOGOTÁ, agosto 22 de 2006

P2006/000173

OLARTERAISBECK 06/173

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad 06-082842- -00000-0000
Fec: 2006-08-22 17:24:04 Dep: 2020 NUEVAS CREACIONES
Tra: 11 PATENTEIYII
Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 527

Industria y Comercio
SUPERINTENDENCIA

PETITORIO - FORMULARIO UNICO 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 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/US2005/005772 Fecha Febrero 24, 2005

Publicación Internacional No WO 2005/087721 Fecha Septiembre 22, 2005

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

Clasificación Internacional (51) C07D 207/00

Prioridad SI [X] N [ ]	(33) País de Origen	(32) Fecha	(31) Numero de Solicitud
	US	Febrero 27, 2004	60/548,507

(9) **Comprobante de pago No** 06-63 709 **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
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [x] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- [x] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional
- [x] Otros Búsqueda Internacional

(11) FIGURA CARACTERÍSTICA.

(12) Solicito la concesión de la patente,

NOMBRE J. IAN RAISBECK FIRMA

C C 79 376 996 Btá T P 135.799

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

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Nacionalidad Estadounidense

5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Tra 11 PATENTEIYII
Eve 379 FASENACIONALII
Act 411 PRESENTACION Folios 527

RECIBO OFICIAL DE CAJA 06 - 63,709
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 RAISBECR	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 _____

6

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E S D

Ref Nueva solicitud de Patente de invención titulada · COMPUESTOS NOVEDOSOS COMO INHIBIDORES DE NS# SERINA PROTEASA 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 ESTE DESPACHO NOTARIAL
DE SANTAFE DE BOGOTA D.C.
Con C.C.
Y manifestó que el contenido de la misma
es cierto y que la firma que aparece
Autorizó a Tue Escrita por el.
El Usuario
HOY 21 JUL. 2000
HUELLA
MARIA EUGENIA ROJAS DE UPUETA
NOTARIA VEINTISIETE
REPUBLICA DE COLOMBIA

Blk dp 74293 CB

Maria Eugenia Rojas de Urueta
NOTARIO

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SCHERING CORPORATION

APOSTILLA

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

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

CERTIFICADO

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

PODER DE REPRESENTACIÓN

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

CERTIFICADO NOTARIAL

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

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

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

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

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

4

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1 COUNTRY UNITED STATES OF AMERICA

2 THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY
MARGUERITE LA CORTE

3 ACTING IN THE CAPACITY OF
NOTARY PUBLIC OF NEW JERSEY

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

CERTIFIED

5 AT TRENTON, NEW JERSEY

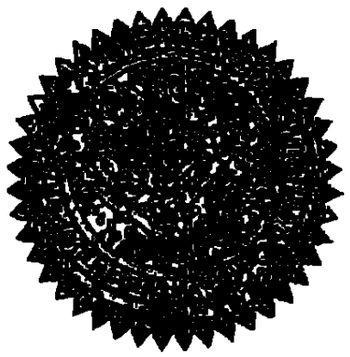
6 THE 29TH DAY OF AUGUST 2003

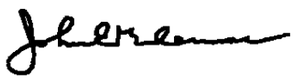
7 BY John E McCormac, CPA, NEW JERSEY TREASURER

8 NO A180345

9 SEAL/STAMP

10 SIGNATURE





OLARTERAISBECK

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FAX +57 1 638-6201

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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 189 Gratenwood 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

manifestó de estado civil casado
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):

PUBLIC (Signature)

Marguerite LaCorte

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

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

(19) World Intellectual Property Organization
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60/548,507 27 February 2004 (27.02.2004) US

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

(72) Inventors, and

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(74) Agent KALYANARAMAN, Palaiyur, S., Schering Plough Corporation, Patent Department K-6-1 1990 2000 Galloping Hill Road, Kenilworth NJ 07033-0530 (US)

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

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

Declaration under Rule 4.17

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

Published

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

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

WO 2005/087721 A2

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

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

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NOVEL COMPOUNDS AS INHIBITORS OF HEPATITIS C VIRUS NS3 SERINE PROTEASE

Field of the Invention

The present invention relates to novel hepatitis C virus ("HCV") protease inhibitors, pharmaceutical compositions containing one or more such inhibitors, methods of preparing such inhibitors and methods of using such inhibitors to treat hepatitis C and related disorders This invention additionally discloses novel compounds as inhibitors of the HCV NS3/NS4a serine protease This application claims priority from U S provisional patent application Serial Number 60/548,507 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 proteas 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

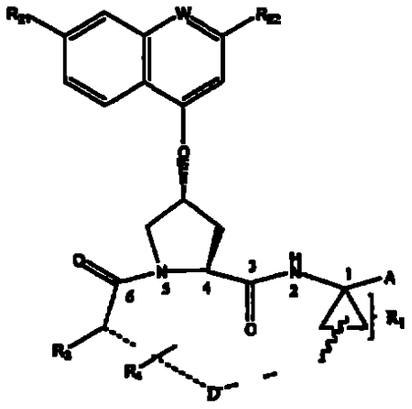
Inhibitors of HCV protease that have been reported include antioxidants (*see*, International Patent Application Publication No WO 98/14181), certain peptides and peptide analogs (*see*, International Patent Application Publication No WO 98/17679, Landro et al. (1997) Biochem 36 9340-9348, Ingallinella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

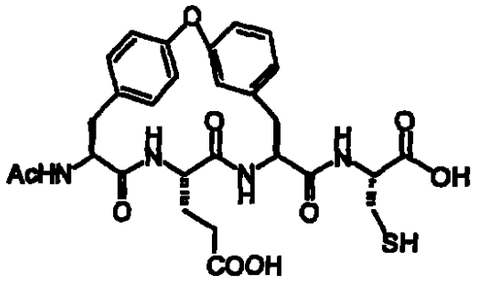
Reference is also made to the PCT Publications, No WO 98/17679, published April 30, 1998 (Vertex Pharmaceuticals Incorporated), WO 98/22496, published May 28, 1998 (F Hoffmann-La Roche AG), and WO 99/07734, published February 18, 1999 (Boehringer Ingelheim Canada Ltd)

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

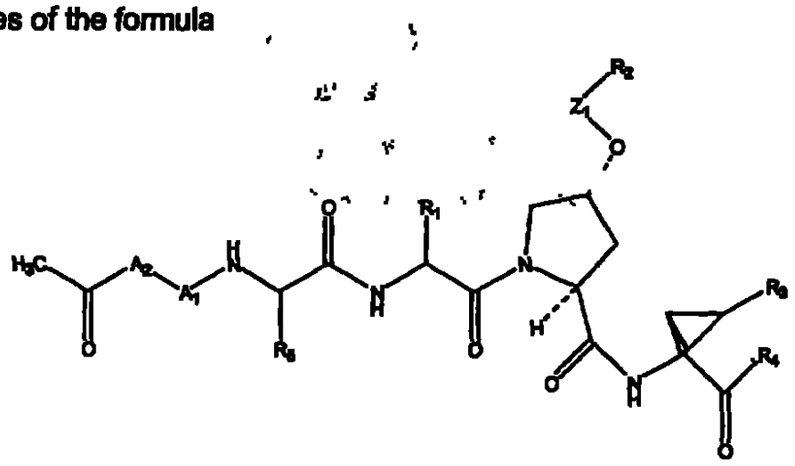


Reference is made to A Marcheth *et al*, *Synlett*, S1, 1000-1002 (1999) describing the synthesis of bicylic analogs of an inhibitor of HCV NS3 protease A compound disclosed therein has the formula

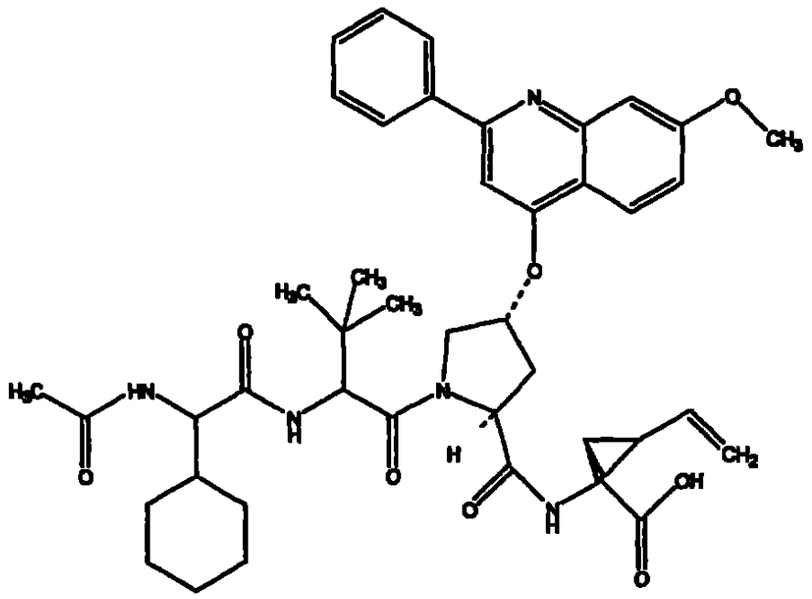


Reference is also made to W Han *et al*, *Bioorganic & Medicinal Chem Lett*, (2000) 10, 711-713, which describes the preparation of certain α-ketoamides, α-ketoesters and α-diketones containing allyl and ethyl functionalities

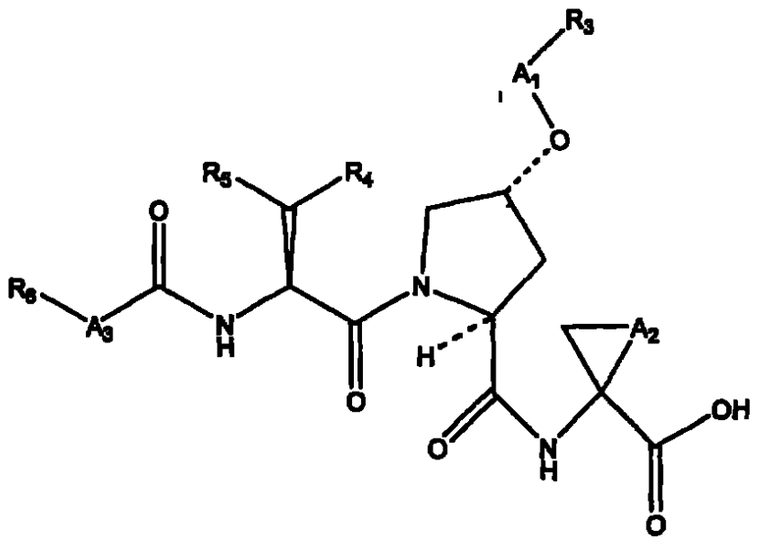
Reference is also made to WO 00/09558 (Assignee Boehringer Ingelheim Limited, Published February 24, 2000) which discloses peptide derivatives of the formula



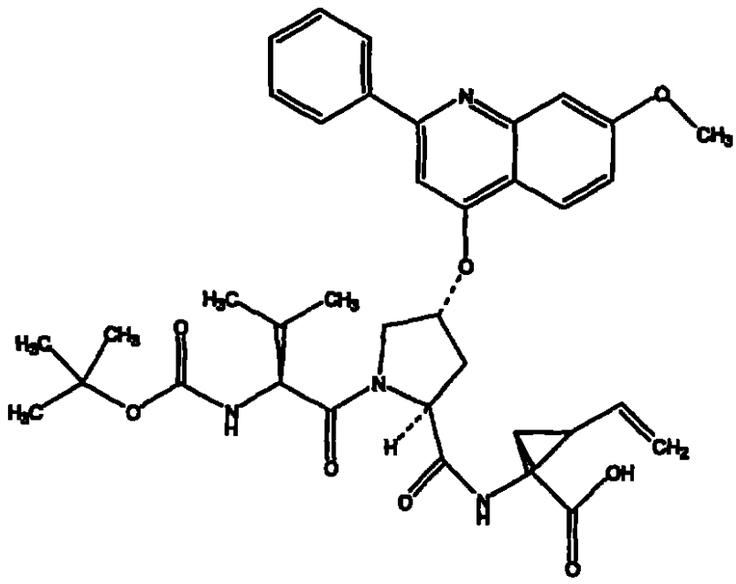
where the various elements are defined therein An illustrative compound of that series is



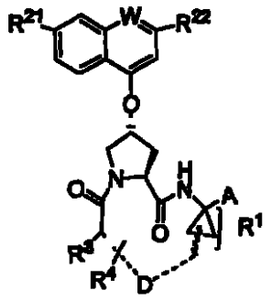
Reference is also made to WO 00/09543 (Assignee Boehringer Ingelheim Limited, Published February 24, 2000) which discloses peptide derivatives of the formula



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



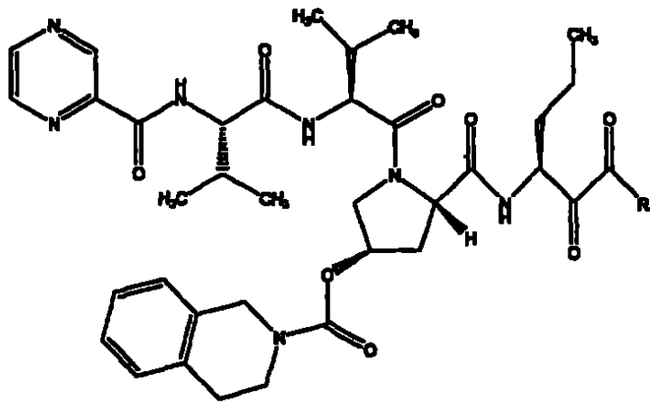
Reference is also made to U S 6,608,027 (Boehringer Ingelheim, Canada) which discloses NS3 protease inhibitors of the type



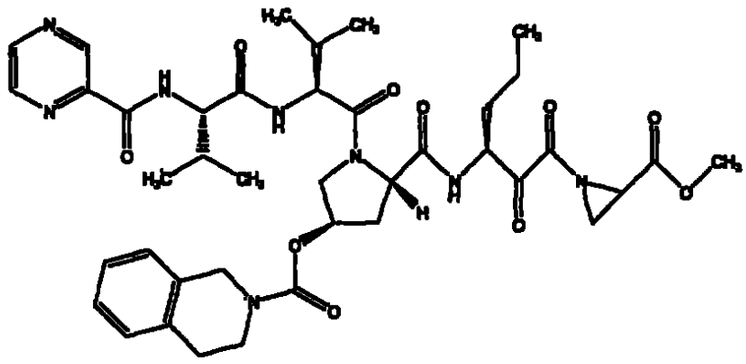
wherein the various moieties are defined therein

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

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



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



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

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

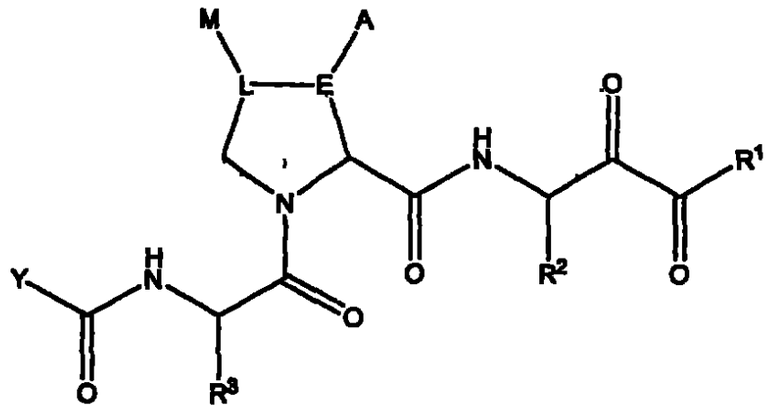
There is a need for methods of treatment or prevention or amelioration of one or more symptoms of hepatitis C

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

There is a need for methods of modulating the processing of the HCV polypeptide using the compounds provided herein

Summary of the Invention

In its many embodiments, the present invention provides a novel class of inhibitors of the HCV protease, pharmaceutical compositions containing one or more of the compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment or prevention of HCV or amelioration of one or more of the symptoms of hepatitis C using one or more such compounds or one or more such formulations Also provided are methods of modulating the interaction of an HCV polypeptide with HCV protease Among the compounds provided herein, compounds that inhibit HCV NS3/NS4a serine protease activity are preferred The present invention discloses compounds, or enantiomers, stereoisomers, rotamers, tautomers, diastereomers and racemates of said compounds, or a pharmaceutically acceptable salt, solvate or ester of said compounds, said compounds having the having the general structure shown in structural Formula 1



Formula I

wherein

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

A and M can be the same or different, each being independently selected from R, NR^9R^{10}, SR, SO_2R, and halo, or A and M are connected to each other such that the moiety



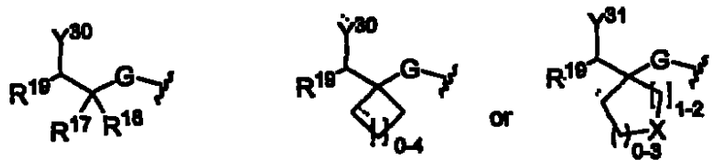
shown above in Formula I (i e , M-L-E-A taken together) forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl,

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

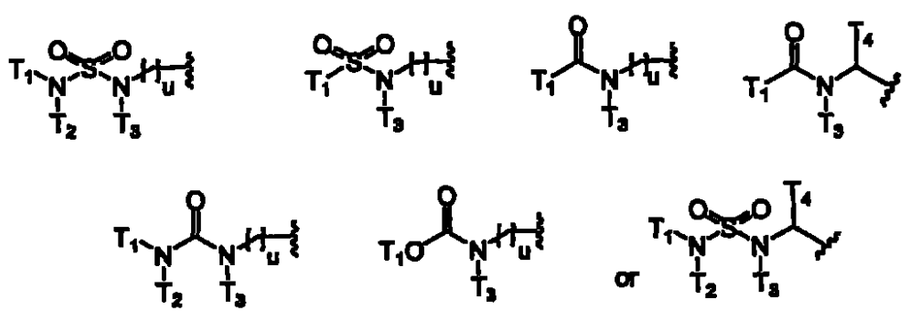
L is C(H), C(R), $CH_2C(R)$, or $C(R)CH_2$,

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 NR^9R^{10} forms a four to eight-membered heterocyclyl,

Y is selected from the following moieties



wherein Y^{30} and Y^{31} are selected from



where u is a number 0-6,

X is selected from O, NR^{15}, $NC(O)R^{16}$, S, S(O) and SO_2,

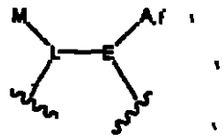
G is NH or O, and

R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, T_1, T_2, T_3 and T_4 can be the same or different, each being independently selected from the group consisting of H, alkyl,

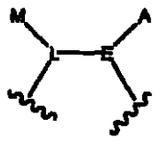
heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately, R^{17} and R^{18} are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl,

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, alkyl, aryl, heteroaryl, alkylsulfonamido, arylsulfonamido, keto, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halo, cyano, and nitro

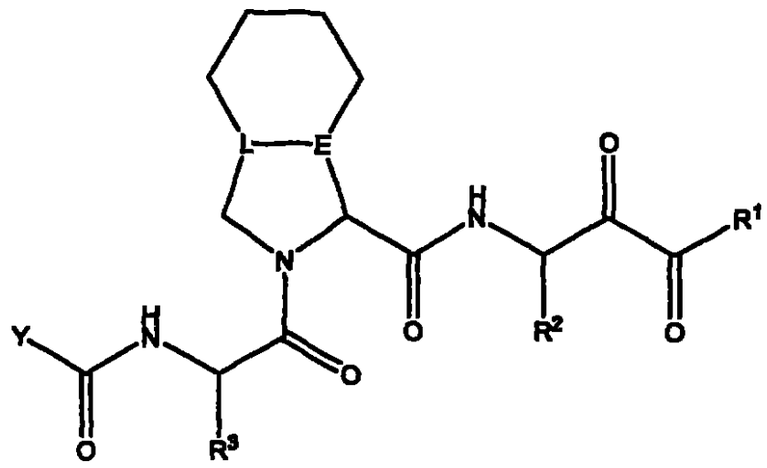
The above-noted statement "A and M are connected to each other such that the moiety



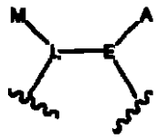
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl" can be illustrated in a non-limiting matter as follows Thus, for example, in the case where A and M are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



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



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



(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

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 (heterocyclyl) has one to six oxygen, nitrogen, sulfur, or phosphorus atoms

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

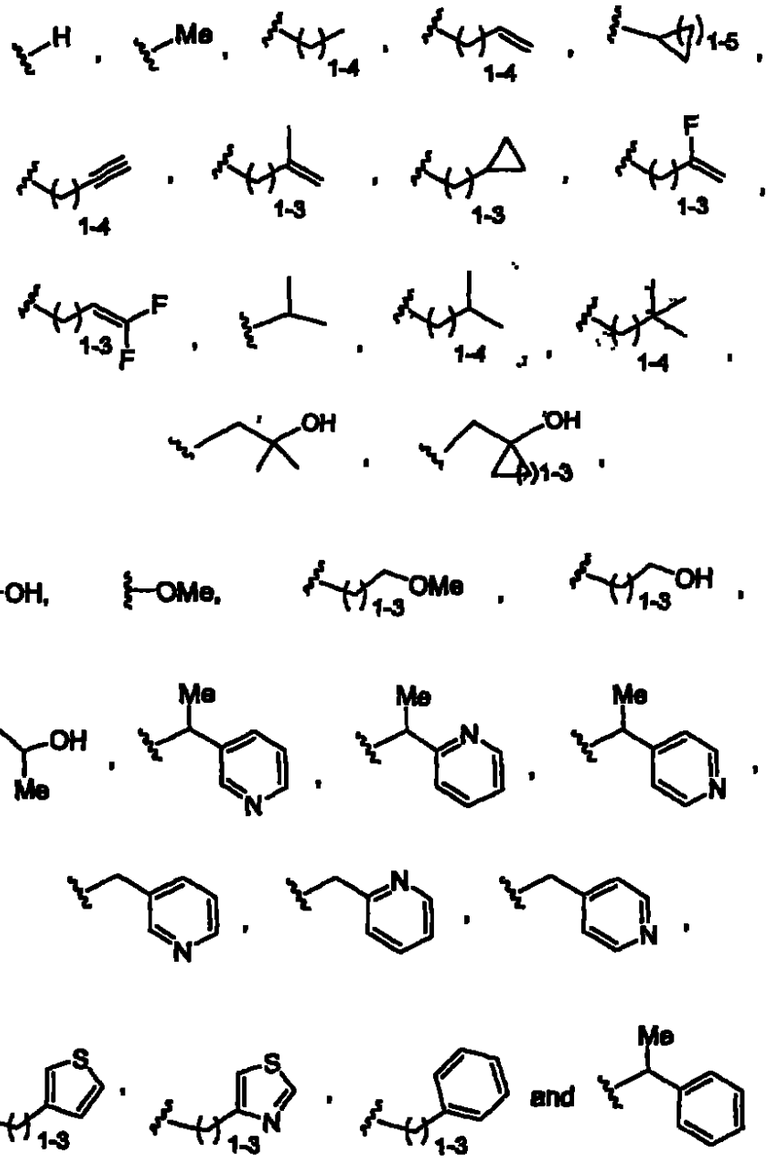
compounds can inhibit such protease They can also modulate the processing of hepatitis C virus (HCV) polypeptide

Detailed Description

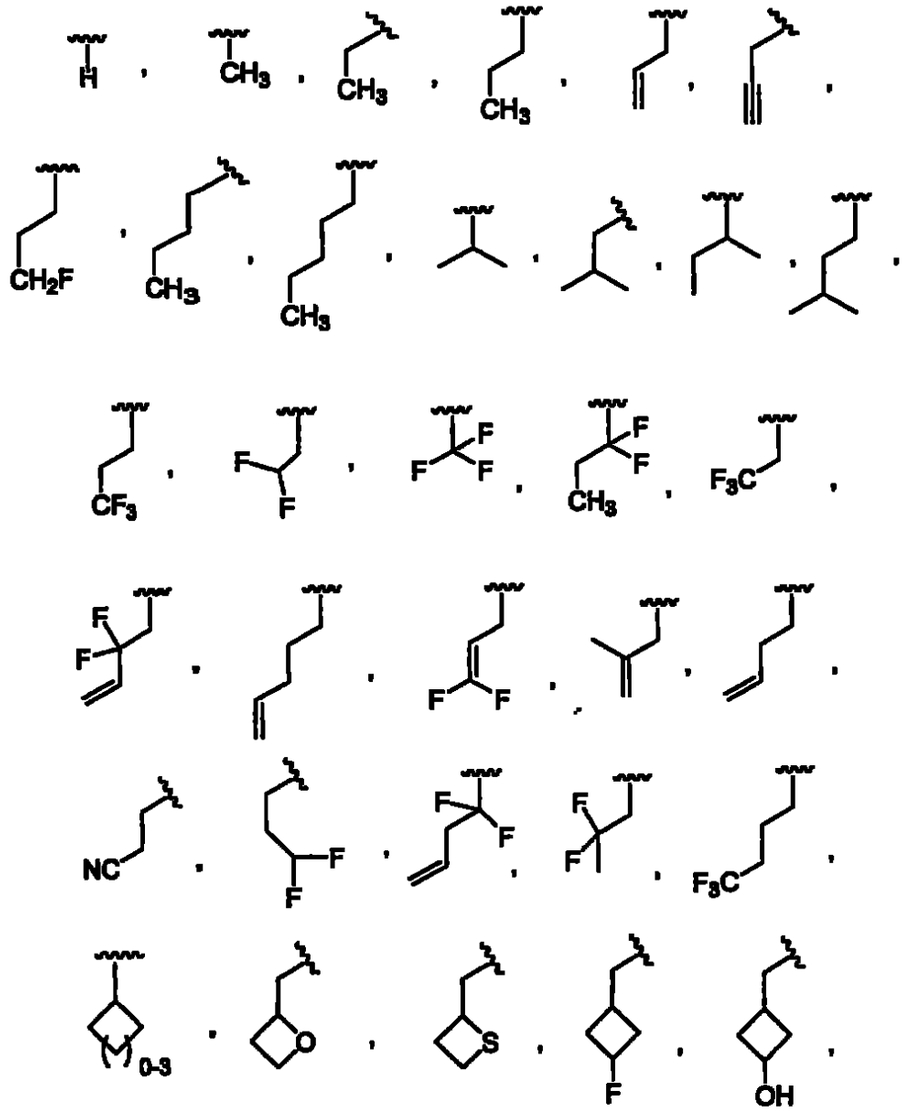
In an embodiment, the present invention discloses compounds which are represented by structural Formula 1 or a pharmaceutically acceptable salt, solvate or ester thereof, wherein the various moieties are as defined above

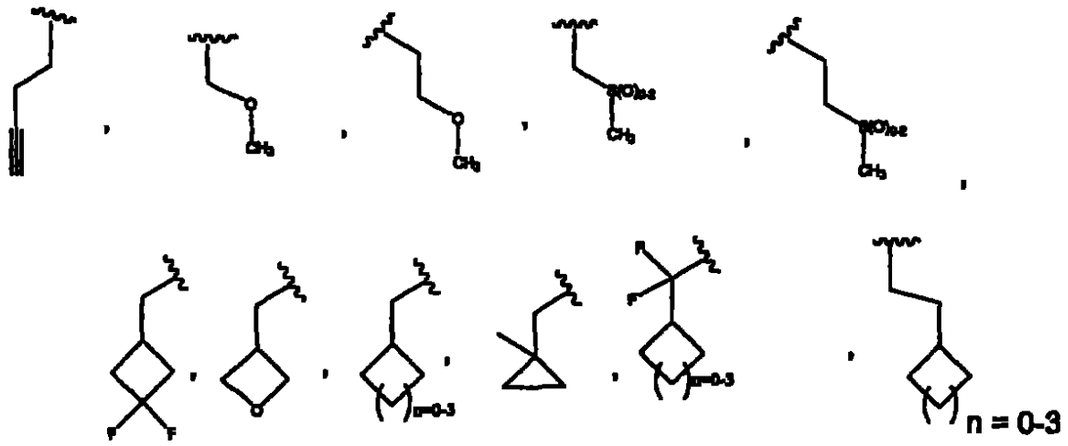
In another embodiment, R^1 is NR^9R^{10}, and R^9 is H, R^{10} is H, or R^{14} wherein R^{14} is H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl, alkenyl, alkynyl or heteroaryl-alkyl

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



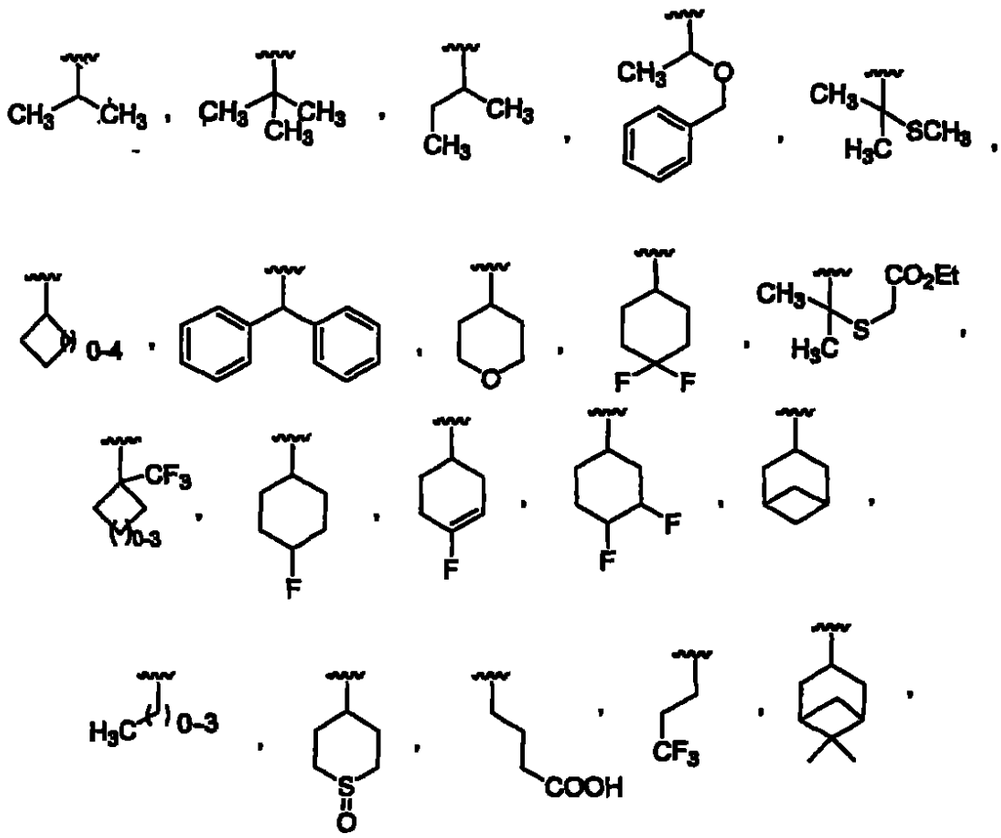
In another embodiment, R^2 is selected from the group consisting of the following moieties

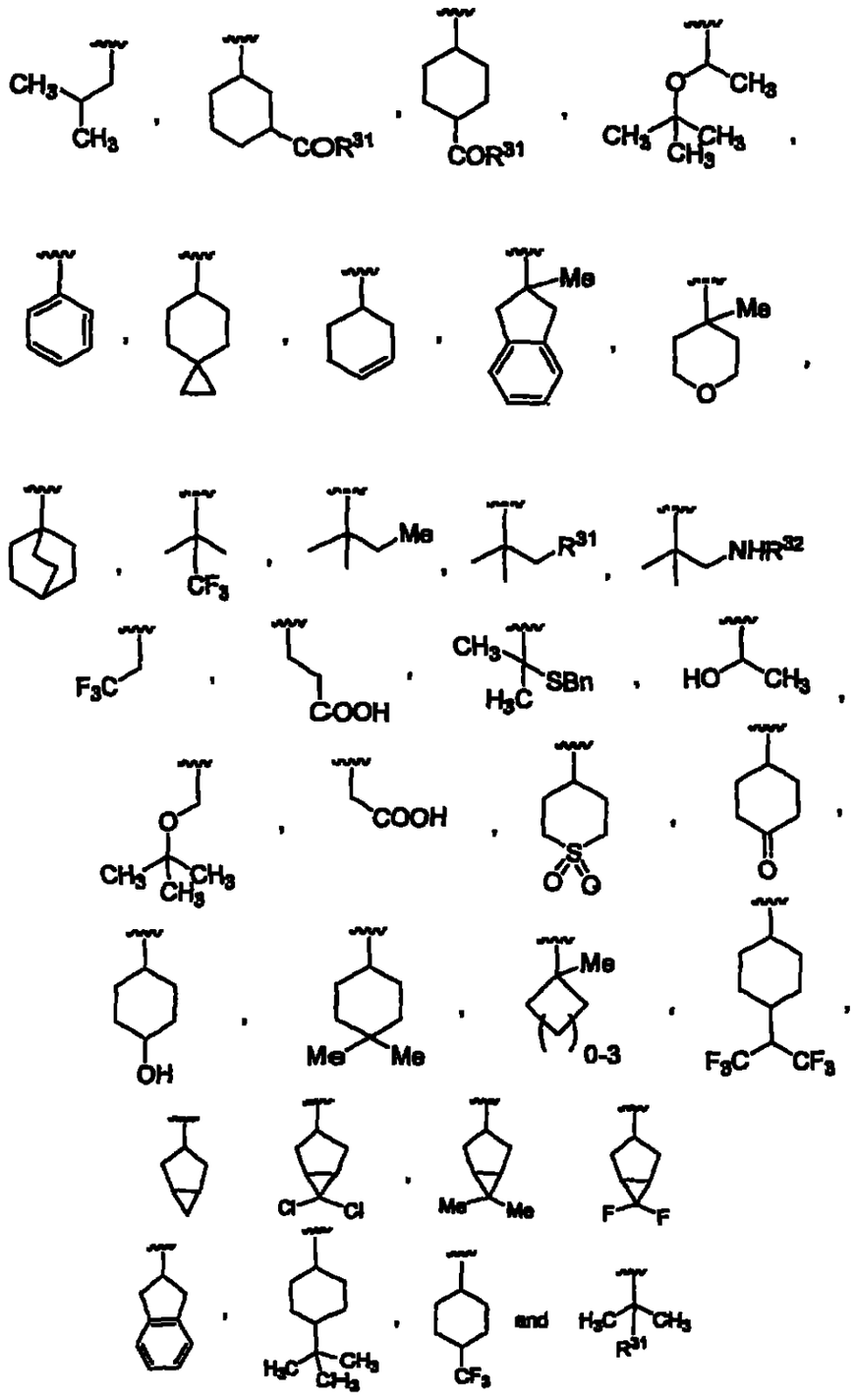






In another embodiment, R^3 is selected from the group consisting of

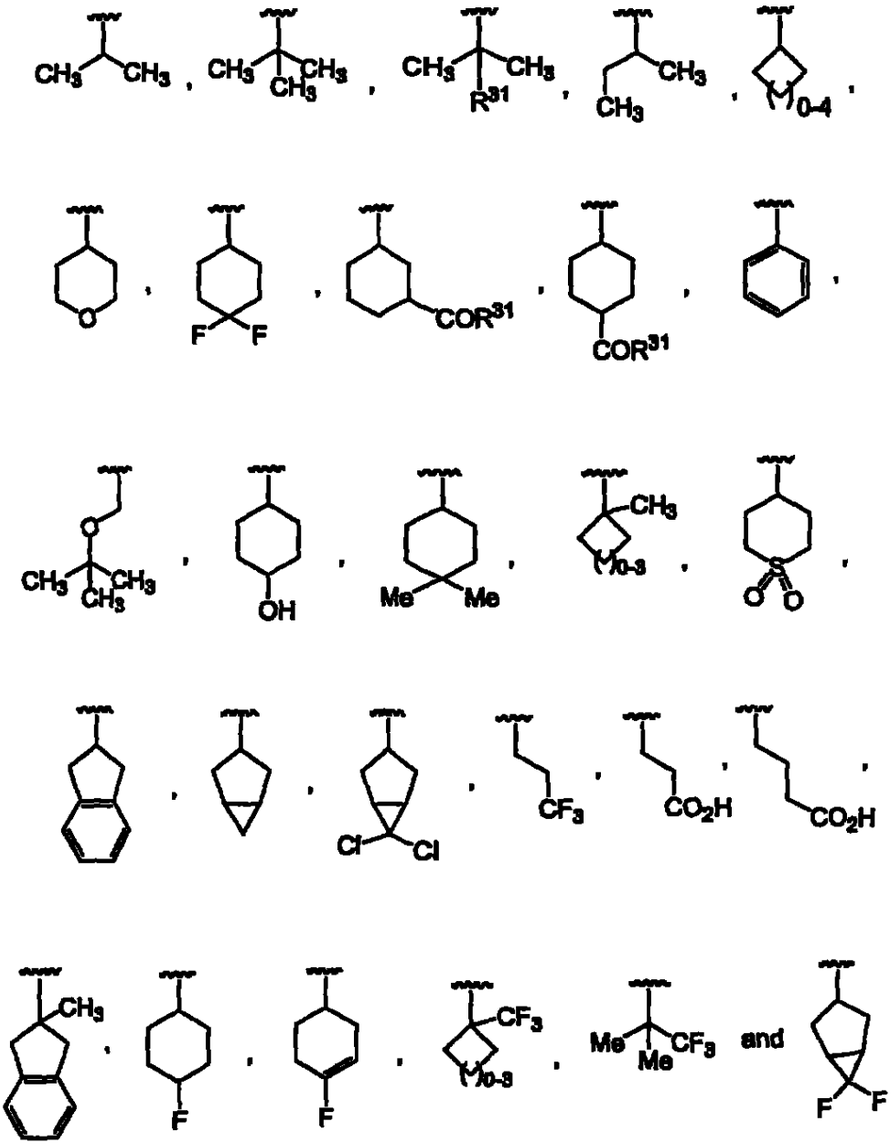




wherein R^{31} is OH or O-alkyl, and

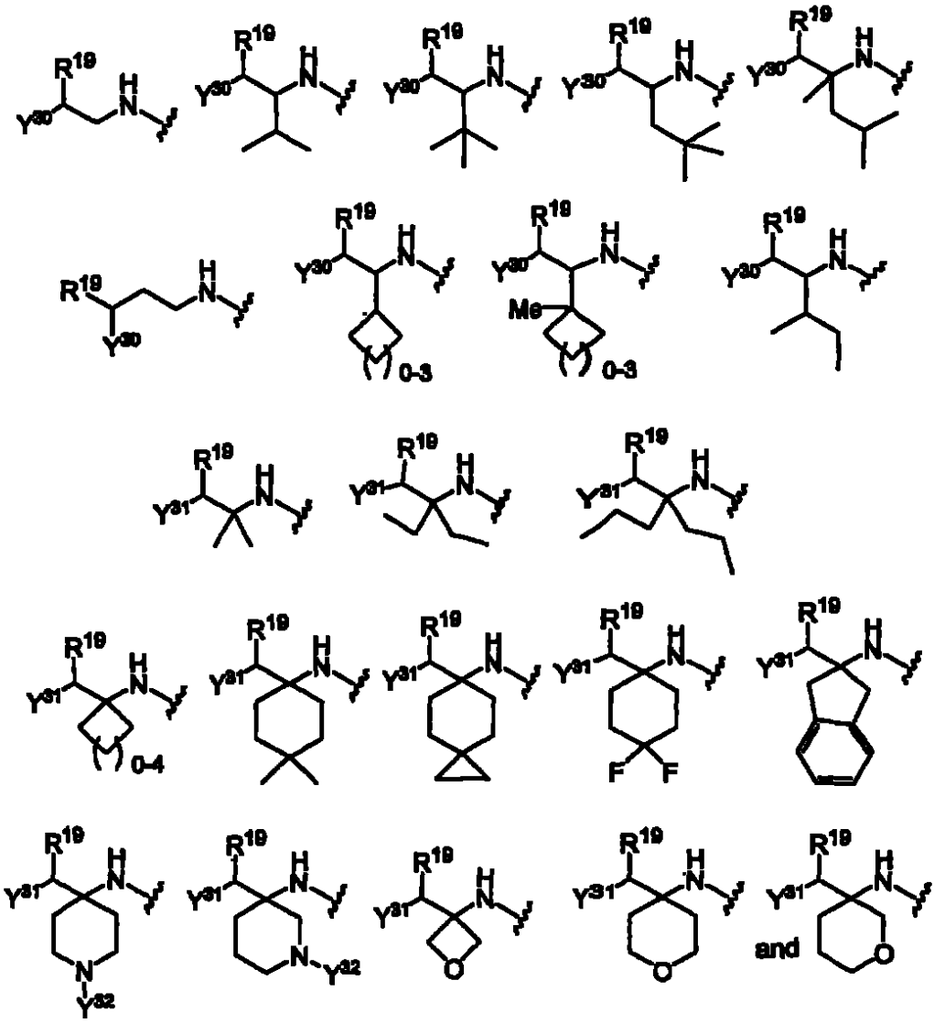
R^{32} is H, C(O)CH_3, C(O)OtBu or C(O)N(H)tBu

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

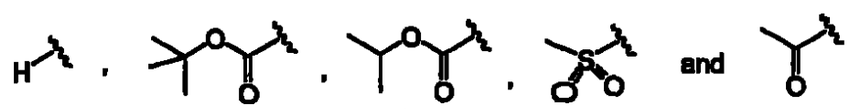


In another embodiment, G is NH

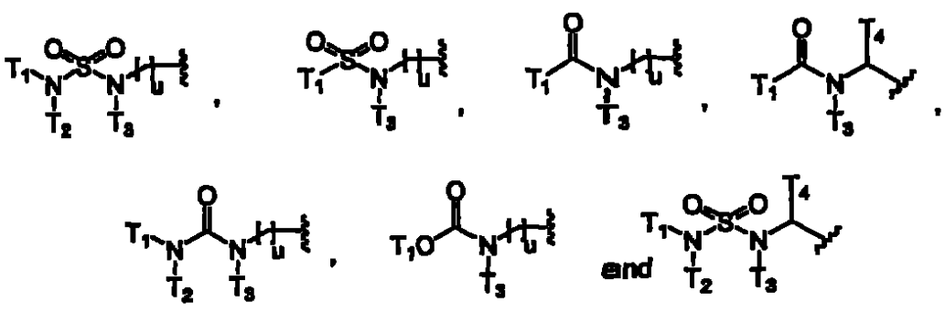
In another embodiment, Y is selected from the following moieties



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



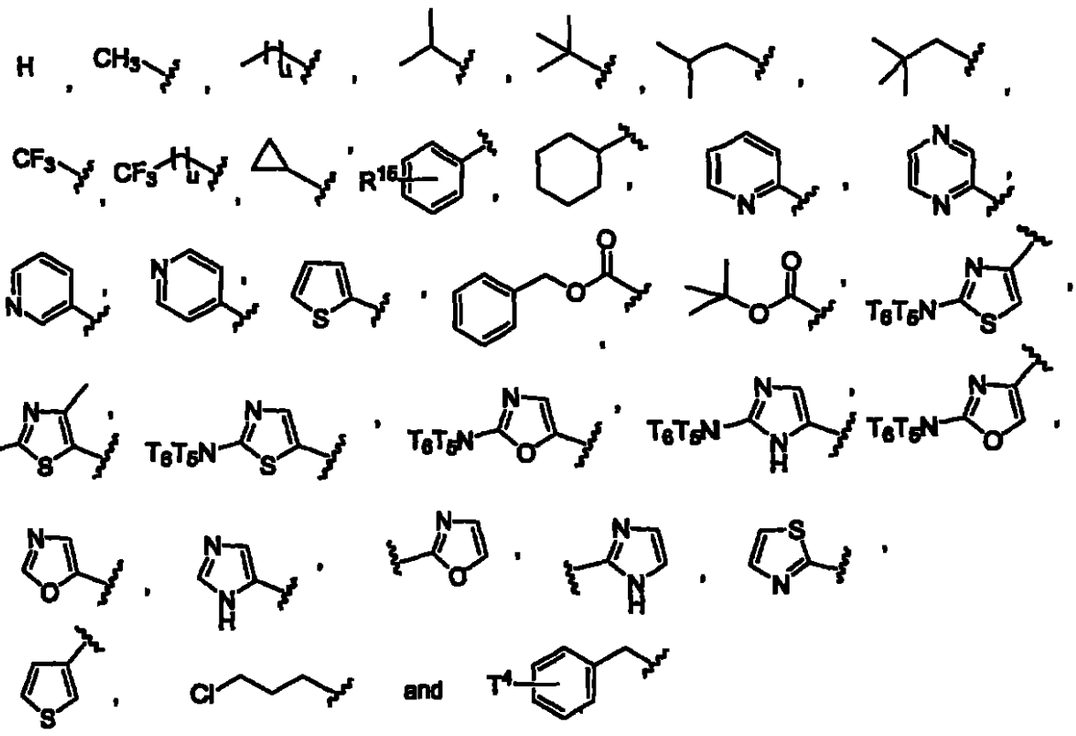
Y^{30} and Y^{31} is selected from



wherein u is a number 0-6, and

and R^{19} is selected from H, alkyl, phenyl or benzyl

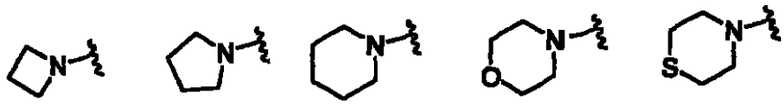
In another embodiment, T_1 and T_2 can be the same or different, each being independently selected from the group consisting of



wherein T_5 and T_6 can be the same or different, each being independently selected from the group consisting of alkyl, aryl, cycloalkyl, heteroaryl and heterocyclyl,

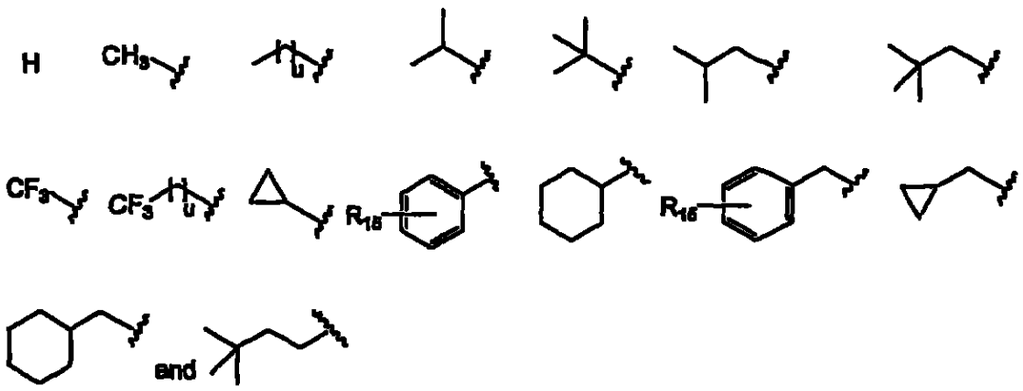
or the moiety

 taken together represents



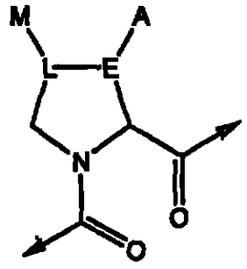
and

T_3 and T_4 can be the same or different, each being independently selected from

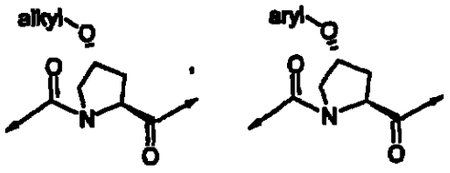


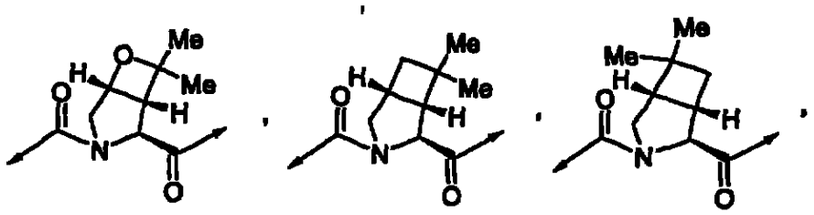
or T_3 and T_4 taken together may form part of a four to seven membered heterocyclic ring, in other words, the molety T_3-N-C-T_4 may form part of a four to seven membered heterocyclic ring

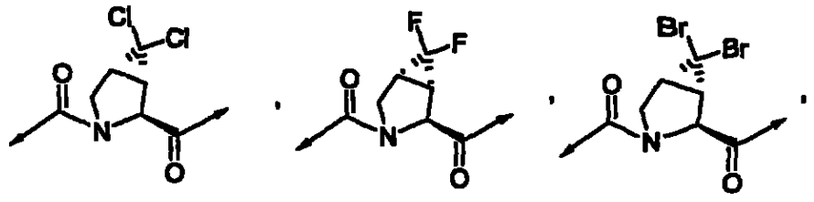
In another embodiment, the molety

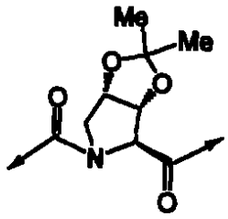
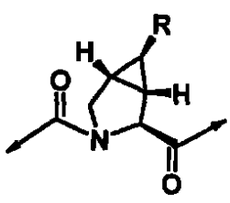
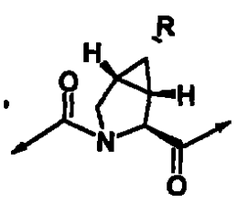
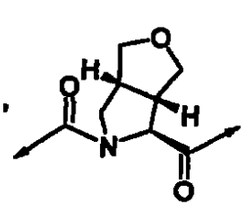
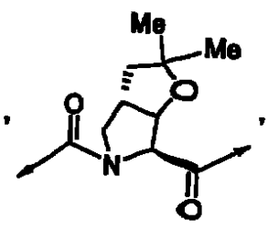
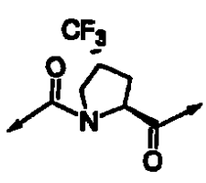
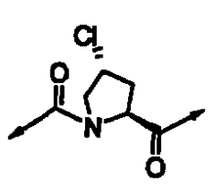
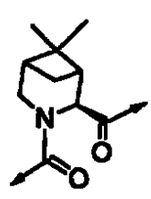
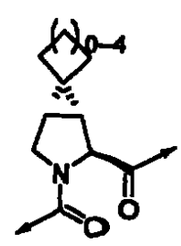


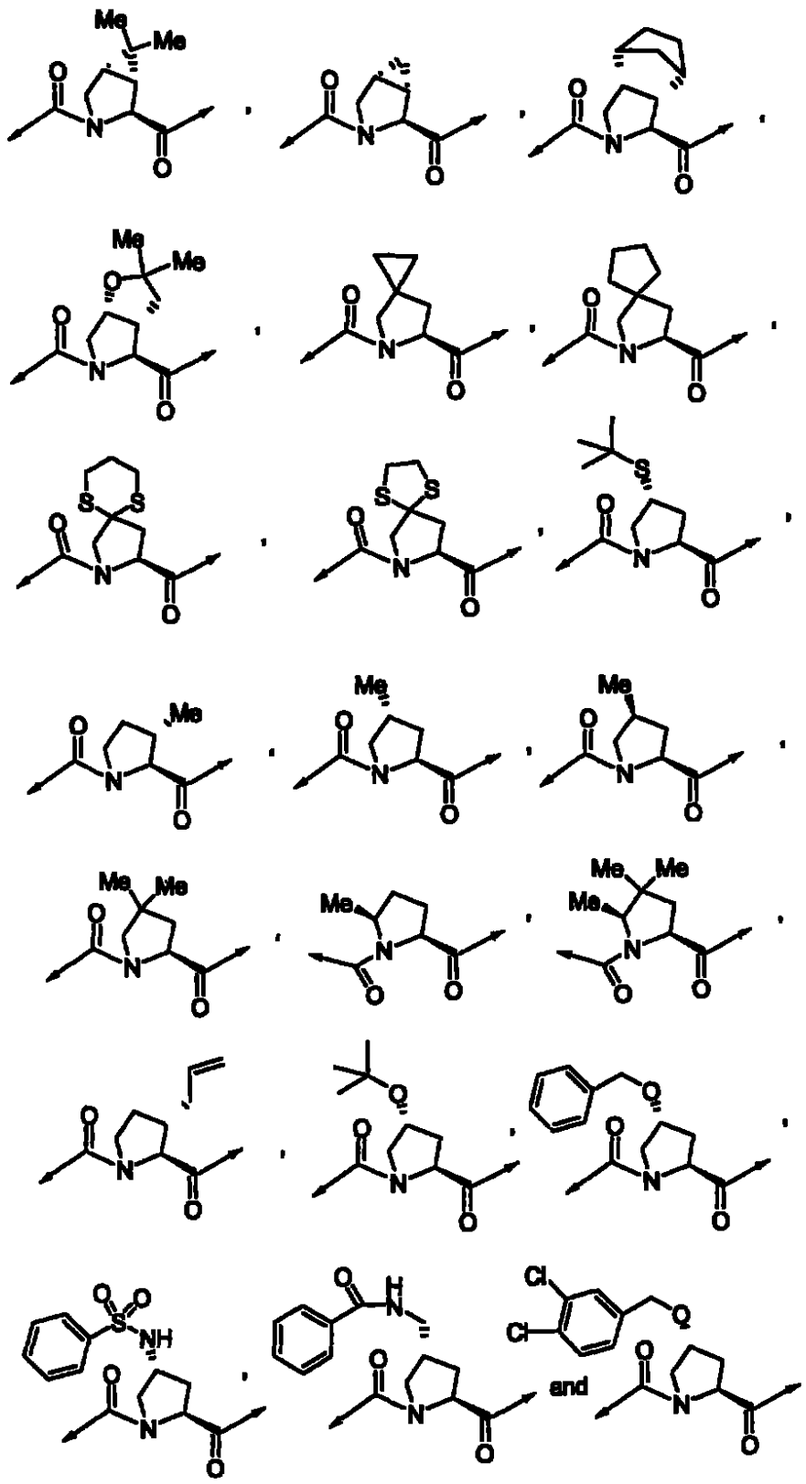
is selected from the following structures



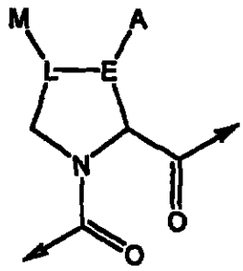




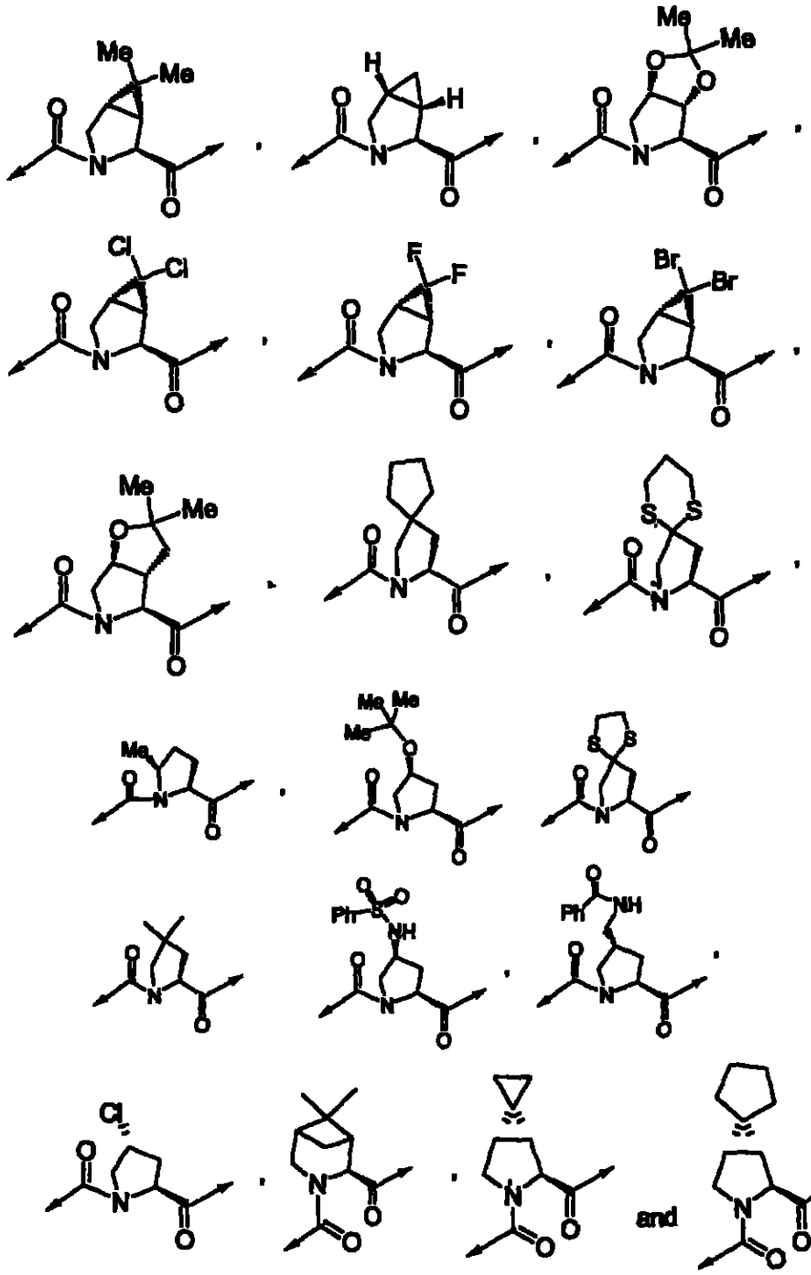












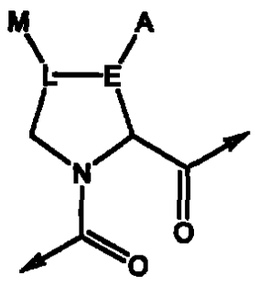
In an additional embodiment, the moiety



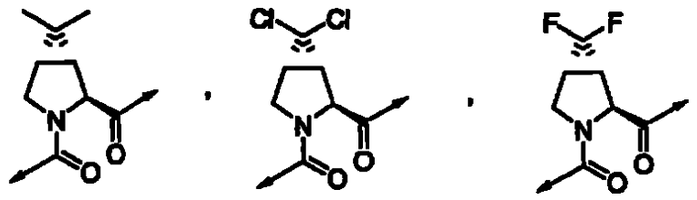
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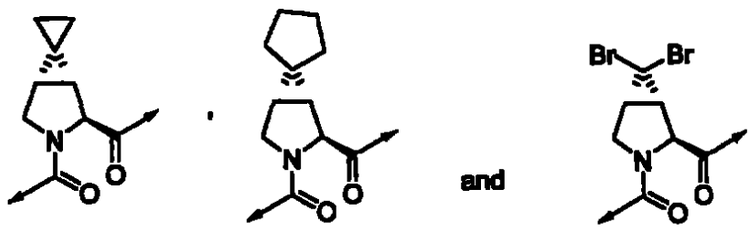


In a still additional embodiment, the moiety



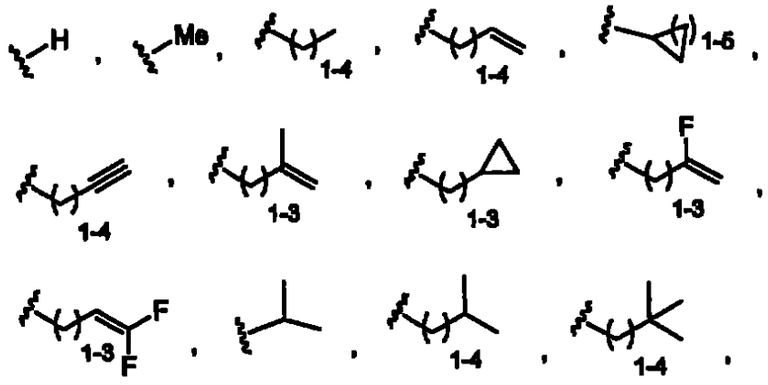
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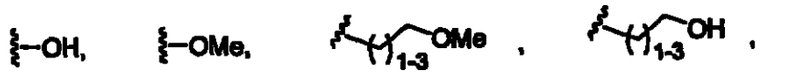


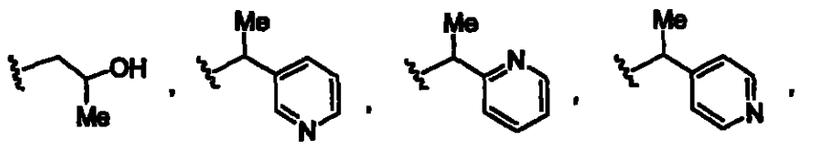


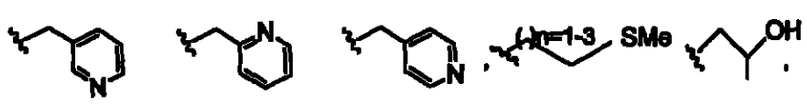
and

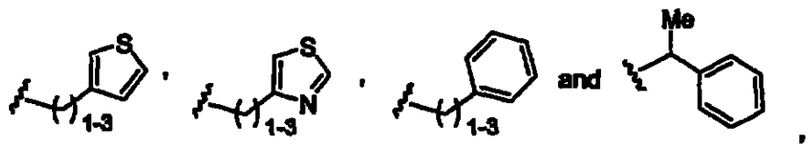
In a further additional embodiment, R^1 is NHR^{14}, where R^{14} is selected from the group consisting of



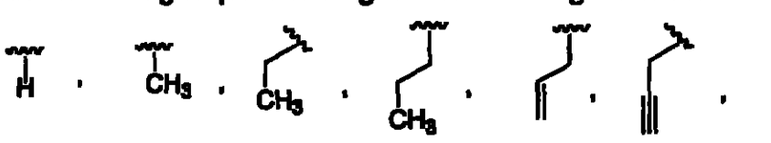


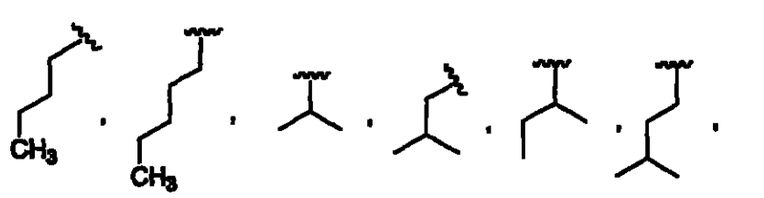


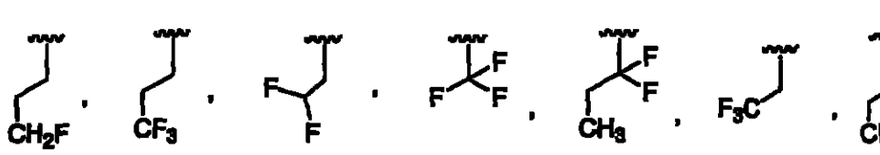


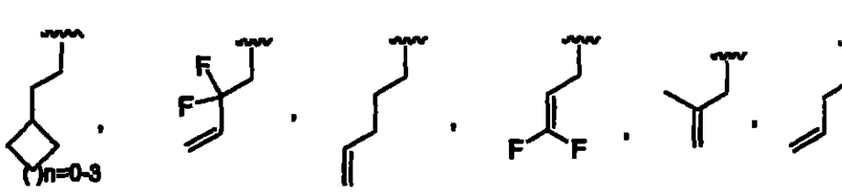


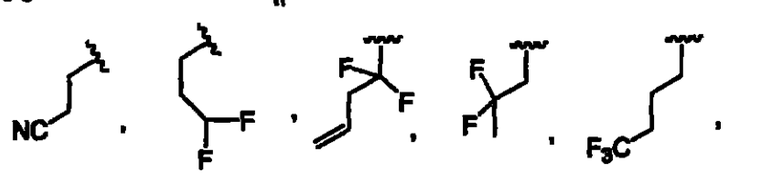
R^2 is selected from the group consisting of the following moieties

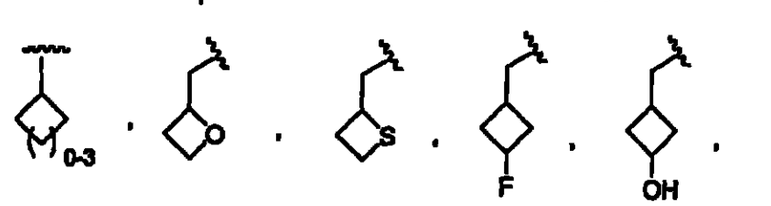




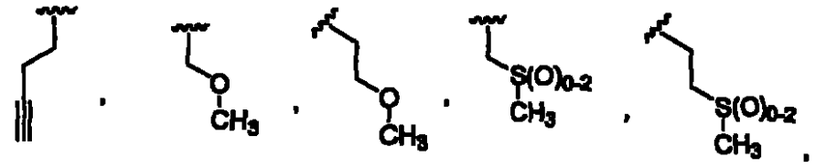


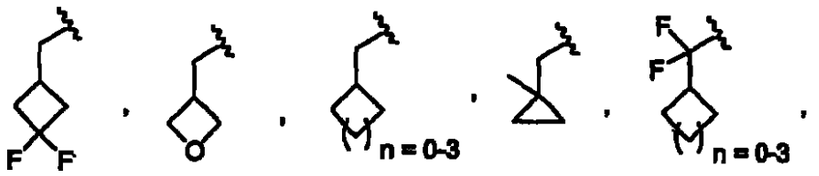


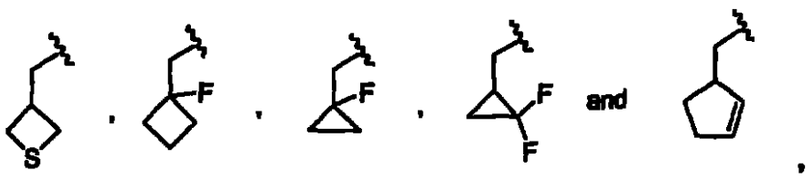




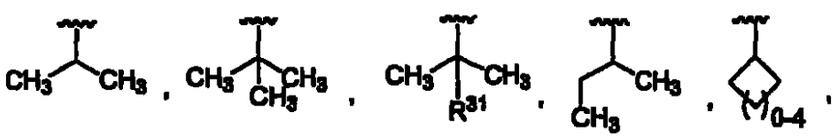


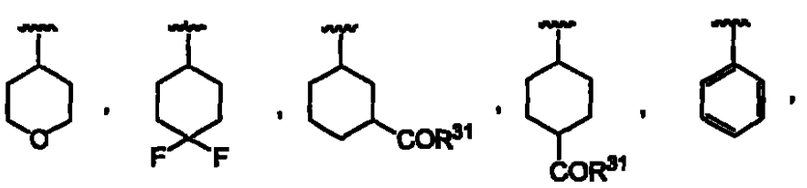


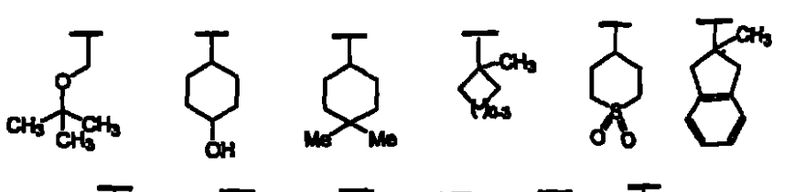


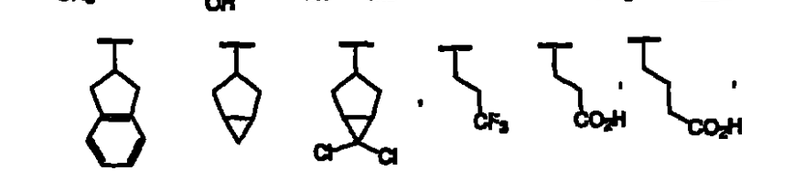


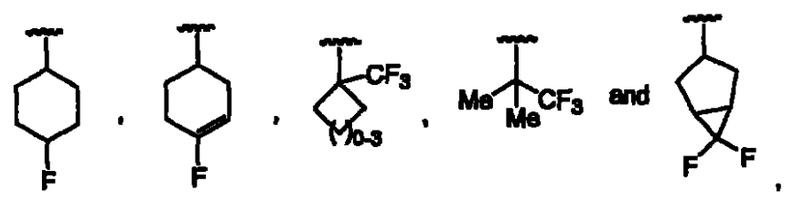
R^3 is selected from the group consisting of the following moieties





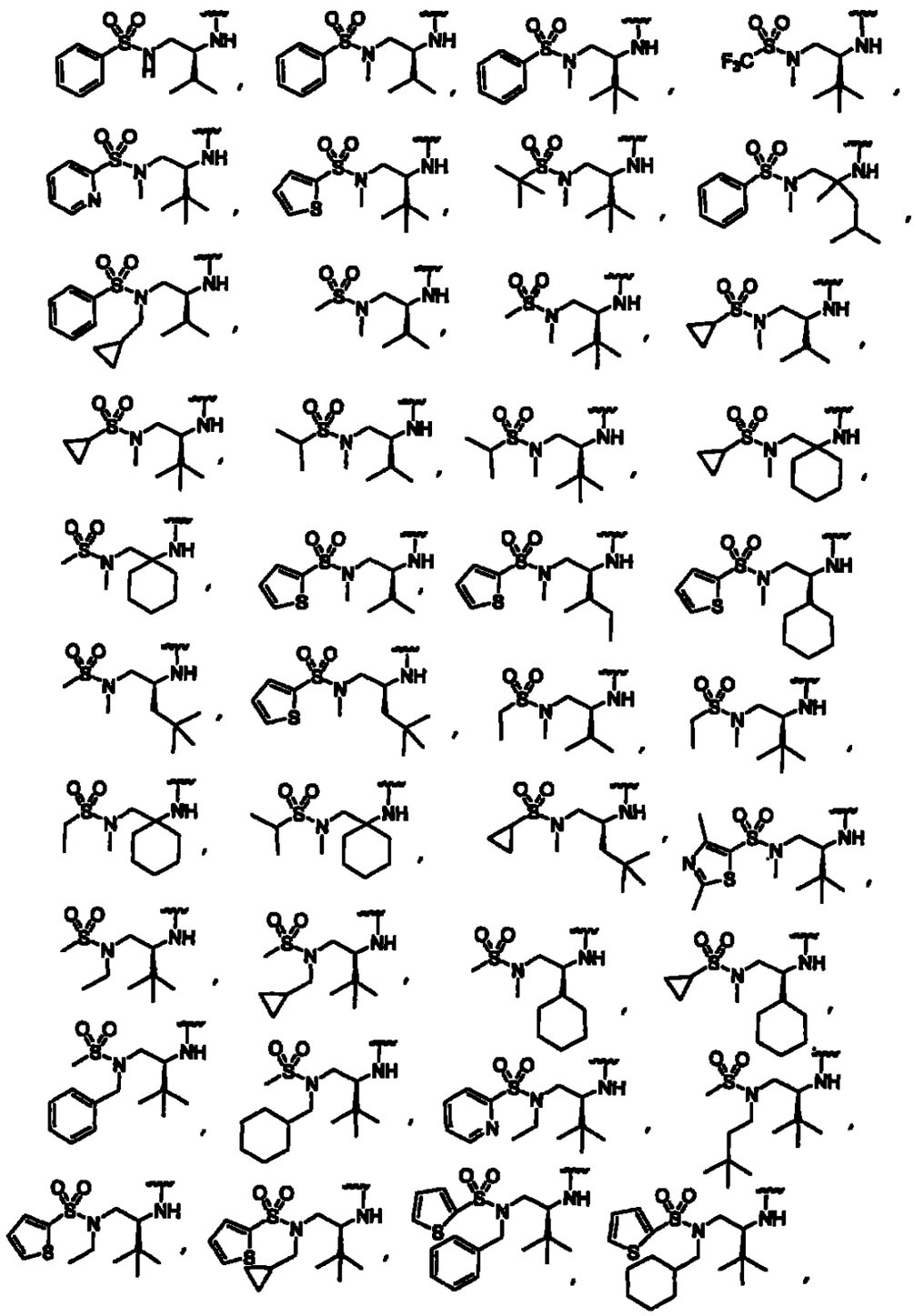


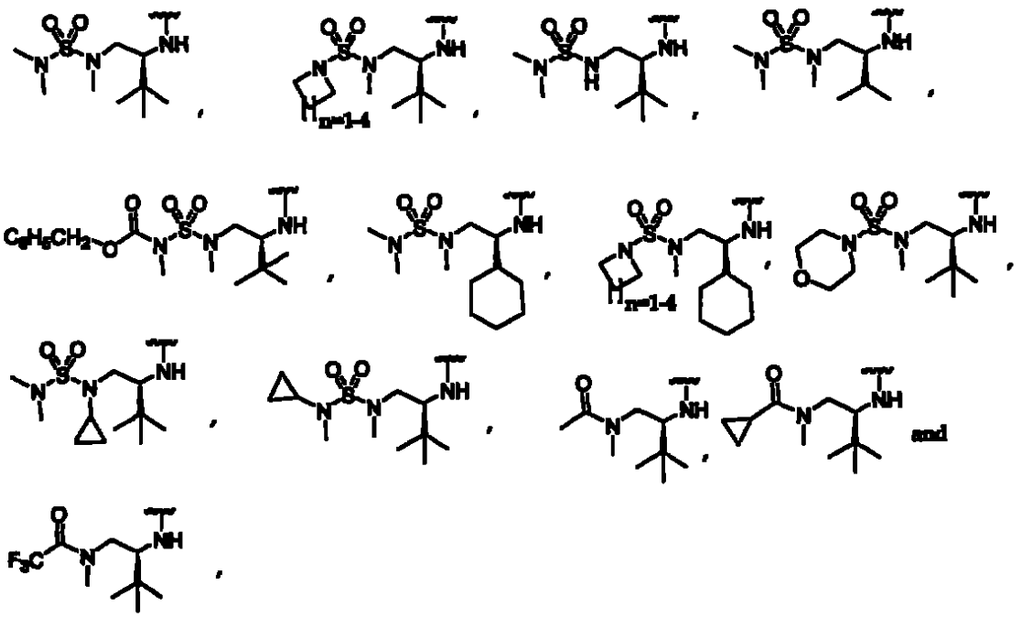




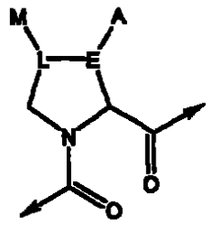


Y is selected from the group consisting of

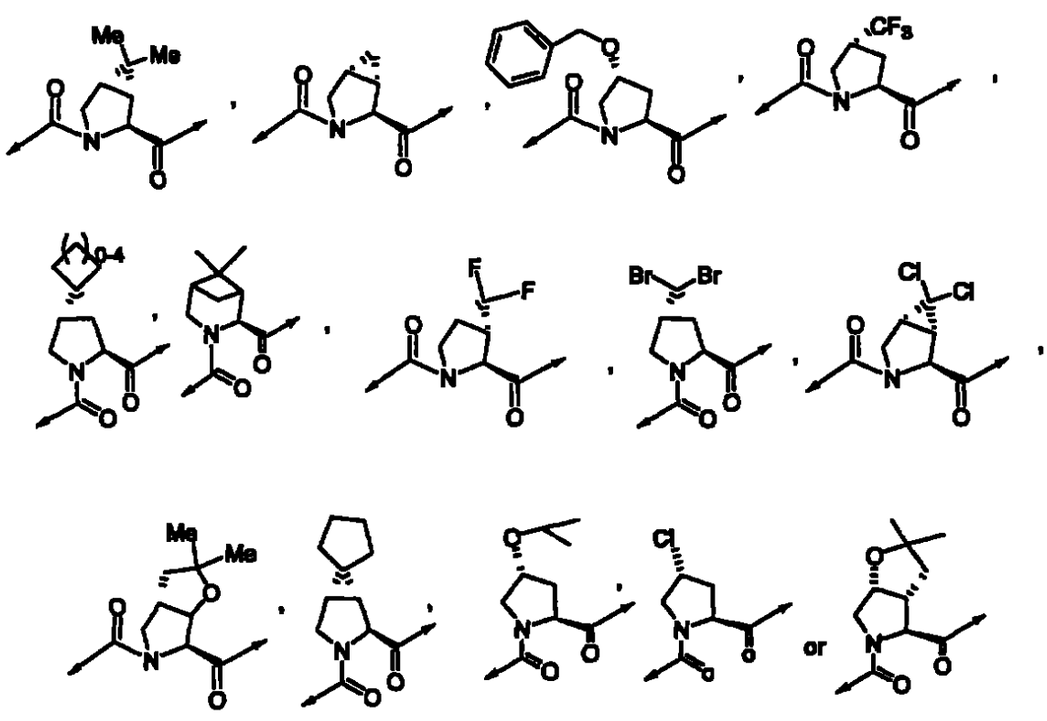




and the moiety



is

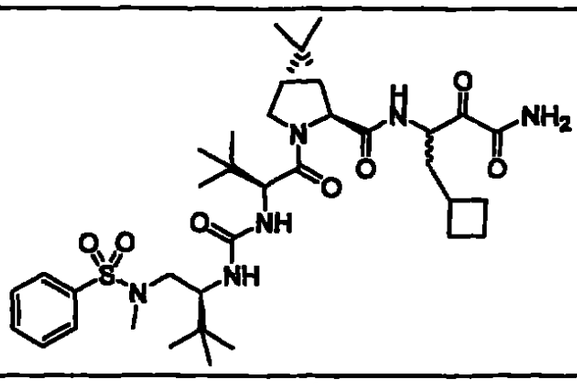
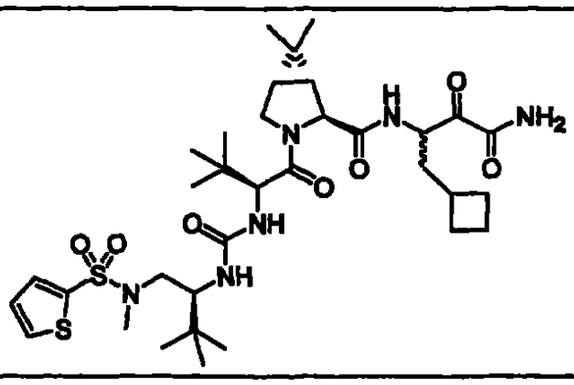
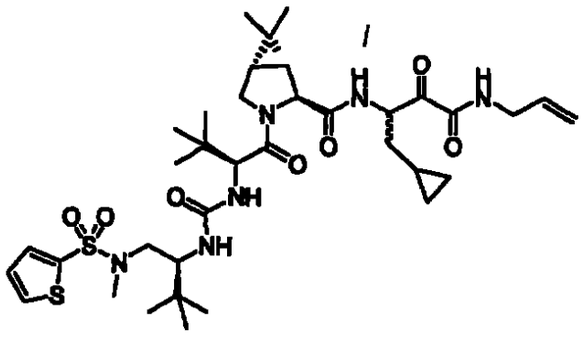


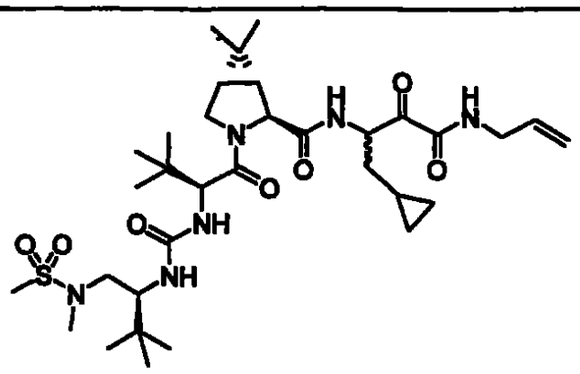
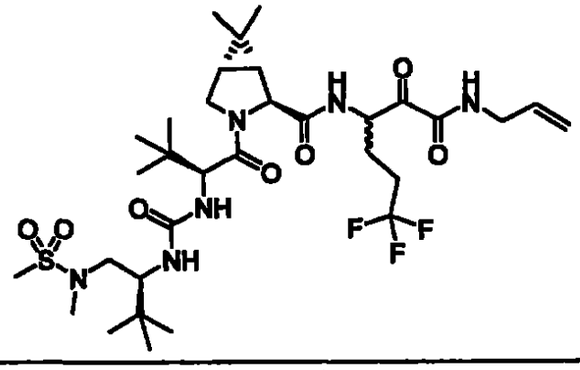
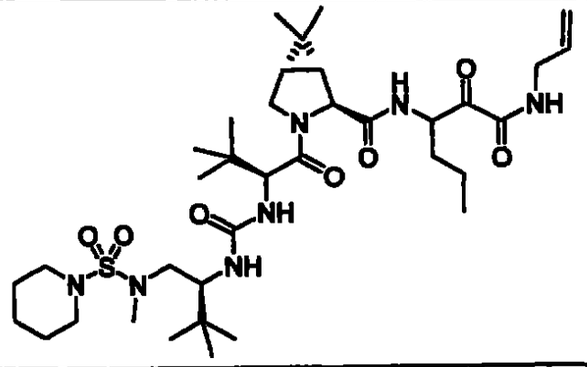
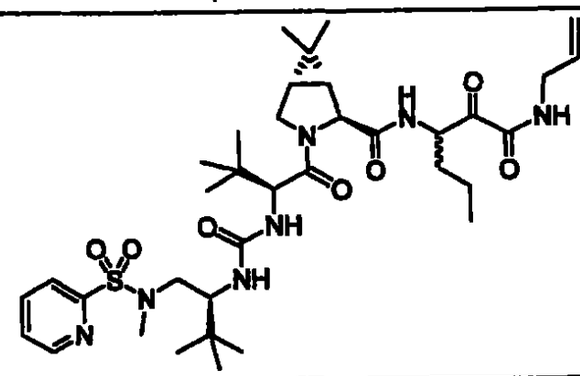
Yet another embodiment of the invention discloses compounds shown in Table 1, Table 2, Table 3, Table 4 and Table 5 later in this Description. Also

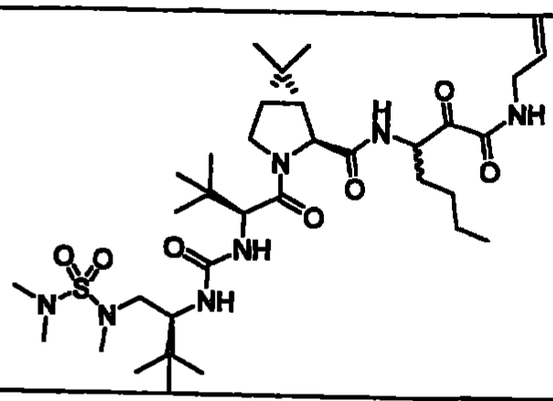
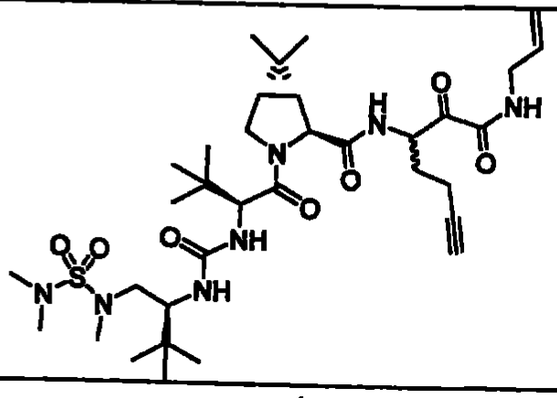
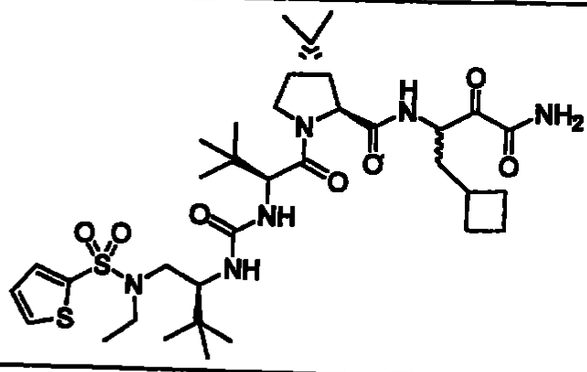
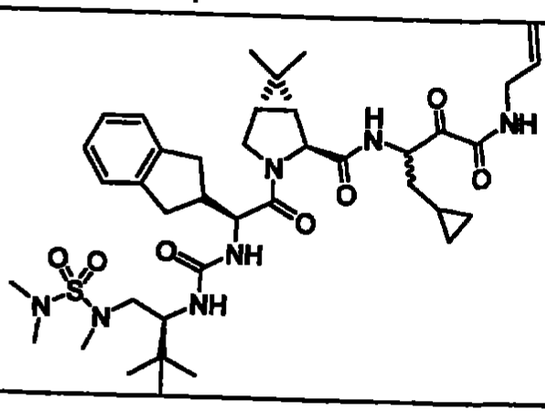
shown in the Tables are the biological activities of several inventive compounds (as KI* values in nanoMolar)

In a still additional embodiment, this invention discloses the following compounds in Table 6

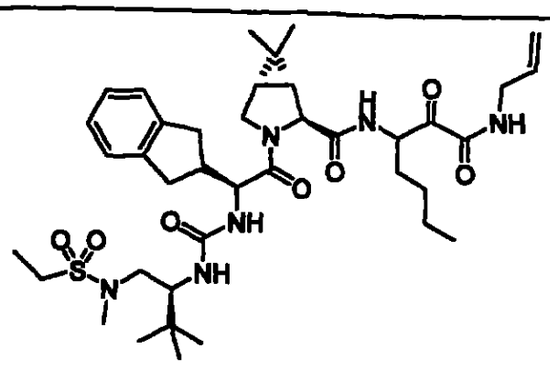
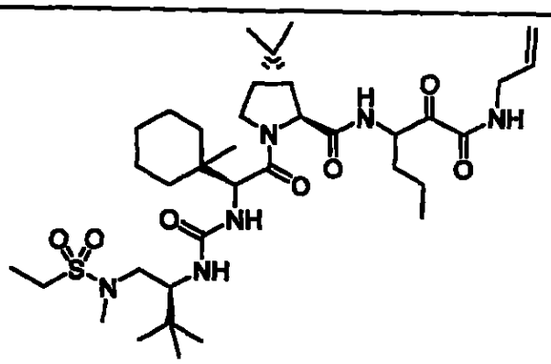
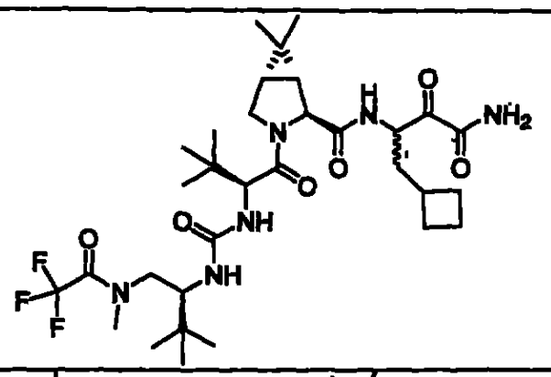
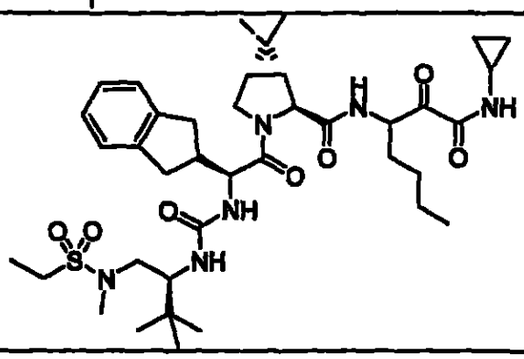
Table 6

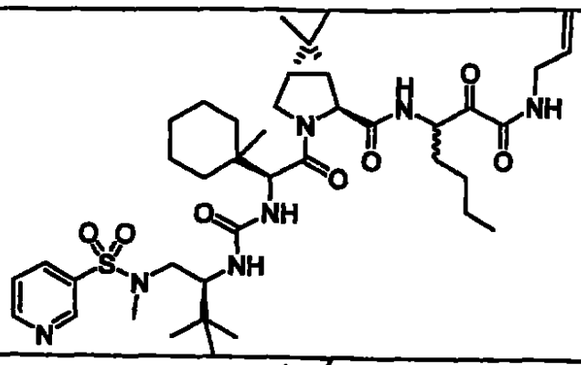
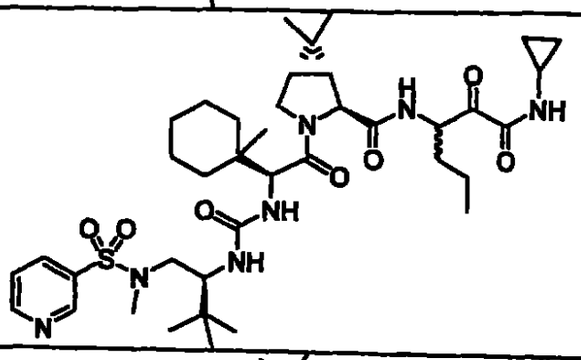
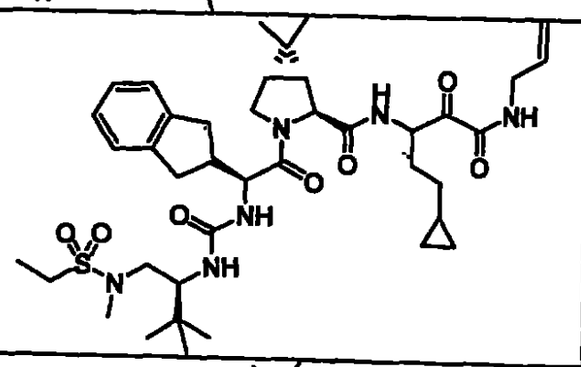
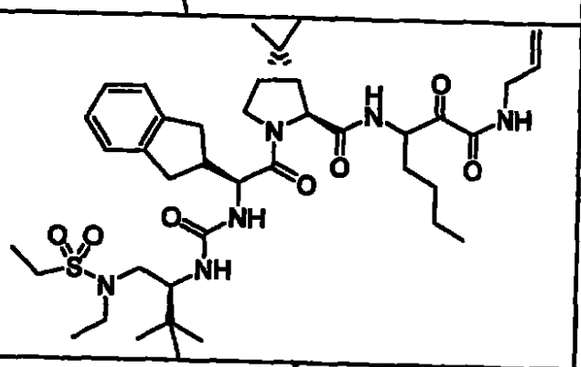
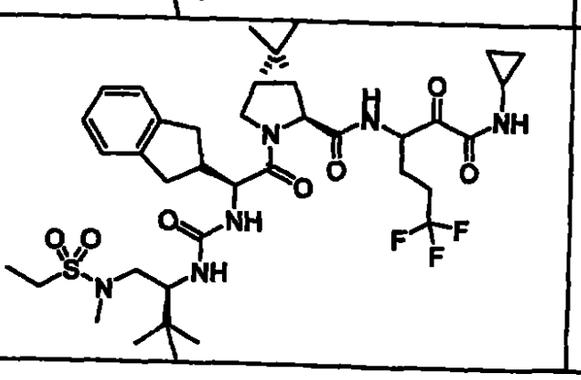
Structure	KI* (nM)
	5
	3 7
	30

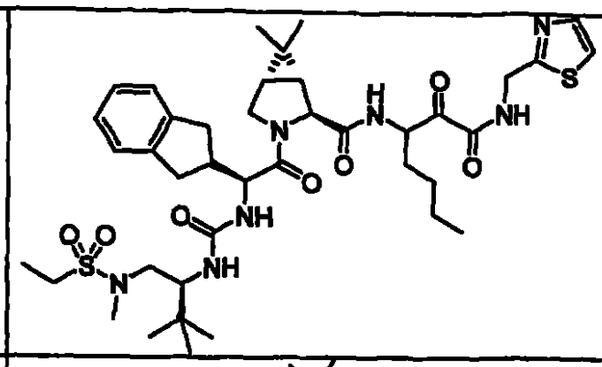
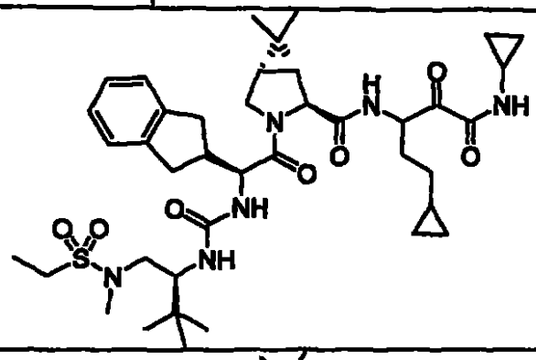
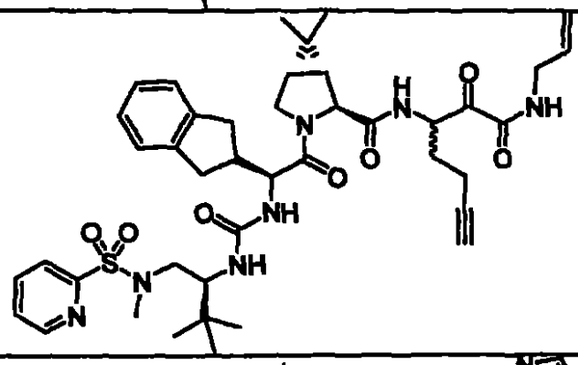
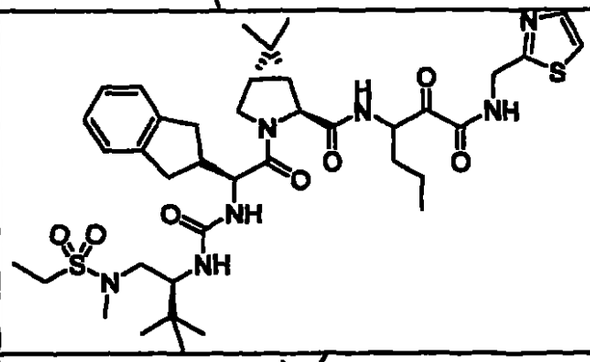
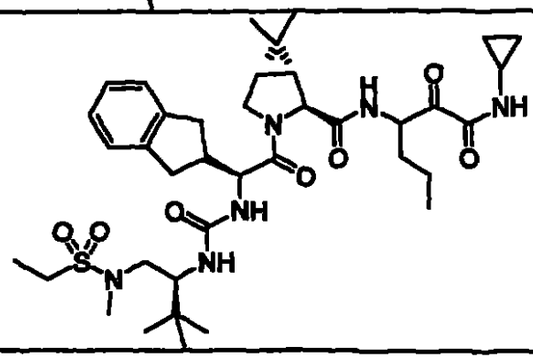
	19
	9
	15
	14

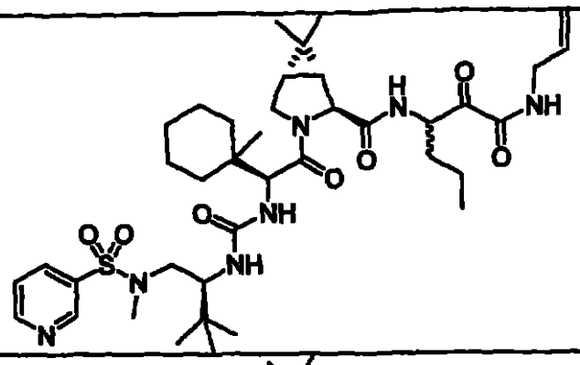
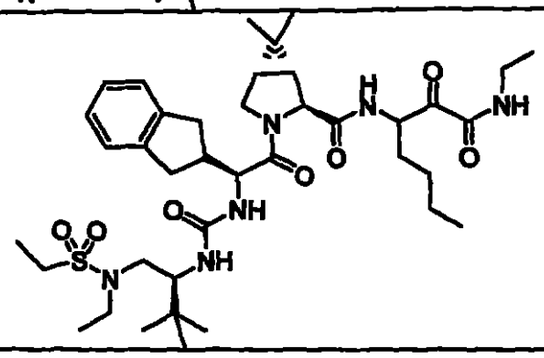
	11
	26
	9
	12

27
27

		58
		10
		2
11399		4

11405		4
11411		5
11417		6
11401		6
11412		7

11418		7
11421		7
11395		8
11420		8
11400		9

11410		9
11402		10

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

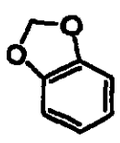
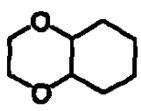
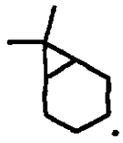
"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described Preferred alkylaryls comprise a lower alkyl group Non-limiting example of a suitable alkylaryl group is tolyl The bond to the parent molety is through the aryl

"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 sam 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

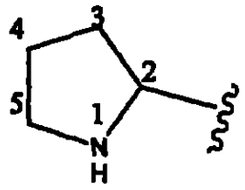
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl,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



are considered equivalent in certain embodiments of this invention

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

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described Preferred heteroaralkyls contain a

lower alkyl group Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl The bond to the parent moiety is through the alkyl

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto

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

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

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

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates,

oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P Stahl *et al*, Camille G (eds) *Handbook of Pharmaceutical Salts Properties, Selection and Use* (2002) Zurich Wiley-VCH, S Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19, P Gould, *International J of Pharmaceutics* (1986) 33 201-217, Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York, and in *The Orange Book* (Food & Drug Administration, Washington, D C on their website) These disclosures are incorporated herein by reference thereto

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

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

Pharmaceutically acceptable esters of the present compounds include the following groups (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino), (2) sulfonate esters,

such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl), (3) amino acid esters (for example, L-valyl or L-isoleucyl), (4) phosphonate esters and (5) mono-, di- or triphosphate esters The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol

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

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

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

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

comprising such compound or compounds and method(s) of treatment involving such compound or compounds

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

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

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

In yet another embodiment, the present invention discloses methods for preparing pharmaceutical compositions comprising the inventive compounds as an active ingredient. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, i e oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert

carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture Powders and tablets may be comprised of from about 5 to about 95 percent inventive composition

Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like Disintegrants include starch, methylcellulose, guar gum and the like

Sweetening and flavoring agents and preservatives may also be included where appropriate Some of the terms noted above, namely disintegrants, diluents, lubricants, binders and the like, are discussed in more detail below

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

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

Aerosol preparations suitable for inhalation may includ 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 hydrophilic semi-solid matrix

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

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

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

Binder - refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" In the formulation Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose, starches derived from wheat, corn rice and potato, natural gums such as acacia, gelatin and tragacanth, derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate, cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose, polyvinylpyrrolidone, and inorganics such as magnesium aluminum silicate The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

Lubricant - refers to a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate, stearic acid, high melting point waxes, and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and d'l-leucine Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press The amount of lubricant in the composition can range from about 0 2 to about 5% by weight of the composition, preferably from about 0 5 to about 2%, more preferably from about 0 3 to about 1 5% by weight

Glident - material that prevents caking and improve the flow characteristics of granulations, so that flow is smooth and uniform Suitable glidents include silicon dioxide and talc The amount of glident in the composition can range from about 0 1% to about 5% by weight of the total composition, preferably from about 0 5 to about 2% by weight.

Coloring agents - excipients that provide coloration to the composition or the dosage form Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum

oxide The amount of the coloring agent can vary from about 0 1 to about 5% by weight of the composition, preferably from about 0 1 to about 1%

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

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

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

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

attached to a PEG molecule. Illustrative PEG-Interferon alpha conjugates include Interferon alpha-2a (Roferon™, from Hoffman La-Roche, Nutley, New Jersey) In the form of pegylated Interferon alpha-2a (e g , as sold under the trade name Pegasys™), interferon alpha-2b (Intron™, from Schering-Plough Corporation) in the form of pegylated Interferon alpha-2b (e g , as sold under the trade name PEG-Intron™), interferon alpha-2c (Berofor Alpha™, from Boehringer Ingelheim, Ingelheim, Germany) or consensus interferon as defined by determination of a consensus sequence of naturally occurring interferon alphas (Infergen™, from Amgen, Thousand Oaks, California)

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

Another embodiment of the invention discloses a method of making the compounds disclosed herein The compounds may be prepared by several techniques known in the art Illustrative procedures are outlined in the following reaction schemes The illustrations should not be construed to limit the scope of the invention which is defined in the appended claims Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art.

It is to be understood that while the following illustrative schemes describe the preparation of a few representative inventive compounds, suitable substitution of any of both the natural and unnatural amino acids will result in the formation of the desired compounds based on such substitution Such variations are contemplated to be within the scope of the invention

For the procedures described below, the following abbreviations are used

Abbreviations

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

THF Tetrahydrofuran

DMF N,N-Dimethylformamide

EtOAc Ethyl acetate

AcOH Acetic acid

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

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

NMM N-Methylmorpholine

ADDP 1,1'-(Azodicarbobyl)dipiperidine

DEAD Diethylazodicarboxylate

MeOH Methanol

EtOH Ethanol

Et_2O Diethyl ether

DMSO Dimethylsulfoxide

HOBt N-Hydroxybenzotriazole

PyBrOP Bromo-tris-pyrrolidinophosphonium hexafluorophosphate

DCM Dichloromethane

DCC 1,3-Dicyclohexylcarbodiimide

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

Phg Phenylglycine

Chg Cyclohexylglycine

Bn Benzyl

Bzl Benzyl

Et. Ethyl

Ph Phenyl

IBoc Isobutoxycarbonyl

IPr Isopropyl

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

Boc *tert*-Butyloxycarbonyl

Cbz Benzyloxycarbonyl

Cp Cylcopentyldienyl

Ts p-toluenesulfonyl

MCPBA 3-chloroperbenzoic acid

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

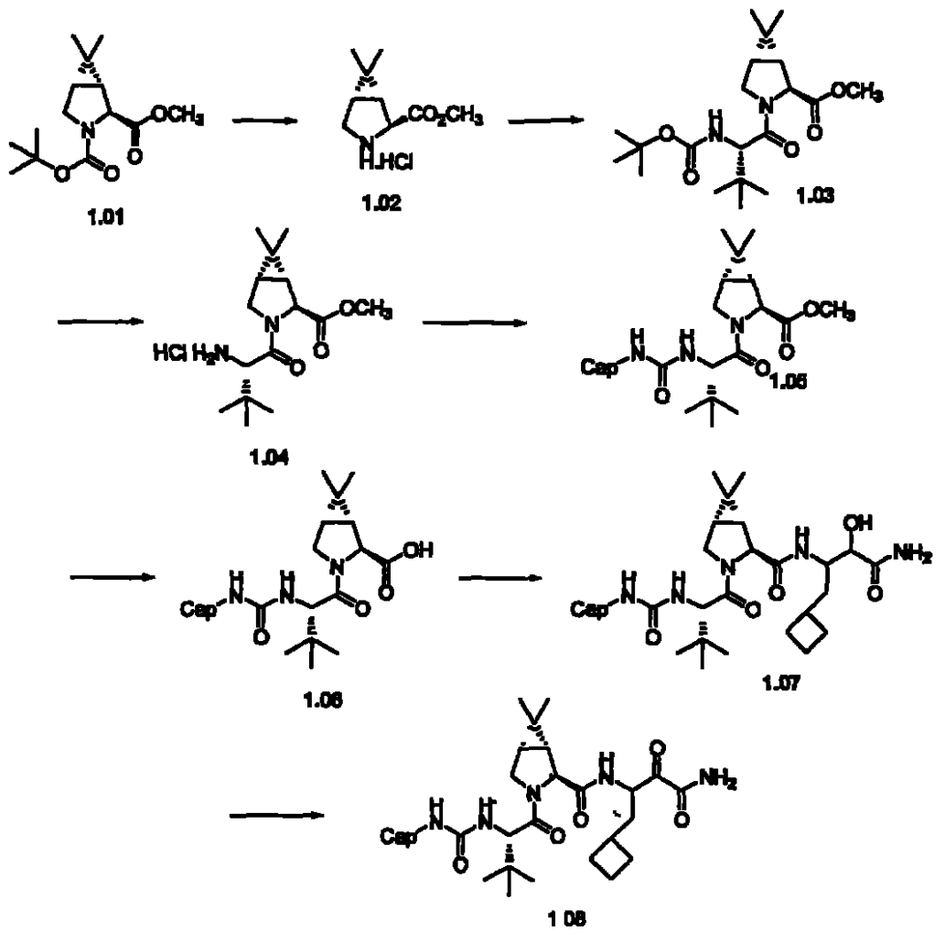
Other abbreviations are commonly used abbreviations Such as according to the guidelines published by *Journal of Organic Chemistry*

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 (Louis A Carpino *et al* "Preparation of uronium and immonium salts for peptide coupling", WO 2002094822, pp 76) to afford 1 03 N-Boc deprotection followed by treatment with appropriate isocyanate gave the urea 1 05 Hydrolysis of th methyl ester provided the acid 1 06 Peptide coupling of the acid 1 06 with the appropriate P_1-P' primary amide moiety afforded the hydroxyl amide 1 07 Oxidation (Moffatt, or Dess-Martin's) resulted in the target compound 1 08

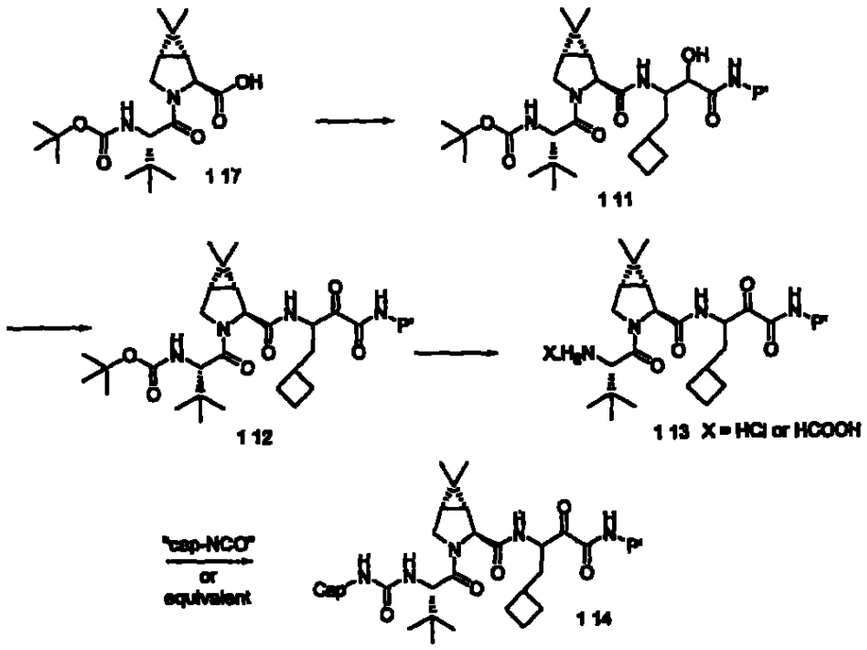


Method B

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

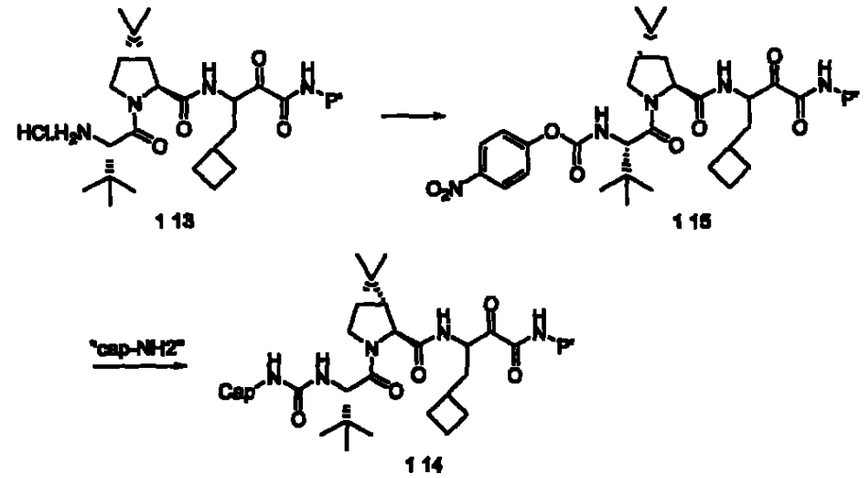
Method C

In another variation, peptide coupling of the N-Boc-P2-P_3-acid 1 03 with the appropriate P_1-P' amide moiety afforded the hydroxyl amide 1 11 Oxidation (Moffatt or Dess-Martin's) resulted in the keto-amide 1 12 Deprotection of the N-Boc using either formic acid or 4 M HCl in dioxane gave the formate or hydrochloride salt 1 13 Treatment with a suitable isocyanate (or isocyanate equivalent) resulted in the target compound 1 14



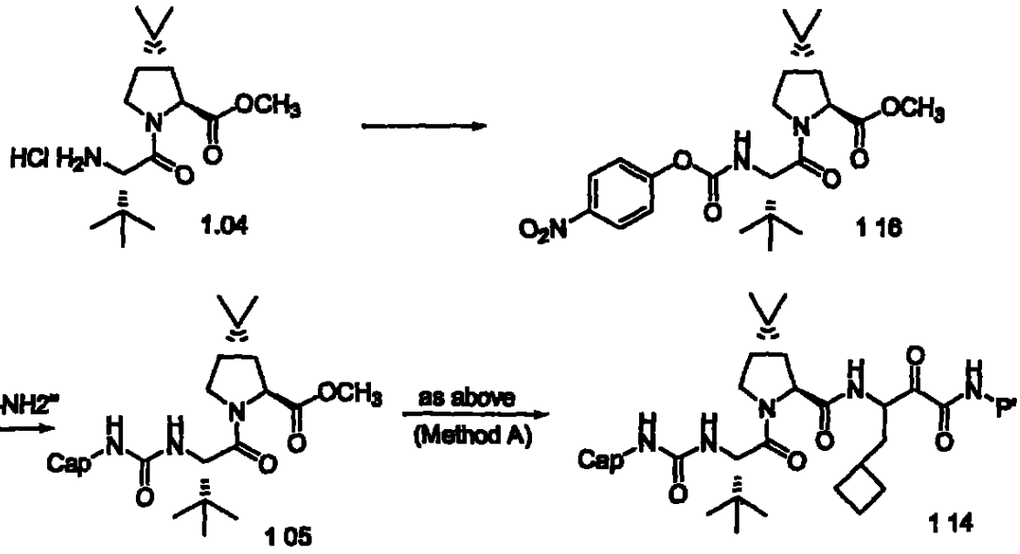
Method D

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 04 was converted to the 4-nitrophenyl carbamate as described above Treatment with an amine (or amine hydrochloride salt) of choice provided the urea derivative 1 05 Hydrolysis and further elaboration as described in Methods A/B provided the target compounds 1 14

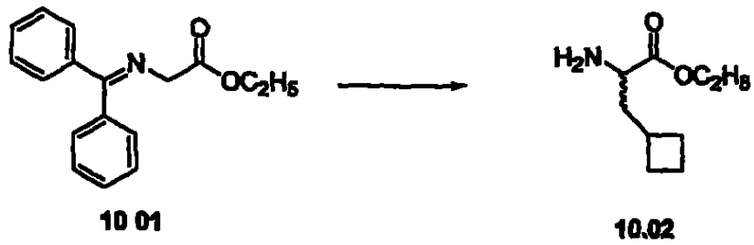


Preparation of Intermediates

Preparation of P1-P' moieties

Preparation of Intermediates 10.11 and 10.12

Step 1

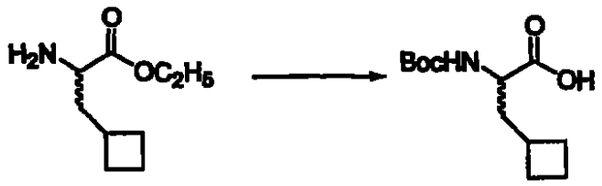


10 01 10.02

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

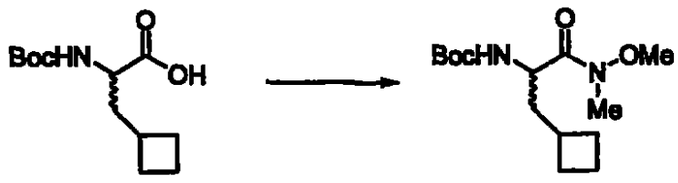
Step 2



10 02 10 03

A solution of the amine 10 02 (18g, 105 2 mmol) at 0 °C in CH_2Cl_2 (350 mL) was treated with di-*tert*-butyldicarbonate (23 g, 105 4 mmol) and stirred at rt for 12 h After the completion of the reaction (TLC), the reaction mixture was concentrated in *vacuo* and the residue was dissolved in THF/H_2O (200 ml, 1 1) and treated with $LiOH \cdot H_2O$ (6 5 g, 158 5 mmol) and stirred at room temperature for 3 h The reaction mixture was concentrated and the basic aqueous layer was extracted with Et_2O The aqueous layer was acidified with conc HCl to pH~1-2 and extracted with CH_2Cl_2 The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 10 03 as a colorless viscous oil which was used for the next step without any further purification

Step 3

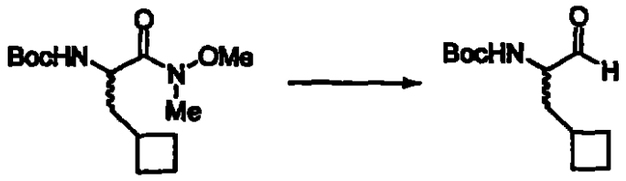


10.03 10.04

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)

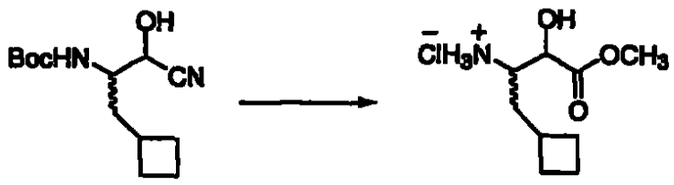
Step 5



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,

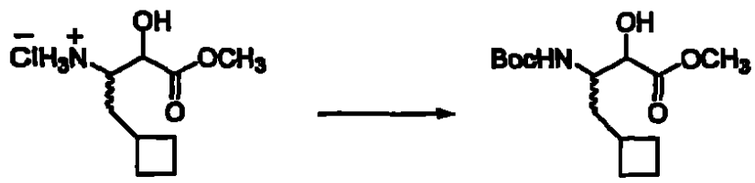


10 06 10 07

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

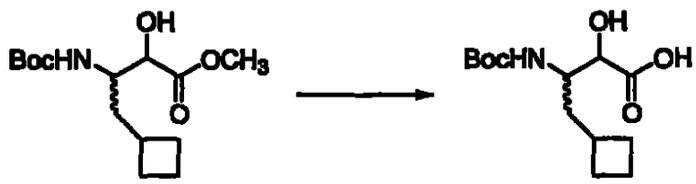
Step 7.



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

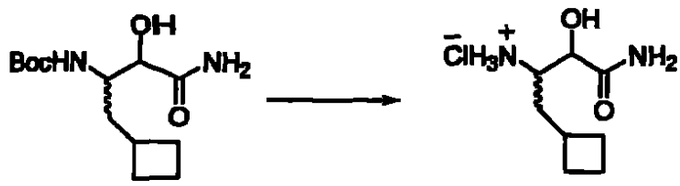
Step 9



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 Sat'd $NaHCO_3$, dried ($MgSO_4$) filtered concentrated in *vacuo* to obtain 10 10, which was used as it was in the following steps (Alternatively 10 10 can also be obtained directly by the reaction of 10 06 (4 5 g, 17 7 mmol) with aq H_2O_2 (10 mL), $LiOH \cdot H_2O$ (820 mg, 20 8 mmol) at 0 °C in 50 mL of CH_3OH for 0 5 h)

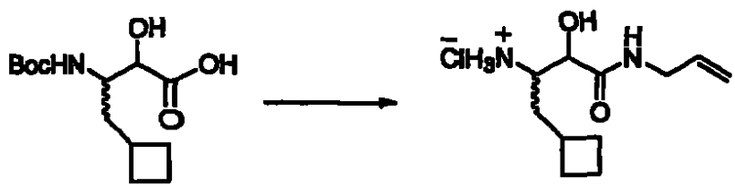
Step 10



10 10 10 11

A solution of 10 10 obtained in the previous step was dissolved in 4 N HCl in dioxane and stirred at rt. for 2 h The reaction mixture was concentrated in *vacuo* to give the intermediate 10 11 as a solid, which was used without further purification

Step 11



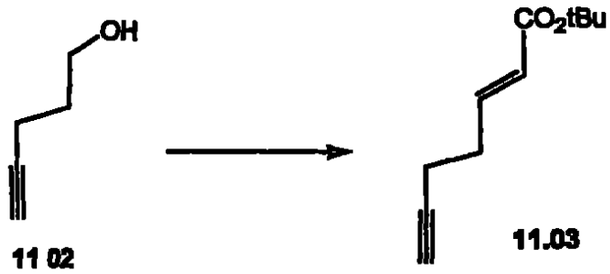
10 09 10 12

The required intermediate 10 12 was obtained from compound 10.09 using essentially the procedures described above in Steps 9, 10 using 2 0 equivalents of allylamine instead of ammonium chloride

42

Preparation of Intermediate 11 01

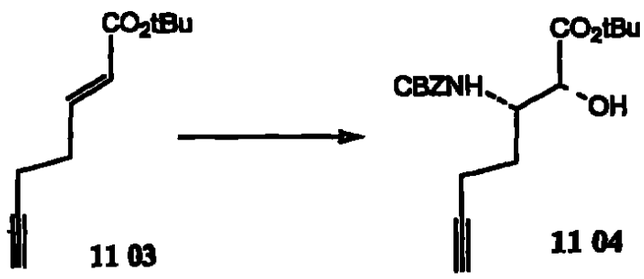
Step 1



11 02 11.03

To a solution of 4-pentyn-1-ol, 11 02 (4 15g, Aldrich) was added Dess-Martin Periodinane (30 25g, Aldrich) and the resulting mixture was stirred for 45min before the addition of (*tert*-Butoxycarbonylmethylene)triphenylphosphorane (26 75g, Aldrich) The resulting dark reaction was stirred overnight, diluted with EtOAc), washed with aq sodium sulfite sat. aq NaHCO3, water, brine and dried The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography using 1% EtOAc in hexanes as eluent to give the desired compound, 11 03 (3 92g) Some impure fractions were also obtained but set aside at this time

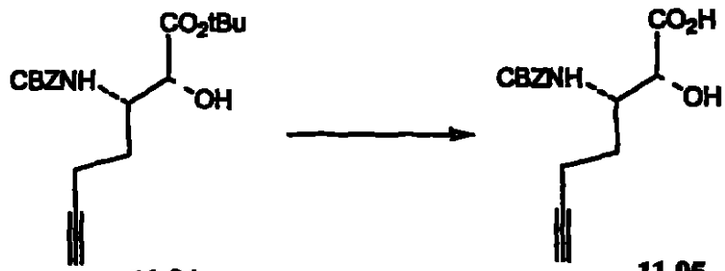
Step 2



11 03 11 04

Using the alkene 11 03 (1 9g) in n-propanol (20ml, Aldrich)), benzyl carbamate (4 95g, Aldrich) in n-propanol (40ml), NaOH (1 29g) in water (79ml), *tert*-butyl hypochlorite (3 7ml), (DHQ)2PHAL (0 423g, Aldrich)) in n-propanol (37 5ml), and potassium osmate dehydrate (0 1544g, Aldrich) and the procedure set forth in *Angew Chem Int. Ed Engl* (1998), 35, (23/24), pp 2813-7 gave a crude product which was purified by silica gel column chromatography using EtOAc Hexanes (1 5) to give the desired amino alcohol 11 04 (1 37g, 37%) as a white solid

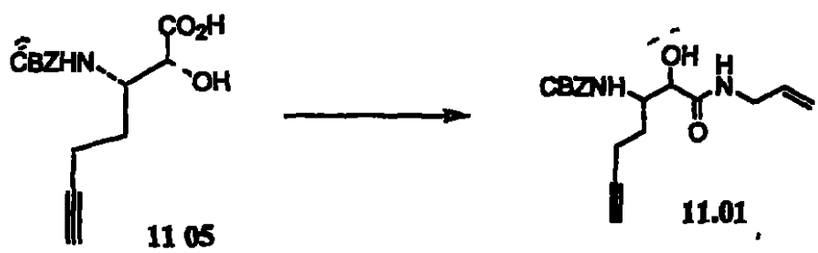
Step 3



11 04 11.05

To the ester 11 04 (0 700g) was added 4M HCl in dioxane (20ml, Aldrich) and the resulting mixture was allowed to stand at room temperature overnight. The volatiles were removed under reduced pressure to give the acid 11 05 (0 621g) as a white solid

Step 4

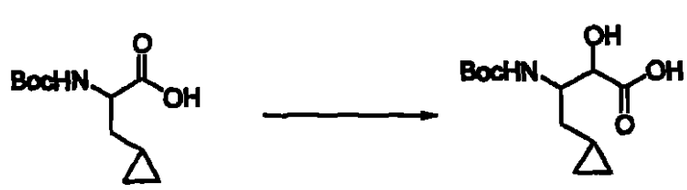


11 05 11.01

BOP reagent (3 65g, Sigma) followed by triethylamine (3 45ml) were added to a dichloromethane (20ml) solution of the carboxylic acid 11.05 (2 00g) and allyl amine (0 616ml) at room temperature and the resulting mixture was stirred overnight The reaction mixture was partitioned between EtOAc and 10% aq HCl The organic phase was separated, washed with sat aq sodium bicarbonate, water, dried (magnesium sulfate) The crude reaction product was purified by silica gel column chromatography using (EtOAc Hexanes, 70 30) as eluent to provide the desired amide 11 01 (1 73g) as a viscous yellow oil

Preparation of Intermediates 12 03 and 12 04

Step 1

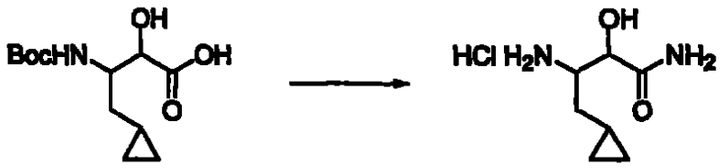


12.01 12 02

Compound 12 01 (Compound 12.01 was obtained commercially or can be synthesized using similar chemistry as outlined for the synthesis of 10 11 using bromomethyl cyclopropane instead of bromomethylcyclobutane) was

converted to the required material 12 02 using essentially the procedures described for Intermediate 10 11, Steps 3-8

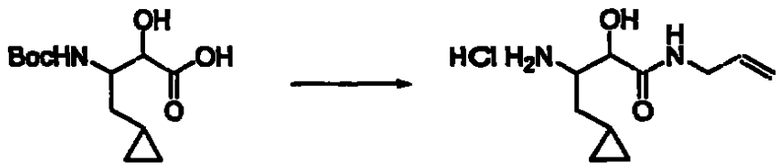
Step 2



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)

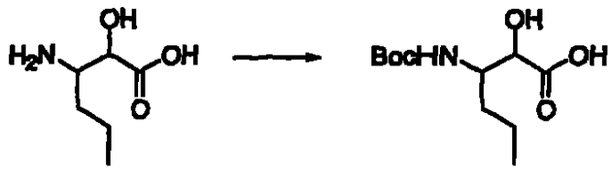
Step 2



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%)

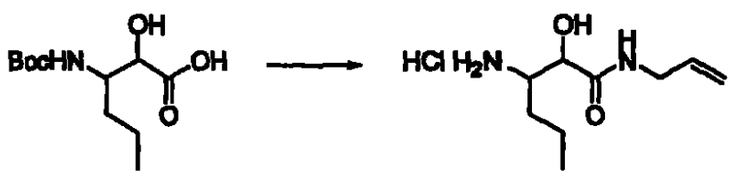
Step 3



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°C for 15 minutes The solution was then warmed to room temperature, stirred for 45 minutes and kept at refrigerator overnight and concentrated to dryness to give a crude material To the solution of this crude material in EtOAc (100 mL) and ice, was added $KHSO_4$ (3 36 g) and H_2O (32 mL) and stirred for 4-6 minutes The organic layer was then separated and the aqueous layer was extracted twice with EtOAc and the combined organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated to dryness to give the product 13 05 as a clear gum (3 0 g, 89% yield)

Step 4

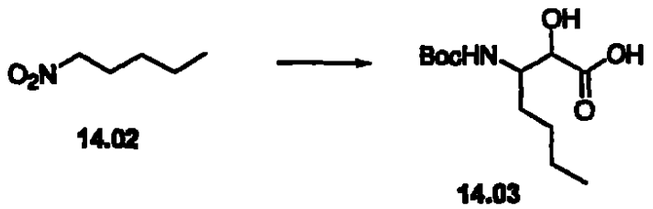


13 05 13.01

Compound 13 05 was converted to the required intermediate 13 01 using essentially the procedures described for Intermediate 10.12, Step 11

Preparation of Intermediate 14 01

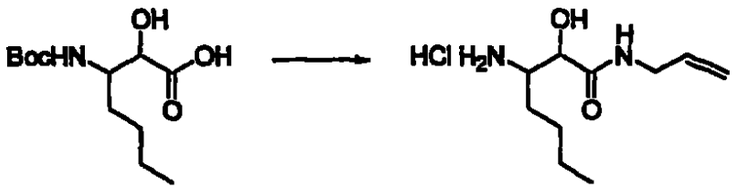
Step 1



14.02 14.03

Compound 14 02 was converted to the required material 14.03 using essentially the procedures described for Intermediate 13 01, Steps 1-3

Step 2

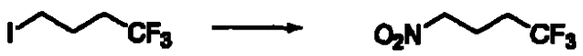


14.03 14 01

Compound 14 03 was converted to the required intermediate 14 01 using essentially the procedures described for Intermediate 10 12, Step 11

Preparation of Intermediate 15 01

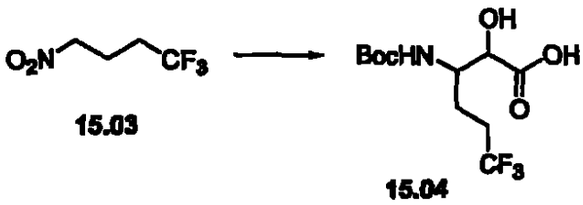
Step 1



15.02 15.03

To a suspension of silver nitrite (9 g, 58 5 mmol) in diethyl ether (25 mL) at 0°C was added a solution of 4-Iodo-1,1,1-trifluorobutane, 15 02 (10 g, 42 0 mmol) in diethyl ether (25 mL) slowly through an addition funnel (approx. 15 min) The resulting mixture was vigorously stirred at 0°C and warmed to rt. After 50 h, the solid material was filtered off through a celite pad The resulting diethyl ether solution was concentrated *in vacuo* to give 15 03 as colorless oil, which was used without further purification

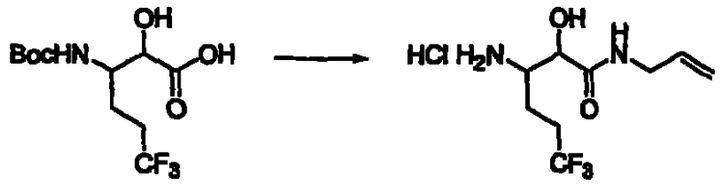
Step 2



15.03 15.04

Compound 15 03 was converted to the required material 15.04 using essentially the procedures described for Intermediate 13 01, Steps 1-3.

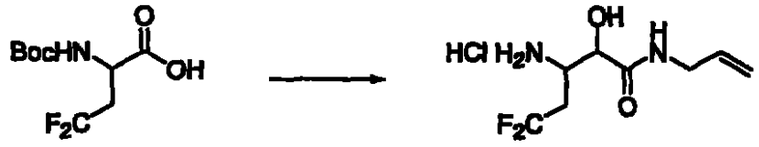
Step 3



15.04 15.01

Compound 15 04 was converted to the required Intermediate 15 01 using essentially the procedures described for Intermediate 10 12, Step 11

Preparation of Intermediate 16 01

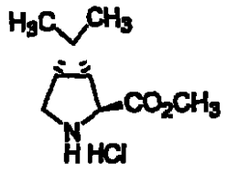


16.02 16.01

The acid 16 02 (Winkler, D , Burger, K , *Synthesis*, 1996, 1419) is processed as described above (preparation of Intermediate 10 12) to give the expected Intermediate 16 01

PREPARATION OF 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 used for the construction of 3,4-dimethylcyclopropyl ring was replaced with the corresponding phosphonium ylide)

Preparation of Intermediate 21.01

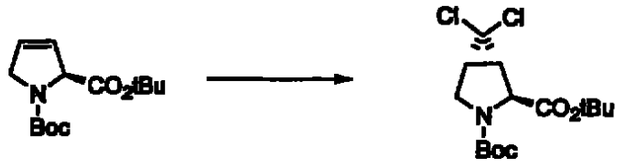
Step 1.



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 m L, 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 m L) 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

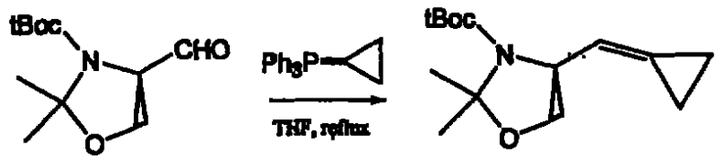


21.05 21 01

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

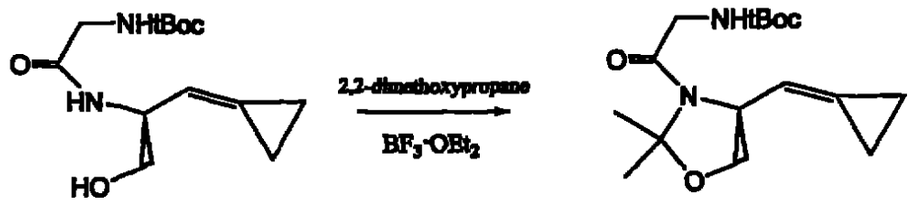
Step 2



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)

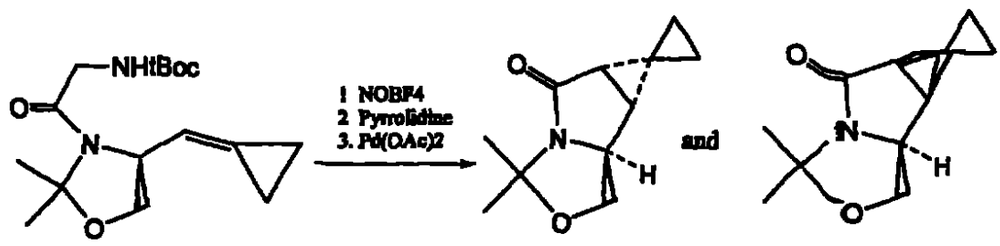
Step 3



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 provid the N,O-acetal 22.05 (8 85g)

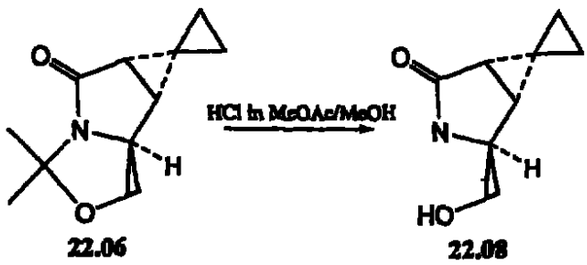
Step 4



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

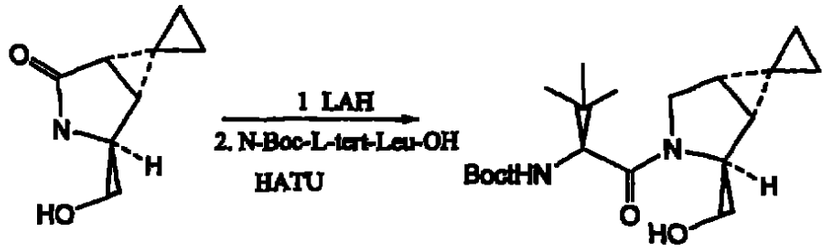


22.06 22.08

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

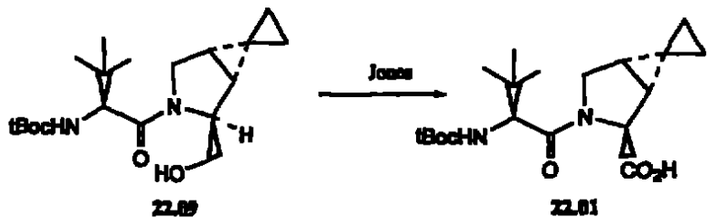
Step 6



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



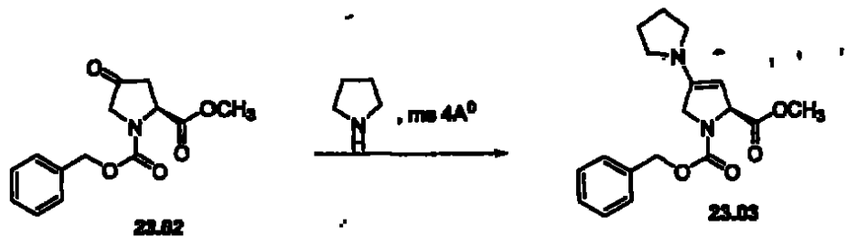
22.09 22.01

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 5C for 0 5h and the cooling bath was removed The reaction was stirred for a further 2h at room temp , before adding to sodium sulfate (28 54g), celite (15g) in EtOAc (100ml) Isopropanol (15ml) was added after 1min and then stirred for a further 10min and filtered The filtrate was concentrated under reduced pressure, providing a brown oil which was dissolved in EtOAc. This solution was washed with water, 3% aq citric acid, brine, dried and concentrated to provide the desired carboxylic acid 22.01 (1 64g) as a white solid

Preparation of Intermediate 23 01

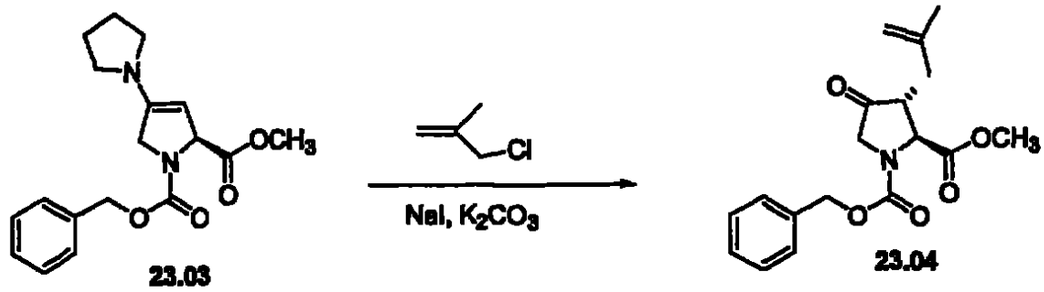
Step 1



23.02 23.03

To the mixture of ester 23 02 (6 0g) and molecular sieve (5.2g) in anhydrous methylene chloride (35 mL) was added pyrrolidine (5 7 mL, 66 36 mmoL) The resulting brown slurry was stirred at room temperature under N_2 for 24 h, filtered and washed with anhydrous CH_3CN The combined filtrate was concentrated to yield the desired product, 23 03

Step 2.



23.03 23.04

To a solution of the product 23 03 from proceeding step in CH_3CN (35 mL) was added anhydrous K_2CO_3, methallyl chloride (2 77g, 30 5 mmoL), NaI (1 07g, 6 7 mmoL) The resulting slurry was stirred at ambient temperature under N_2 for 24 h 50 mL of ice-cold water was added followed by 2N $KHSO_4$ solution until pH was 1 EtOAc (100 mL) was added and the mixture was

stirred for 0 75h Combined organic layer was collected and washed with brine, dried over $MgSO_4$, and evaporated to yield the desired product, **23 04**

Step 3



23 04 **23 05**

The product **23 04** from the preceding step (2 7 g, 8 16 mmoL) was dissolved in dioxane (20 mL) and treated with freshly prepared 1N LiOH (9 mL) The reaction mixture was stirred at ambient temperature under N_2 for 20 h The reaction mixture was taken in EtOAc and washed with H_2O The combined aqueous phase was cooled to 0^0C and acidified to pH 1 65 using 1N HCl The turbid mixture was extracted with EtOAc (2 x 100 mL) Combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give the desired acid, **23 05** (3 40 g)

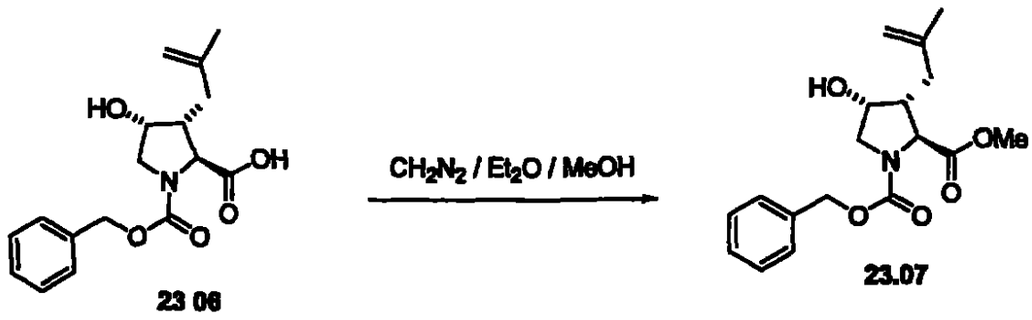
Step 4



23.05 **23 06**

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**

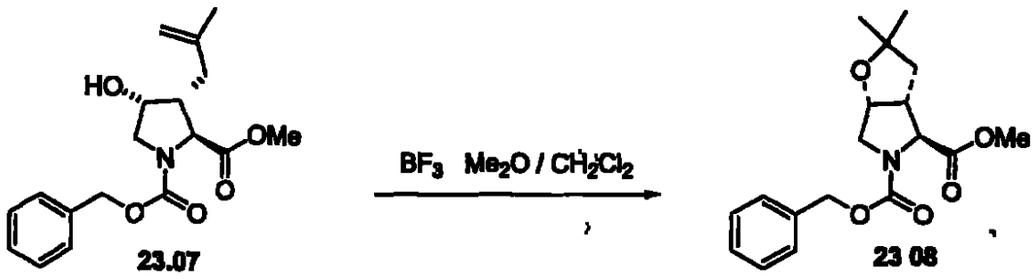
Step 5



23 06 23.07

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

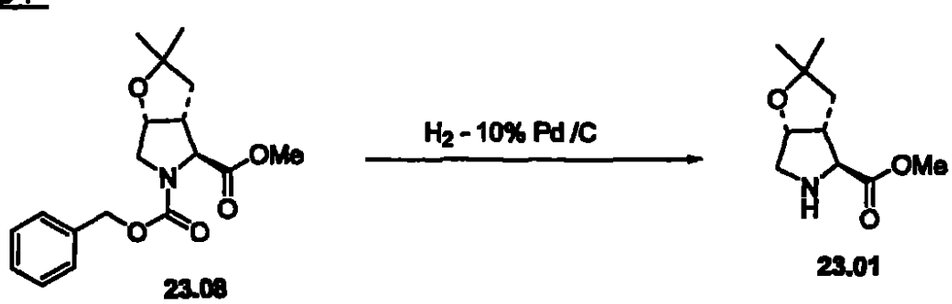
Step 6



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 5 02 (15 g) in MeOH (150 mL) was added conc HCl (3-4 mL) and the mixture was refluxed for 16 h The reaction mixture was cooled to room temperature and concentrated The residue was taken in diethyl ether (250 mL) and washed with cold saturated sodium bicarbonate solution, and brine -The organic layer was dried (Na_2SO_4) and concentrated to afford the methyl ester 50 03 (12 98 g) which was carried forward without further purification

Step 2



50 03 50 04

The methyl ester 50 03 from above was dissolved in methylene chloride (100 mL) and cooled to -78°C, under nitrogen atmosphere DIBAL (1 0 M solution in methylene chloride, 200 mL) was added dropwise over 2 h period The reaction mixture was warmed to room temperature over 16 h The reaction mixture was cooled to 0°C and MeOH (5-8 mL) was added dropwise A solution of aqueous 10% sodium potassium tartarate (200 mL) was slowly added with stirring Diluted with methylene chloride (100 mL) and separated the organic layer (along with some white precipitate) The organic layer was washed with 1 N HCl (250 mL), brine (200 mL), dried (Na_2SO_4) and concentrated to provide the alcohol 50 04 (11 00 g) as a clear oil

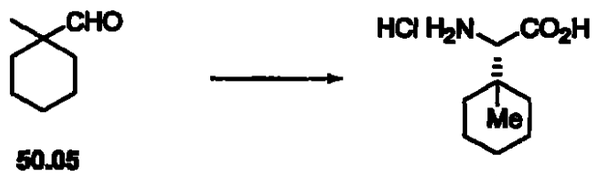
Step 3



50 04 50 05

The alcohol 50 04from above was dissolved in methylene chlonde (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

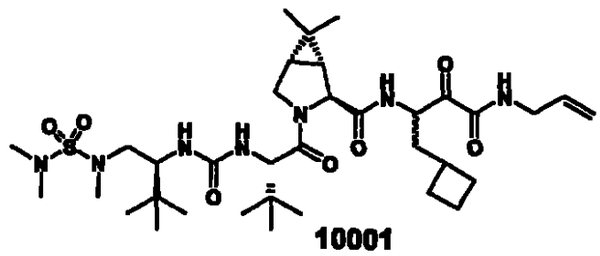


50.05 50 01

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 1 Synthesis of compound of Formula 10001



10001

Step A



10001a 10001b

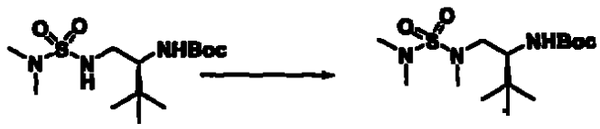
The amine, 10001a, (C A Busacca *et al, Tetrahedron Asymmetry*; (2000) 9 1907) (1 5 g, 6 9 mmol, 1 equiv) was dissolved in dry

dichloromethane 20 ml) and cooled to -78 °C Added 3 ml (3 equiv) of Et_3N followed by the slow addition of dimethylsulfamyl chloride (1 5 eq , Sigma-Aldrich) dissolved in DCM The temperature was kept at -78 °C until the addition is complete and then stirred overnight allowing it to raise to room temperature Diluted with methylene chloride and washed with water, aq 1N HCl and finally brine The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo* Crude product isolated was purified via flash column (10→30 % EtOAc-Hexane) to afford 1 27g (58%) of **10001b**

^{1}H NMR ($CDCl_3$, 300 MHz) δ, 4 6 (d, 1 H), 3 45 (m, 1 H,), 3 25 (d, 1 H), 2 89 (s, 6 H), 1 89 (bs, NH), 1 22 (s, 9H), 0 98 (s, 9 H)

MS (ESI), m/z, relative intensity 324 [(M+1) 85], 268 (100), 224 (50).

Step B



10001b **10001c**

To the Boc protected sulfonyl urea **10001b** (440 mg,1 25 mmol, 1 equiv) in DMF(10 mL) at 0° C was added Cs_2CO_3 (613 mg, 1 5 equiv, 1 88 mmol) and MeI (6 36 mmol, 5 equiv , 0 601 mL) under inert atmosphere The reaction mixture was stirred at room temperature for 90 min and quenched with water The aqueous layers were extracted with EtOAc, washed 4 times with water and brine The organic layers was dried over anhydrous sodium sulfate, filtered and evaporated off the solvent to afford 420 mg (91%) of **10001c** that was used in the next reaction without further purification

^{1}H NMR ($CDCl_3$, 300 MHz) δ, 4 59 (d, 1 H), 3 62-3 58 (m, 1 H,), 3 29-3 22 (m, 1 H), 2 80 (s, 3 H), 2 79 (s, 6H), 1 89 (bs, NH), 1 22 (s, 9 H), 0 98 (s, 9 H)

MS (ESI), m/z, relative intensity 338 [(M+1) 60], 282 (100), 238 (90)

Step C



10001c **10001d**

To the Boc-protected sulfonyl urea 10001c (890 mg, 1 equiv) was added 4M solution of HCl in dioxane (25 mL) at room temp and stirred for 1 hr After the disappearance of starting material (TLC), the reaction mixture was concentrated and azeotroped with hexanes and ether The residue was triturated with ether and the solid separating out was filtered and dried in vacuum to afford a pale yellow solid (720 mg, ~100%) It was used in further reaction without purification

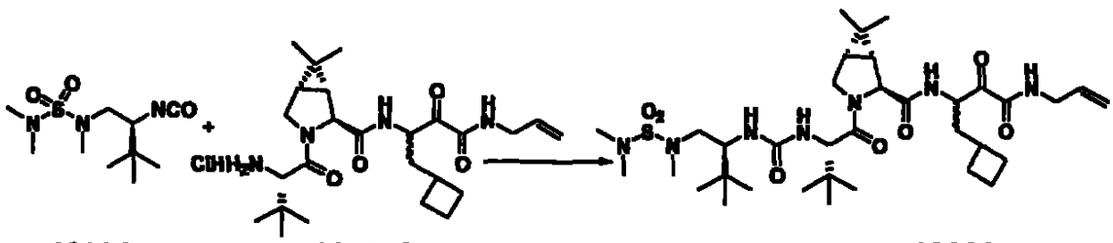
Step D



10001d 10001e

To the amine hydrochloride salt 10001d (720 mg, 2 63 mmol) in dichloromethane (1 5 ml) was added 15 ml of aq saturated $NaHCO_3$ and stirred vigorously at 0 °C for 5 min A solution of phosgene (2 equiv 20% in toluene) was syringed out to the lower layer and restored the vigorous stirring immediately Checked the TLC at times and after 2 hrs, it showed complete consumption of starting material The methylene chloride layer was separated and the aqueous layer was extracted with dichloromethane (30 ml) The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated using rotary evaporator under reduced pressure at rt. to half the volume and then flushed N_2 for 15 minutes Diluted the solution to 130 mL with dichloromethane and used as 0 02 M solution in further reactions

Step E



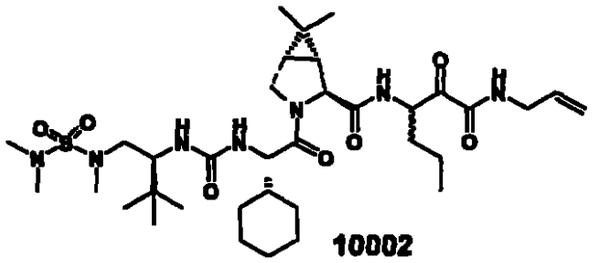
10001e 10001f 10001

To the amine hydrochloride salt, 10001f (synthesized by coupling of Intermediate 10 12 and 1 17 using HATU followed by Dess-Martin oxidation and Boc deprotection following method C or the procedure outlined for the synthesis of 13001h) (130 mg, 0 261mmol, 1 equiv) in dichloromethane (5

ml) was added DIPEA (6 equiv) at 0 °C A solution of isocyanate **10001e** (1 equiv, 13ml of 0 02M soln) under N_2 atmosphere and stirred for 30 min at ice temperature and 90 min at room temperature The reaction mixture was quenched with citric acid and extracted with EtOAc The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo* The crude product was purified using flash column chromatography (SiO_2, 10-40% acetone-hexane) to afford 110 mg (59%) of **10001** as a colorless solid

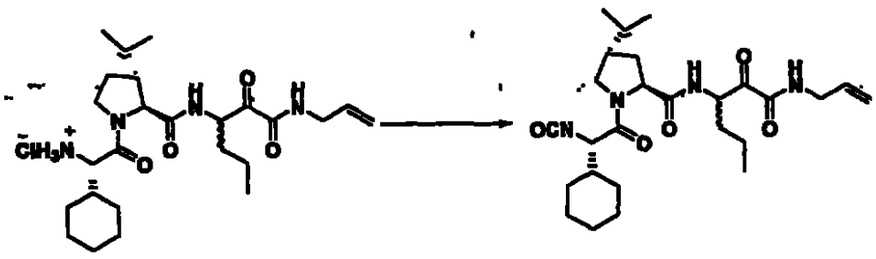
MS (ESI), m/z, relative intensity 724[(M+1) 45], 377 (100)

Example 2 Synthesis of compound of Formula 10002



10002

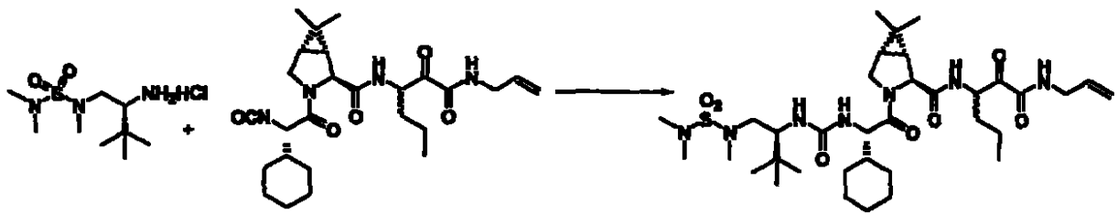
Step A:



10002a **10002b**

To a solution of amine hydrochloride salt **10002a** (500 mg, 1 00 mmol, 1 equiv) in dichloromethane (15 ml) was added a solution of aq sat. $NaHCO_3$ (15 mL) The reaction mixture was stirred vigorously at ice temperature for 5 min A solution of phosgene (2 equiv 20 % in toluene) was syringed out to the lower layer and restored the vigorous stirring immediately Checked the TLC at times and after 2 hrs it showed complete consumption of starting material and then separated the layers Washed the water layer one more time with DCM (3 ml) and dried over sodium sulfate Filtered and evaporated at high vacuum to half the volume and then purged N_2 for 15 minutes Used **10002b** as a stock solution of 0 02M by diluting with 50 mL of dichloromethane

Step B

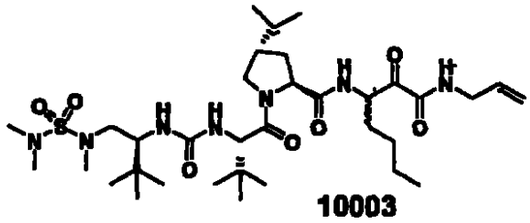


10001d 10002b 10002

To the ammonium salt **10001d**, (80 mg, 0 293 mmol, 1 equiv) in dichloromethane (10 ml) was added DIPEA (6 equiv) at ice temperature Added isocyanate **10002b** (1 equiv, 14 6 ml of 0 02M solution) under N_2 atm , and stirred for 30 min at ice temperature and 90 min at room temperature Quenched with citric acid and extracted with EtOAc and washed with brine Dried over anhydrous sodium sulfate and filtered and evaporated off the solvent. The crude product was purified using silica gel flash chromatography (10-40% acetone-hexane) to afford 120 mg (57 %)of **10002** as a colorless solid

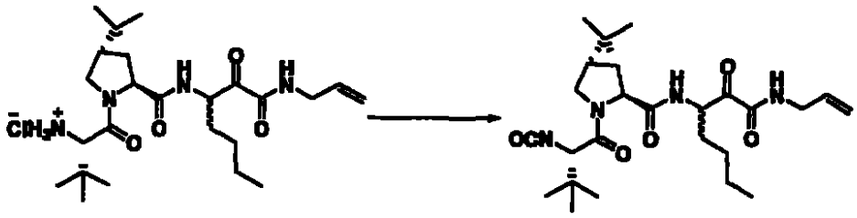
MS (ESI), m/z, relative intensity 724 [(M+1) 100], 461 (45), 403 (80)

Example 3 Synthesis of compound of Formula 10003



10003

Step A

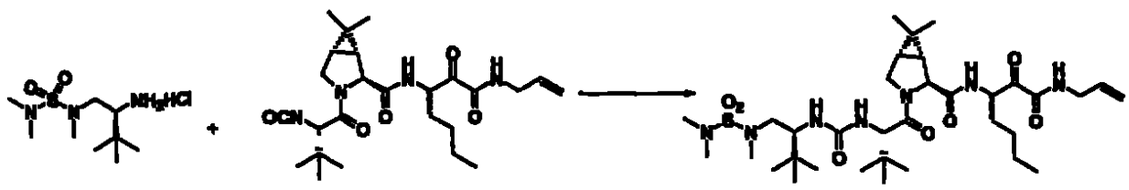


10003a **10003b**

To the amine hydrochloride **10003a**, prepared as described before, (500 mg, 1 03 mmol, 1 equiv) in DCM (15 ml) was added 15 ml of sat $NaHCO_3$ Stirred vigorously at ice temperature for 5 min Stopped stirring and phosgene (1 11mL, 2 equiv , 20 % in toluene) was syringed out to the lower layer and restored the vigorous stirring immediately Checked the TLC at times and after 2 hrs it showed complete consumption of starting material and

then separated the layers Washed the water layer one more time with DCM(3 ml) and dried over sodium sulfate Filtered and evaporated at high vacuum to half the volume and then purged N_2 for 15 minutes Used as a stock solution of **10003b** (0 02M) by diluting with 50 mL of dichloromethane

Step B

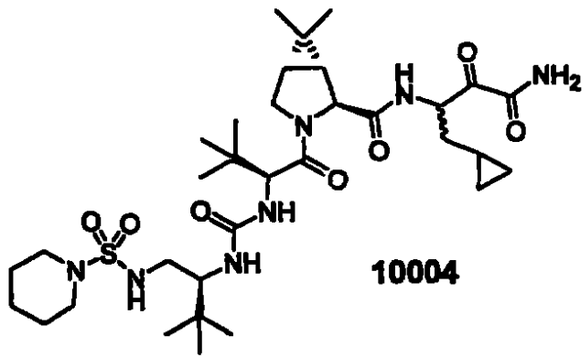


10001d **10003b** **10003**

To a solution of ammonium salt, **10001d**, (20 mg, 0 073mmol, 1 equiv) In DCM (5 ml) was added DIPEA (6 equiv) at ice temperature was added Isocyanate **10003b** (1 equiv, 0 073 mmol, 3 66 mL of 0 02M soln) under N_2 atm. and stirred for 30 min at ice temperature and 90 min at room temperature Quenched with citric acid and extracted with EtOAc and washed with brine Dried over anhydrous sodium sulfate, filtered and evaporated off the solvent The crude product was purified via flash silica column (10-40 % acetone-hexane) to afford 28 mg , 55 %of **10003**

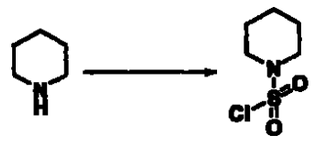
MS (ESI), m/z, relative intensity 724 [(M+1) 100], 461 (45), 403 (80)

Example 4 Synthesis of compound of Formula 10004



10004

Step A.

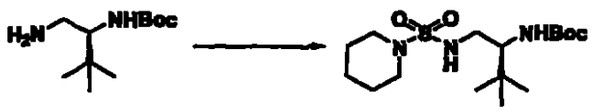


10004a **10004b**

To 0 95mL (11 7mmol) of sulfuryl chloride in 20 mL ether was added dropwise 2 3mL (23 4mmol) of piperidine at -78° C The reaction was stirred

at rt for 3hrs The insoluble solid was removed by filtration and the filtrate was washed with 1N HCl, sat $NaHCO_3$ and brine The organic layer was dried over $MgSO_4$, filtered and the filtrate was concentrated to dryness to give 1 00g of **10004b** yield 46%

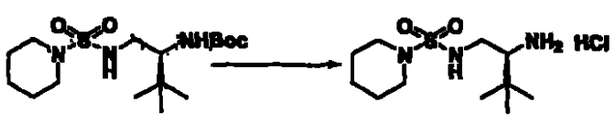
Step B



10001a **10004c**

To 0 350g (1 62mmol) of **10001a** in 10mL CH_2Cl_2 was added 0 23 mL (1 62mmol) of Et_3N, then 0 446g (2 42mmol) of **10004b** in 5 mL CH_2Cl_2 drop wise at rt The reaction mixture was stirred at rt overnight The reaction mixture was diluted with EtOAc, washed with a solution of aq NH_4Cl and brine The organic layers was dried over $MgSO_4$, filtered, concentrated in *vacuo* and purified by silica gel chromatography with 6→24% EtOAc in Hexane to yield 0 353g of product Yield 60%

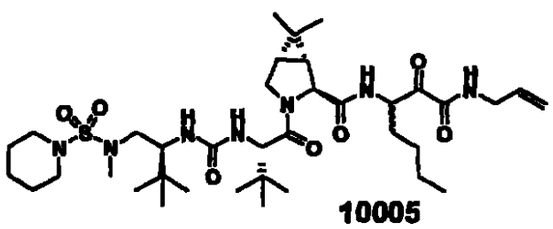
Step C



10004c **10004d**

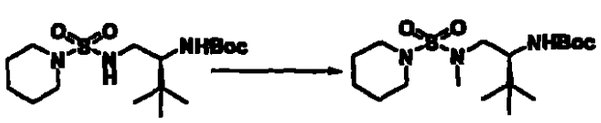
To 15mg (0 041mmol) of **10004c** in a flask was added 2ml (8 mmol) of 4M HCl (in dioxane) and stirred at RT for 50 min The reaction mixture was concentrated to dryness in *vacuo* to give 32mg of **2004d** Yield 100%
Note The conversion of **10004d** to **10004** was identical to step B in preparative example 3 Synthesis of compound of formula **10003**

Example 5 Synthesis of compound of Formula 10005



10005

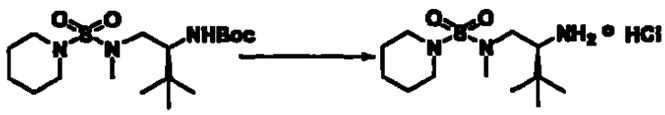
Step A.



10004c **10005a**

To a solution of 0 275 g (0 76mmol) of **10004c** in DMF was added 0 369g (1 13mmol) of Cs_2CO_3 and 0 085mL (1 37mmol) of MeI at 0 °C The reaction was stirred at rt overnight The reaction mixture was diluted with water and extracted with EtOAc The organic layer was washed with brine, dried, concentrated in *vacuo* and the residue was purified by chromatography (SiO_2 8~32% EtOAc in hexane) to give 0.256 g of product **10005a** Yield 89%

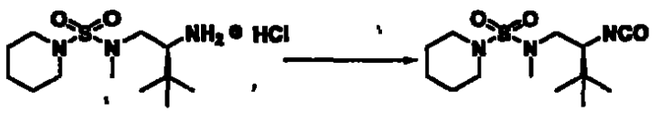
Step B



10005a **10005b**

To a solution of 0 291 g (0 77mmol) of **10005a** in flask was added 3mL(12mmol) of 4M HCl (in dioxane) and stirred at rt. for 50 min After the completion of reaction as indicated by TLC the reaction mixture was concentrated in *vacuo* to dryness to yield 0 241g of **10005b**

Step C



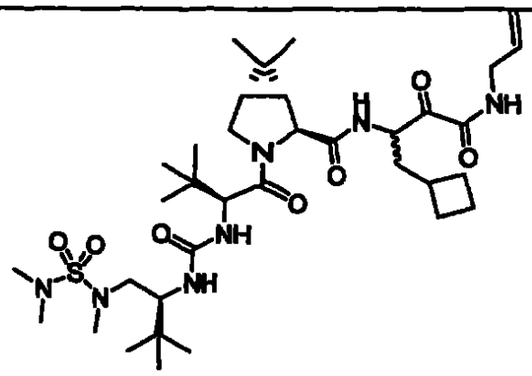
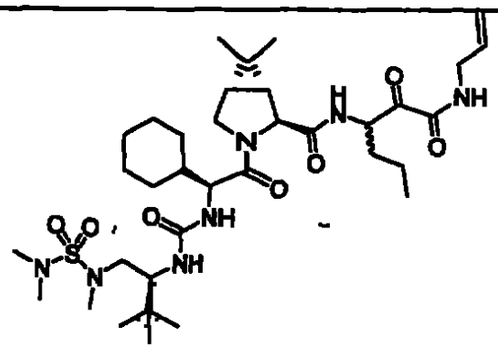
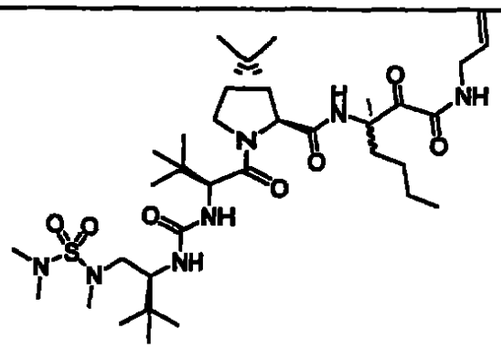
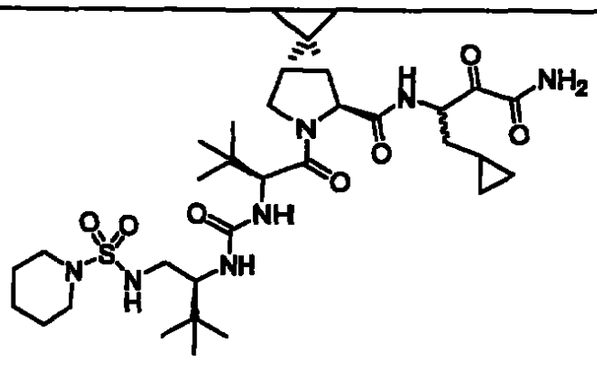
10005b **10005c**

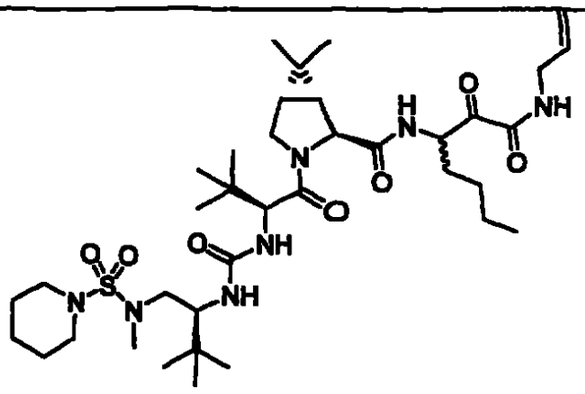
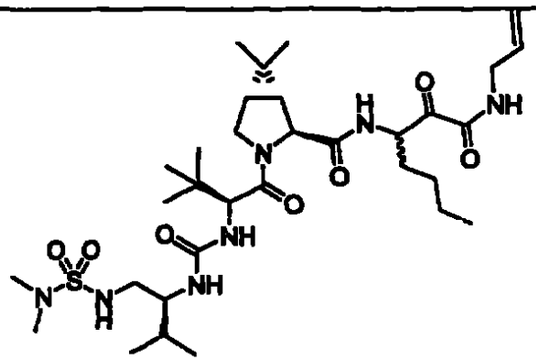
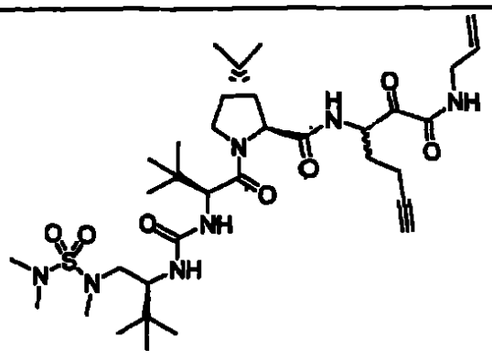
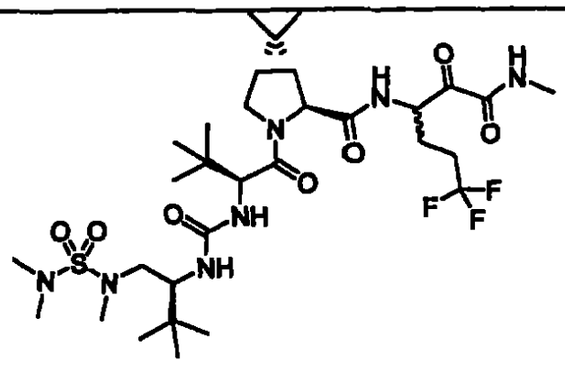
To 0 241g (0 77mol) of **10005c** in CH_2Cl_2 at 0° C was added 0 81mL (1 54 mmol) of 1 9 M solution of phosgene in toluene and 10 mL of saturated aqueous $NaHCO_3$ solution The reaction mixture was stirred at rt for 1 0 h The organic layer was separated and dried over (Na_2SO_4), filtered concentrated to half volume It was further diluted with CH_2Cl_2 to afford a 0 07 M solution

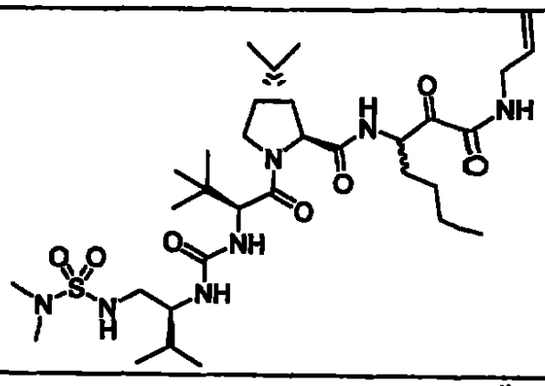
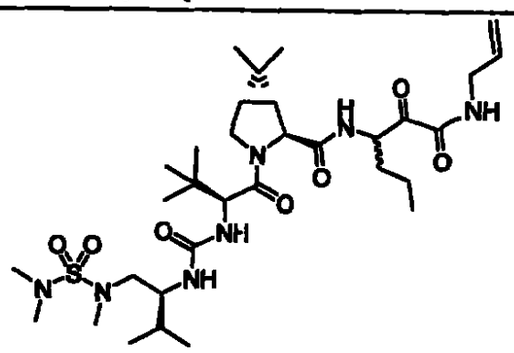
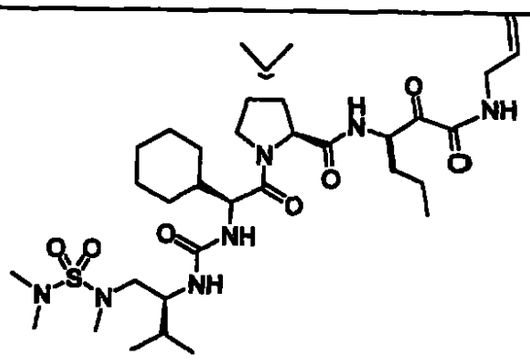
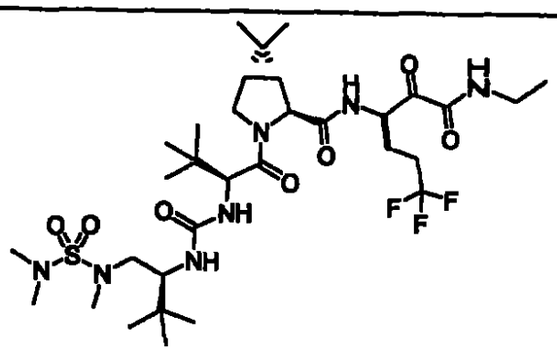
Note The conversion of **10005c** to **10005** was identical to step B in preparative example 3 Synthesis of compounds **10003**

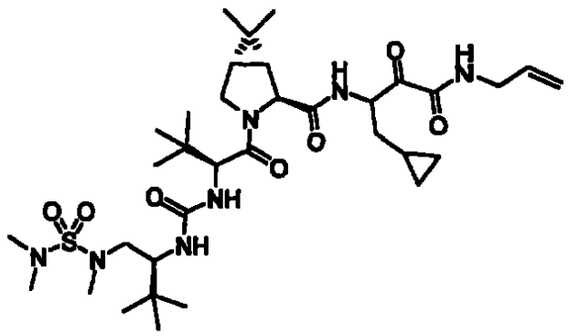
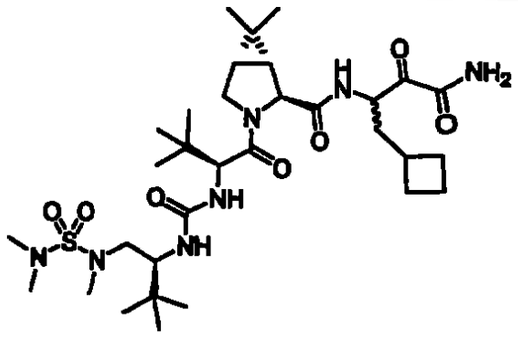
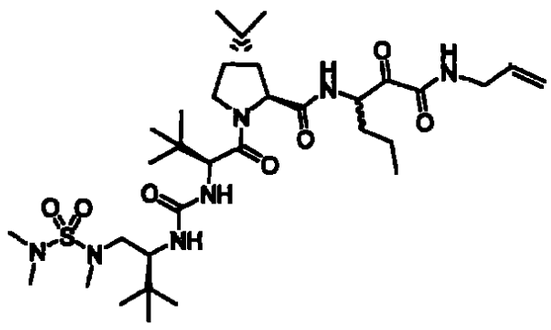
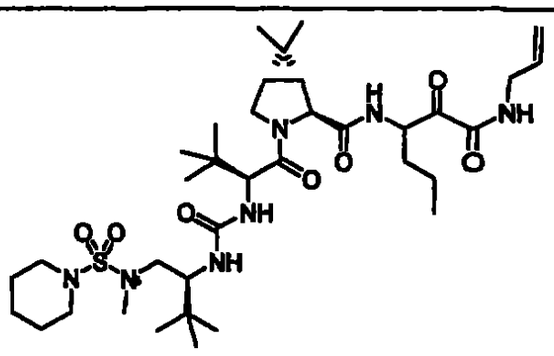
Compounds indicated in the following **Table 1** were synthesized using similar reactions as shown in Examples 1-5 Range of Ki* indicated A≤75 nM, 75<B ≤ 250 nM, C>250 nM

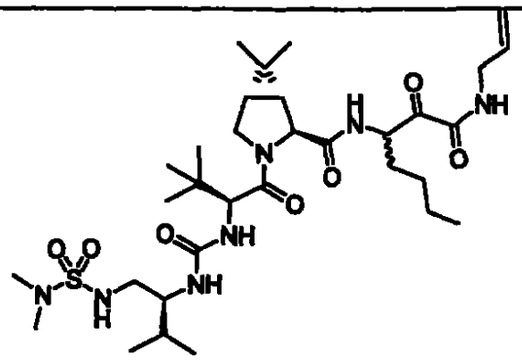
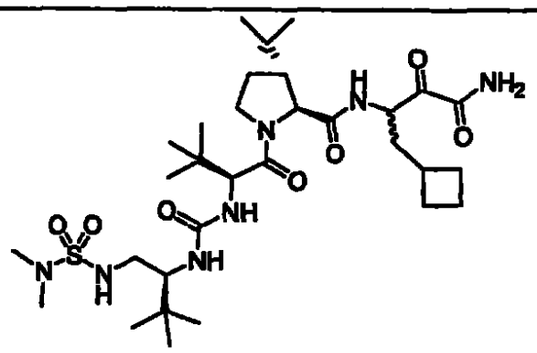
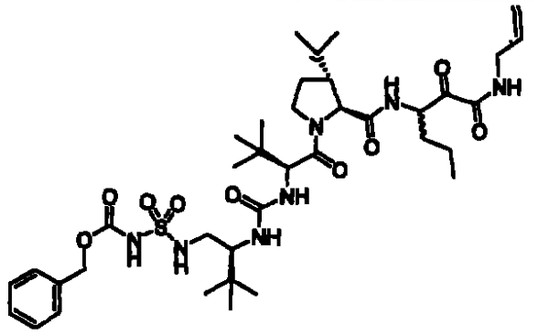
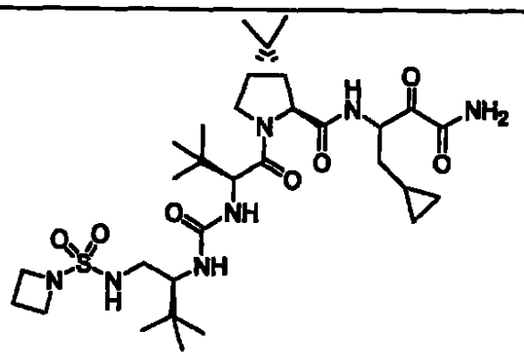
Table 1

Entry	Structure	K_i*
10001		A
10002		A
10003		A
10004		A

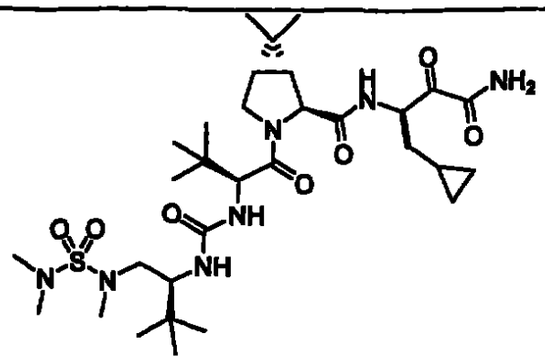
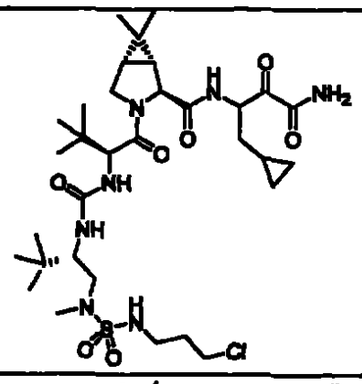
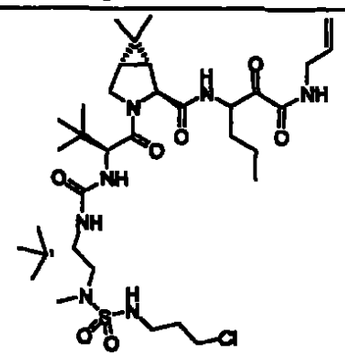
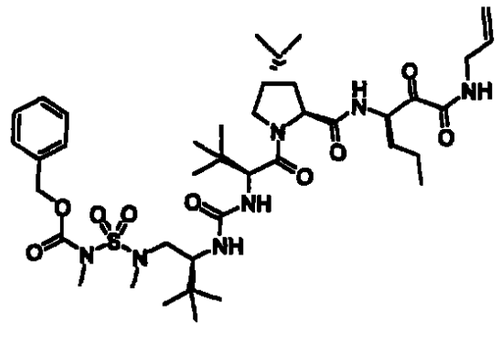
10005		A
10006		B
10007		A
10008		A

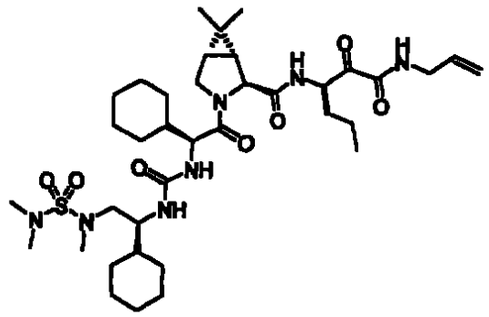
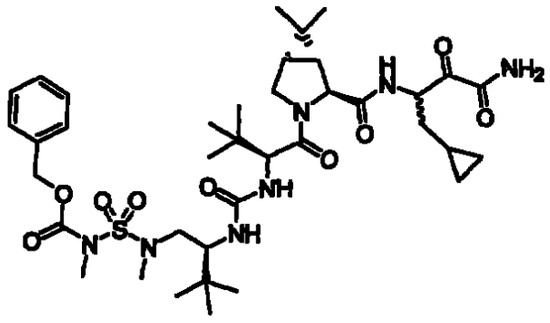
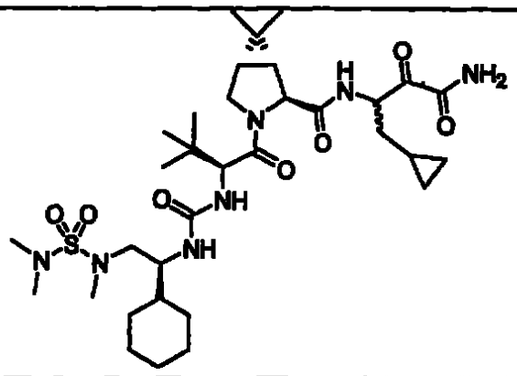
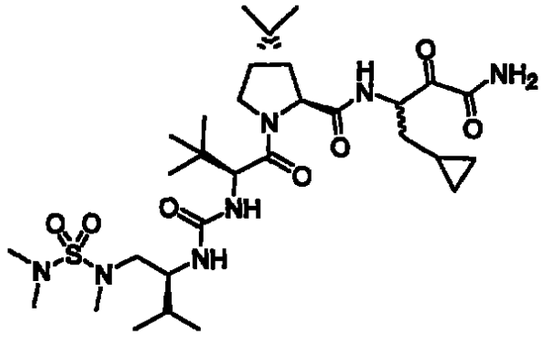
10009		B
10010		A
10011		A
10012		A

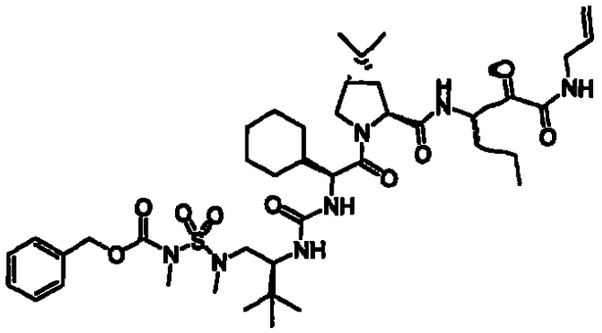
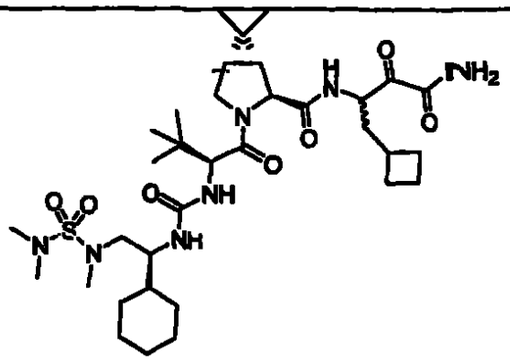
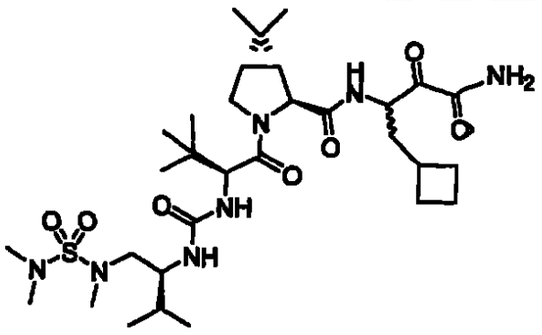
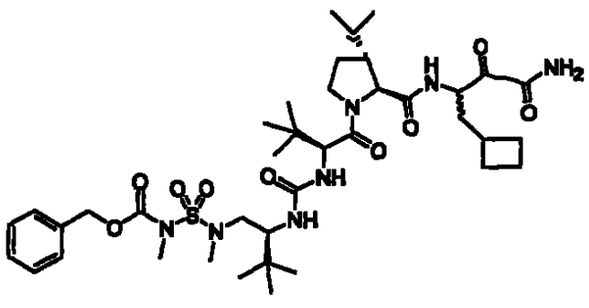
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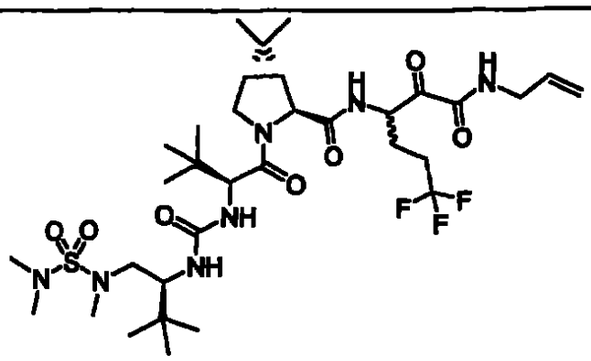
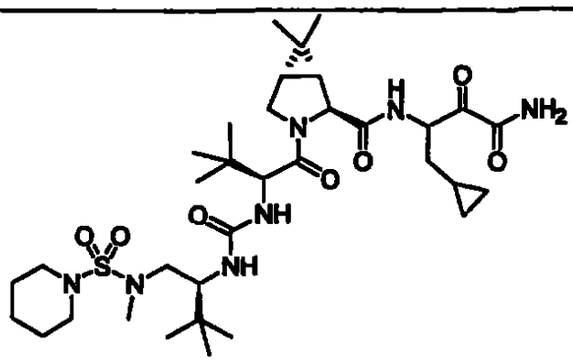
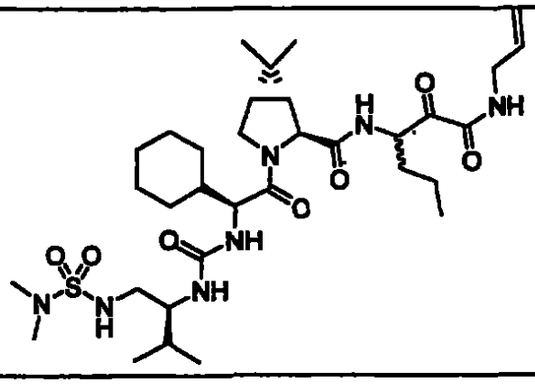
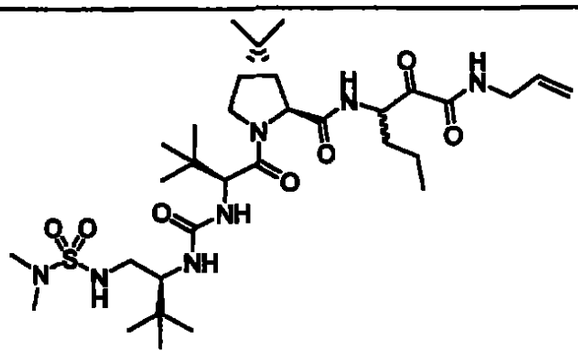
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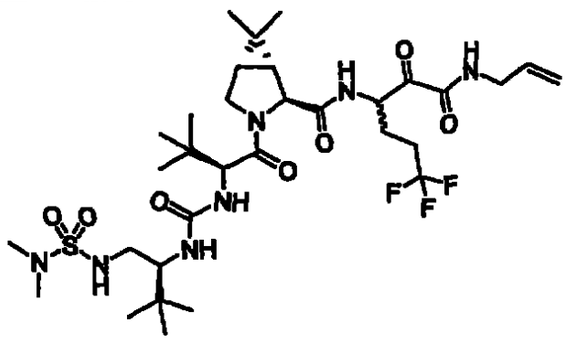
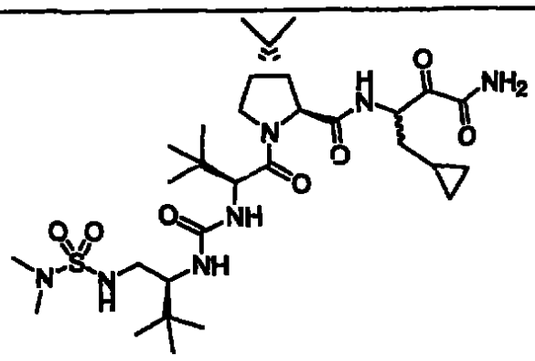
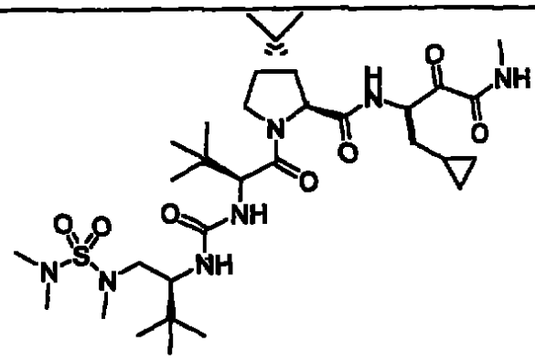
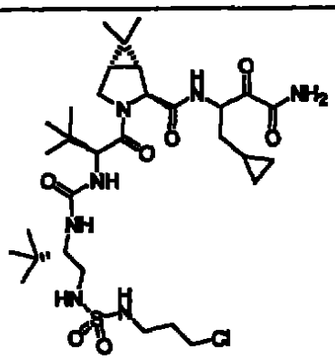
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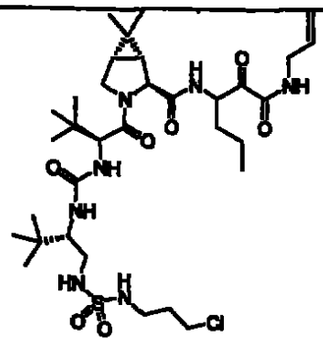
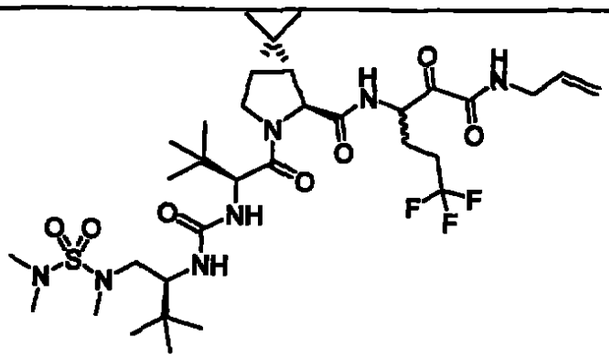
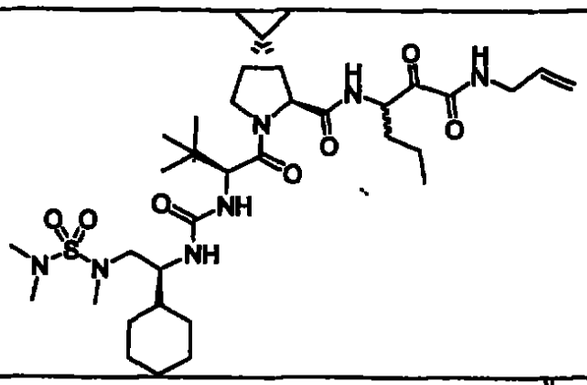
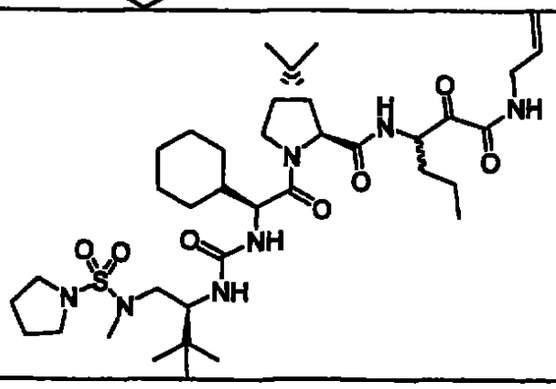
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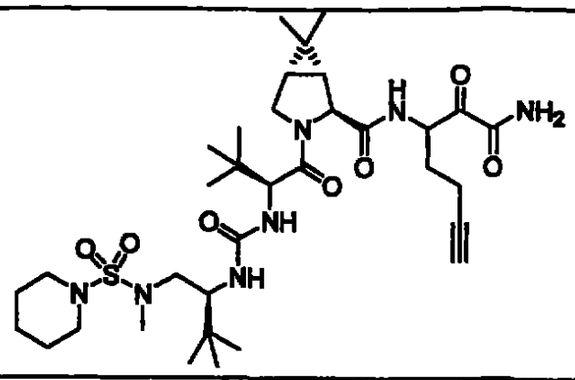
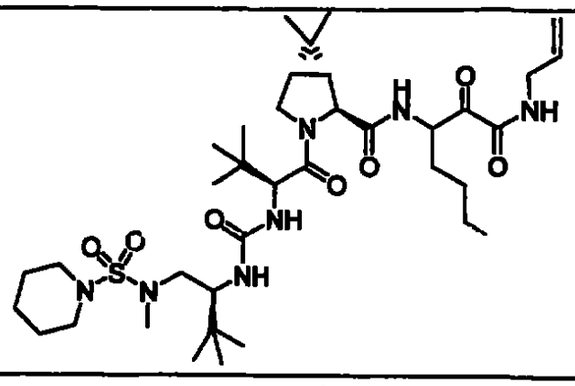
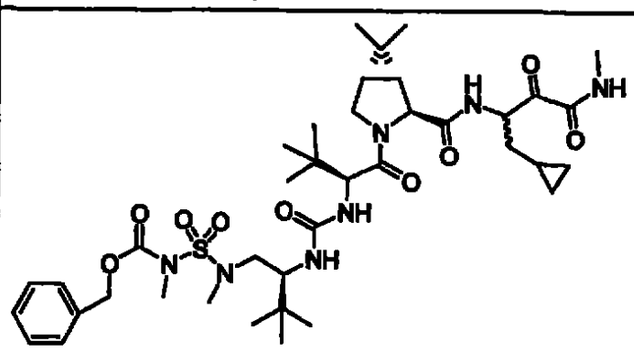
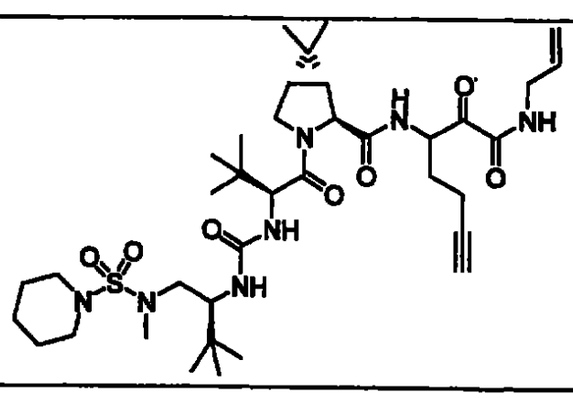
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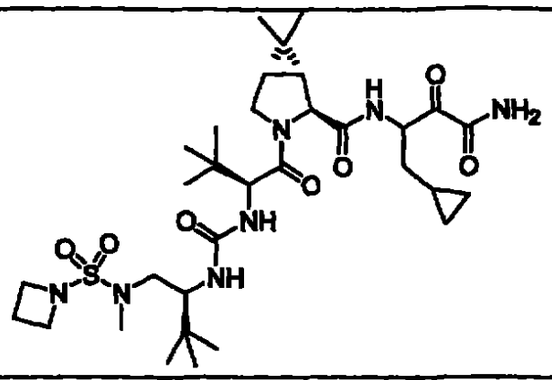
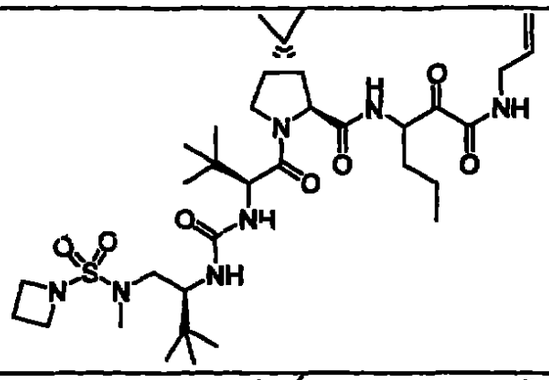
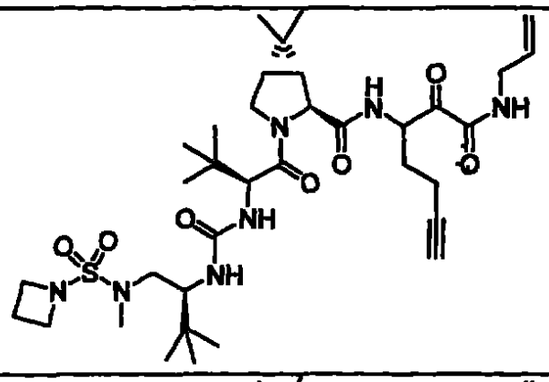
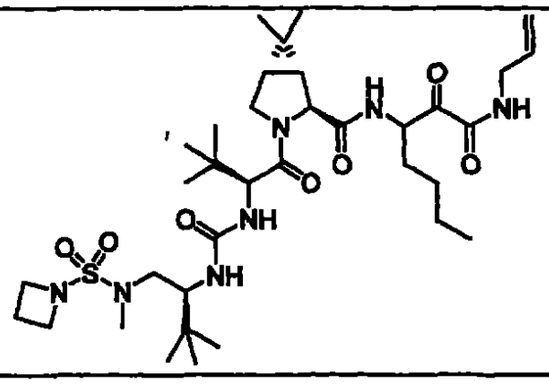
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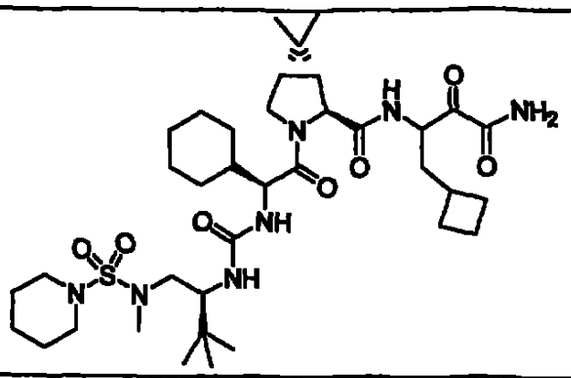
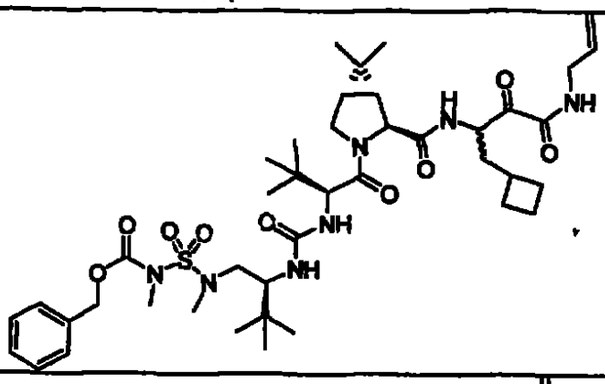
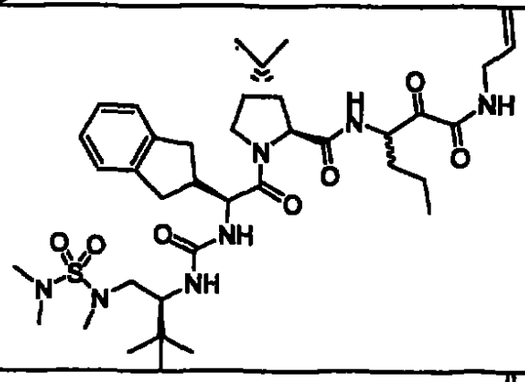
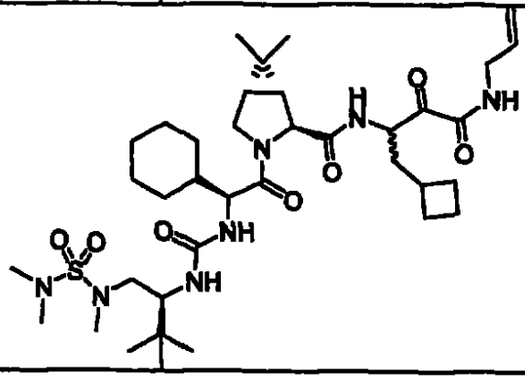
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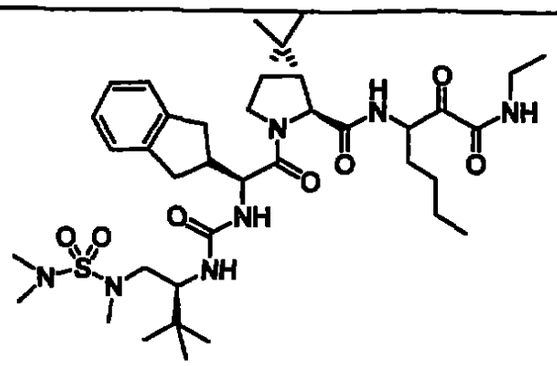
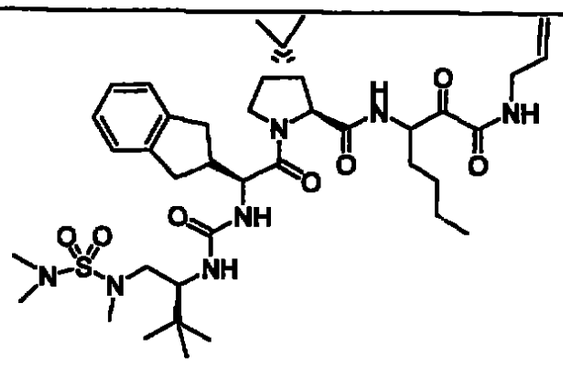
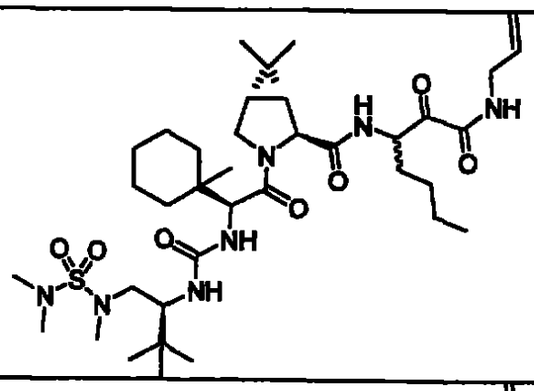
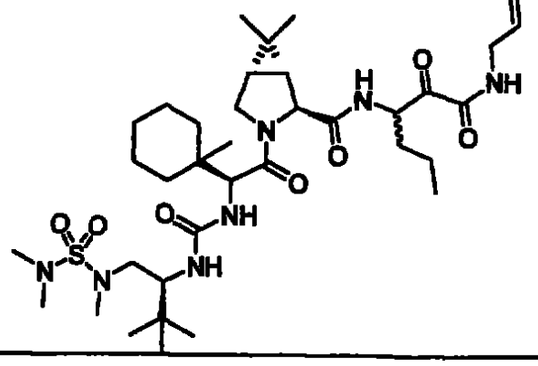
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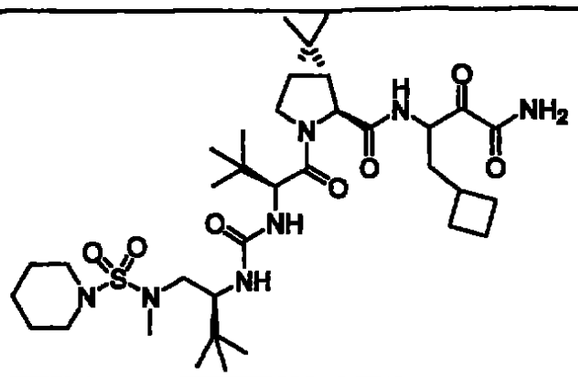
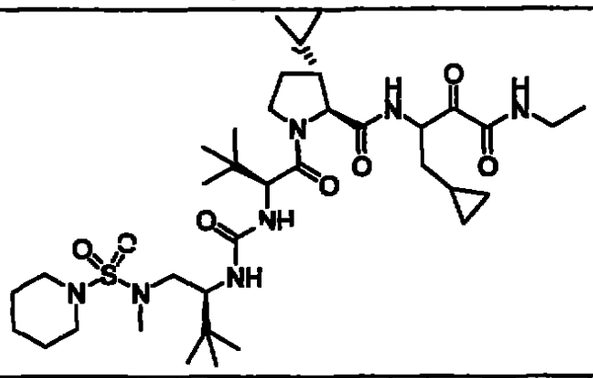
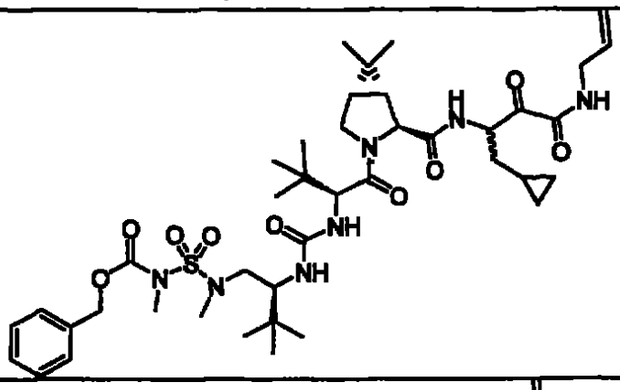
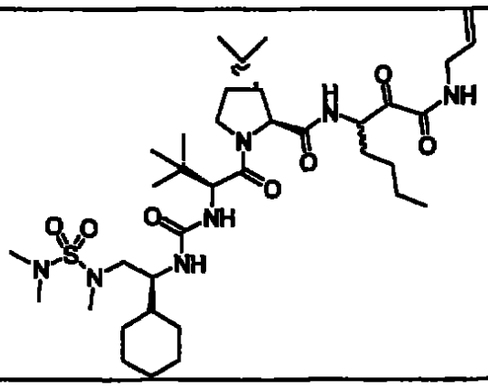
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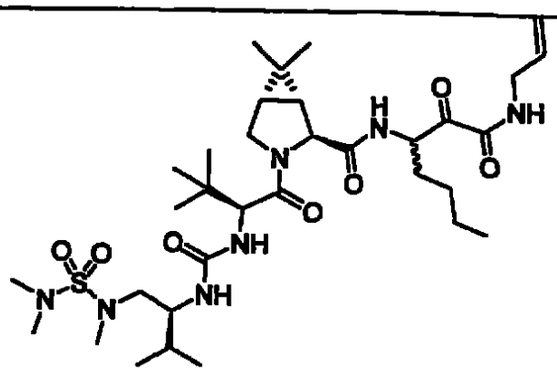
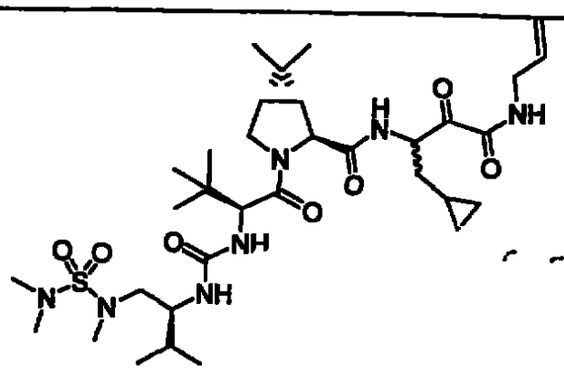
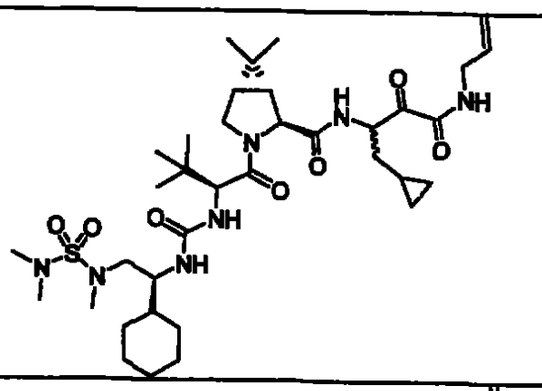
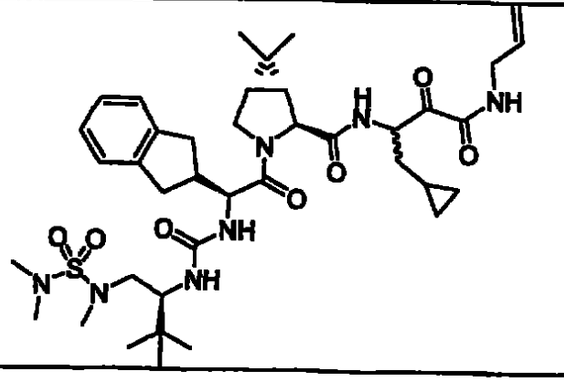
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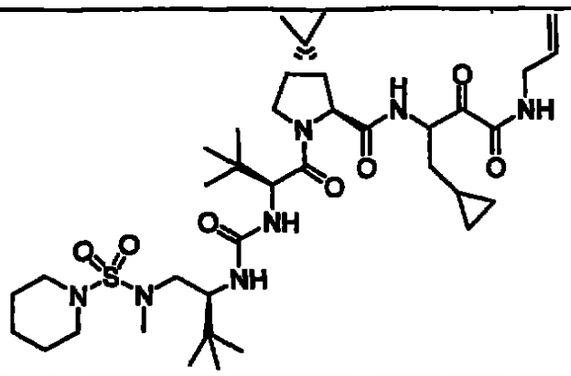
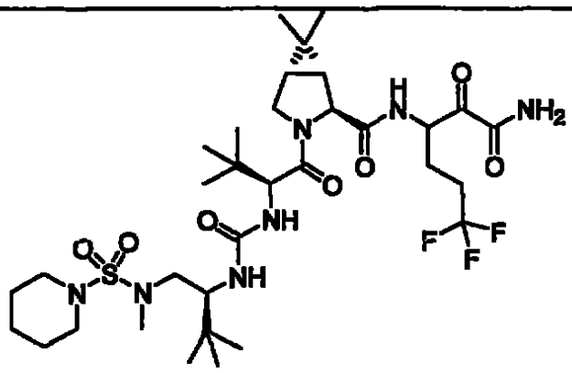
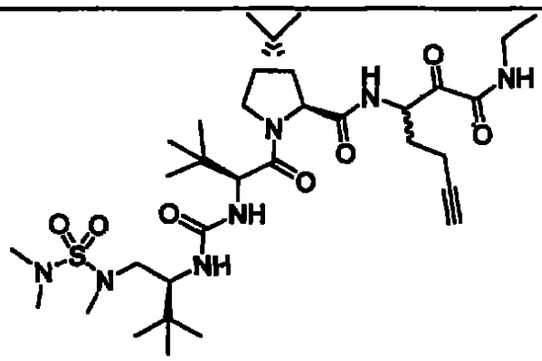
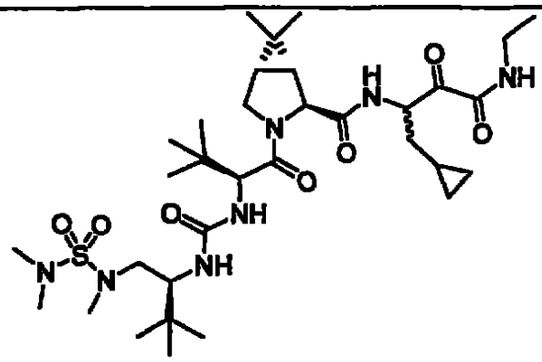
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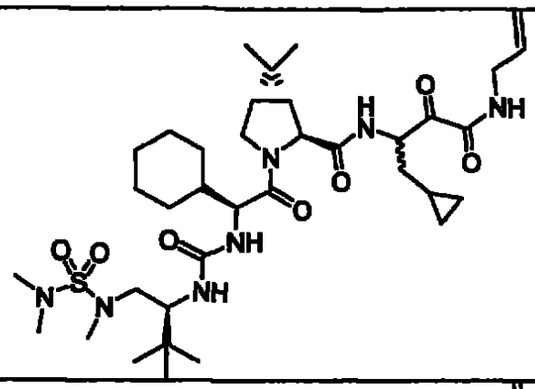
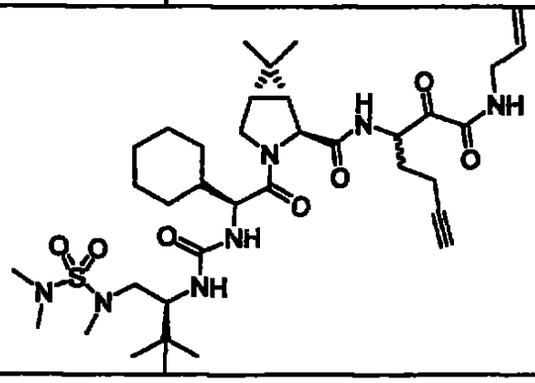
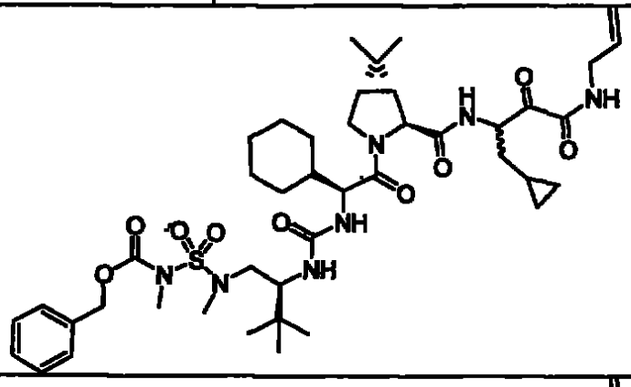
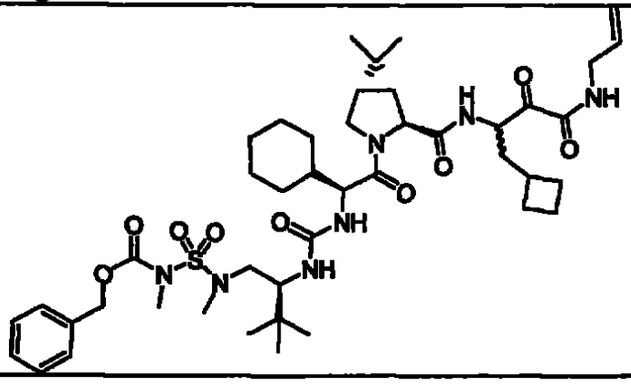
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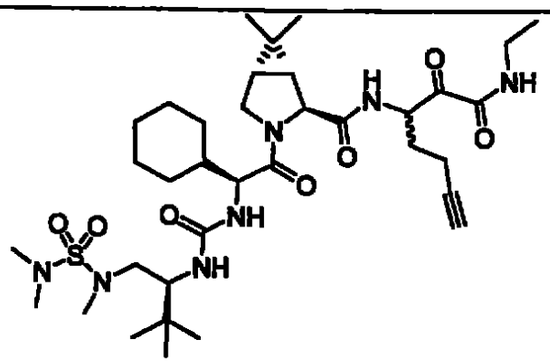
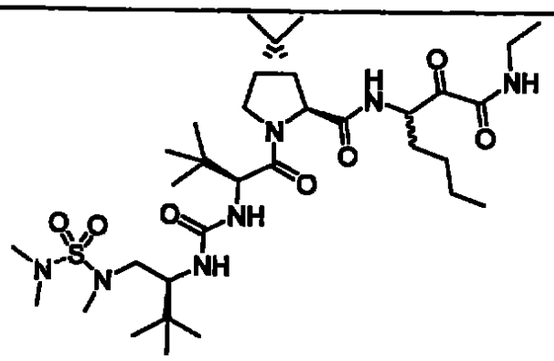
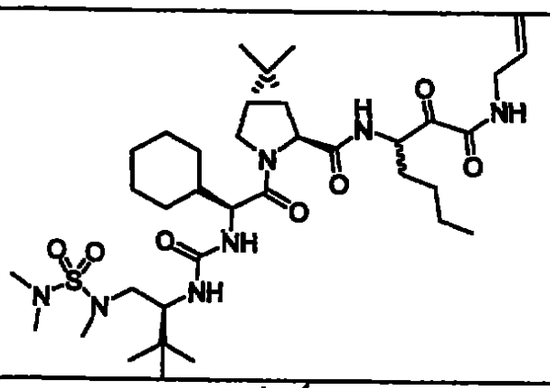
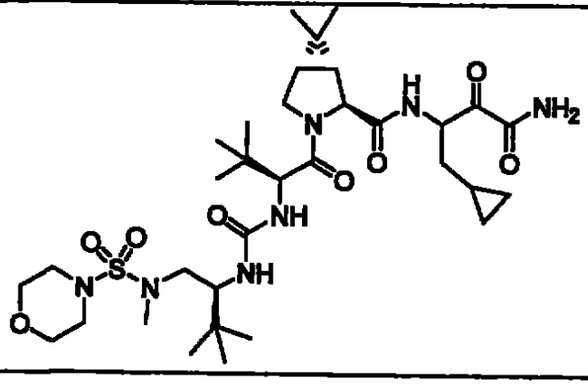
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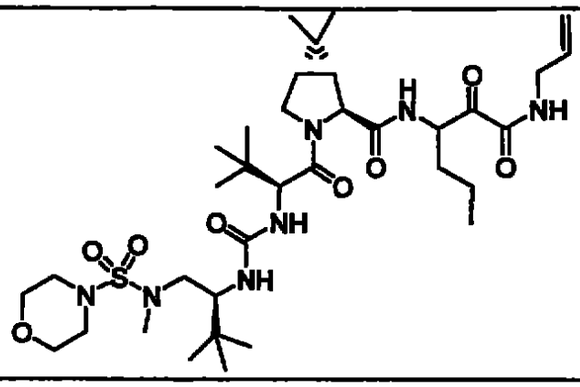
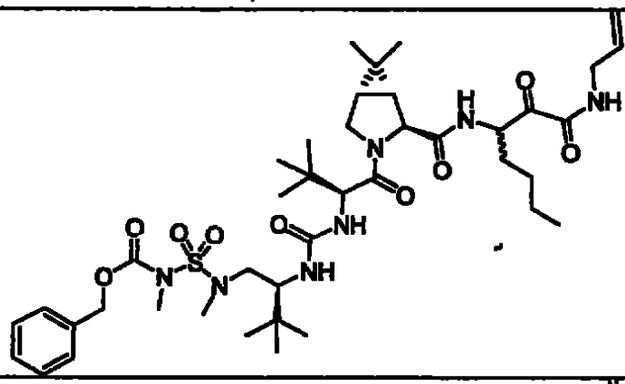
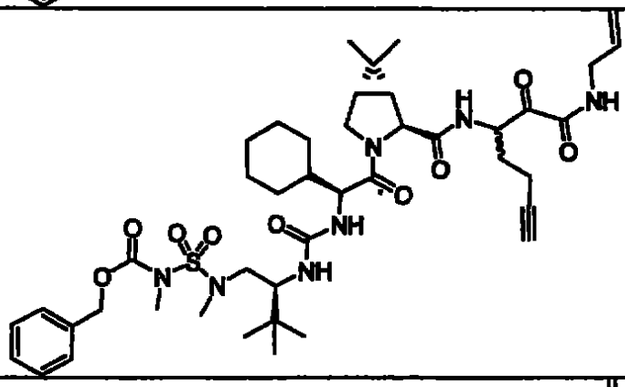
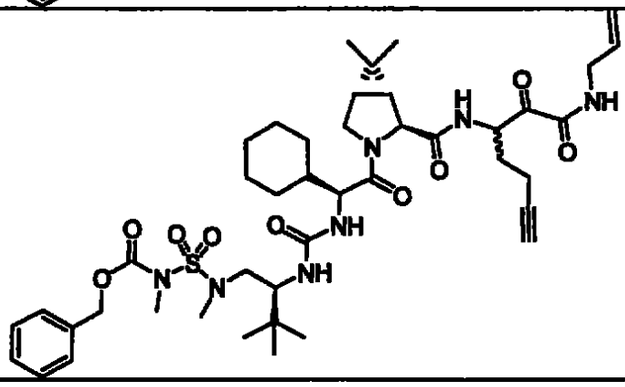
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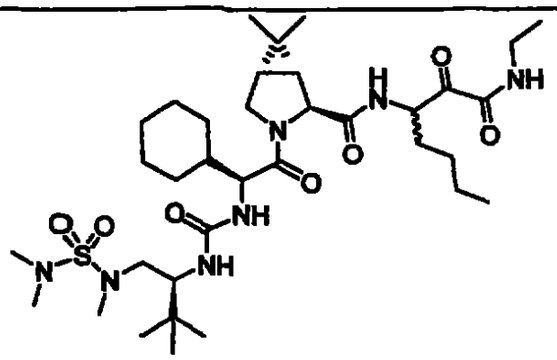
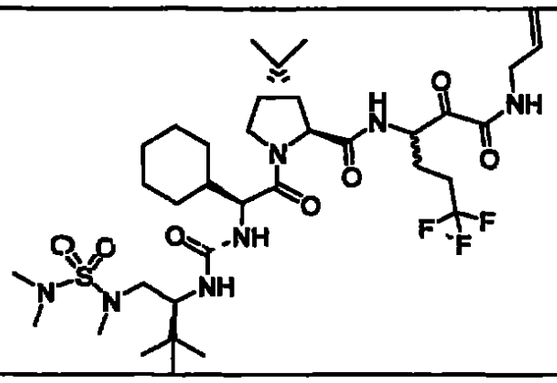
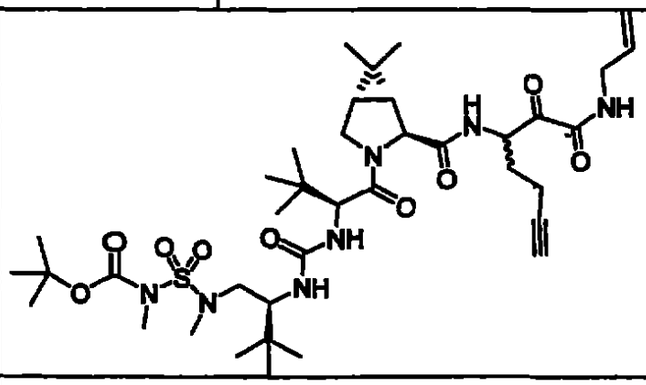
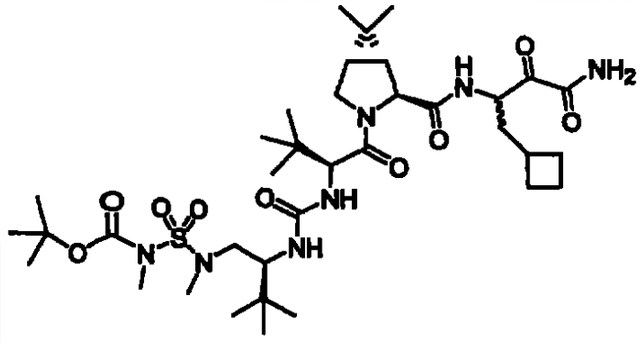
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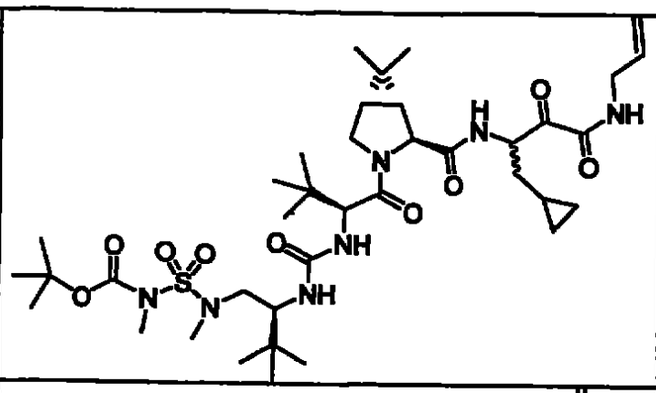
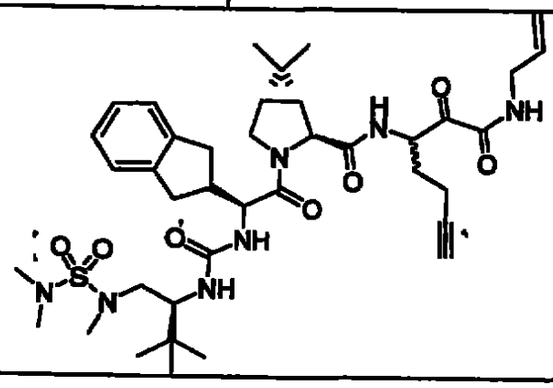
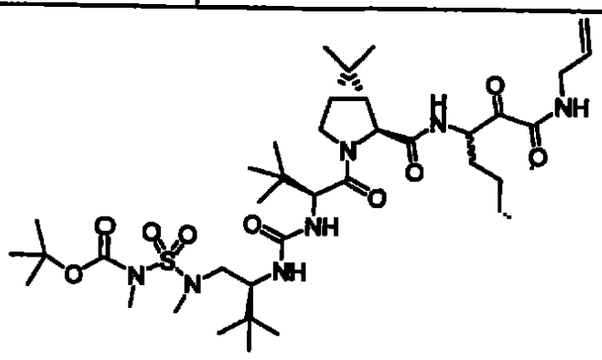
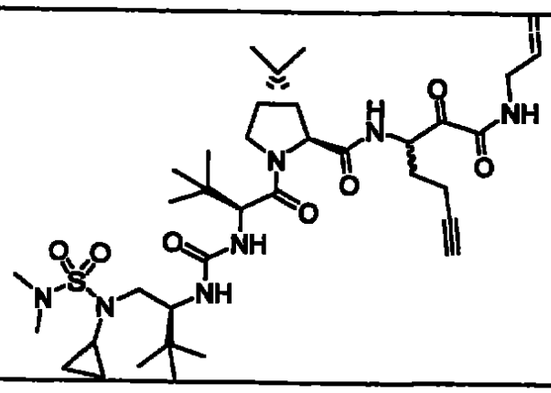
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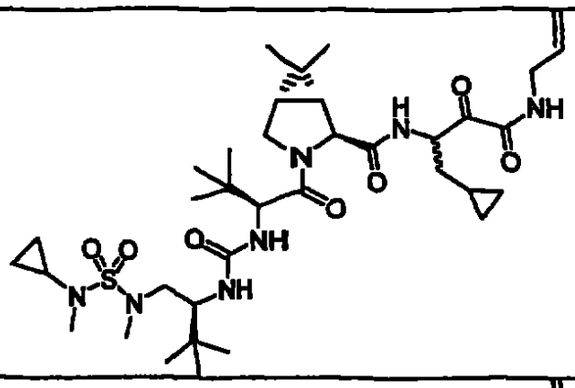
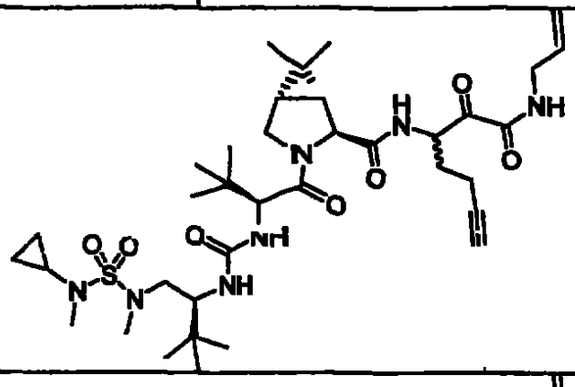
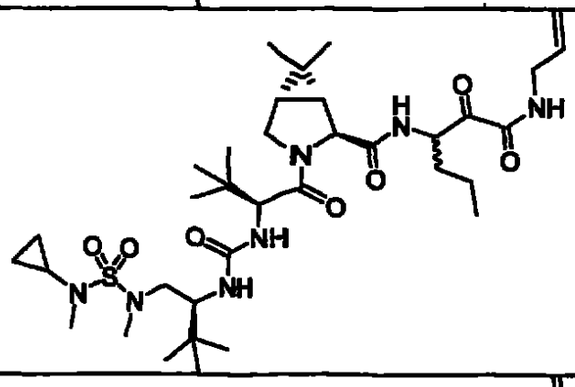
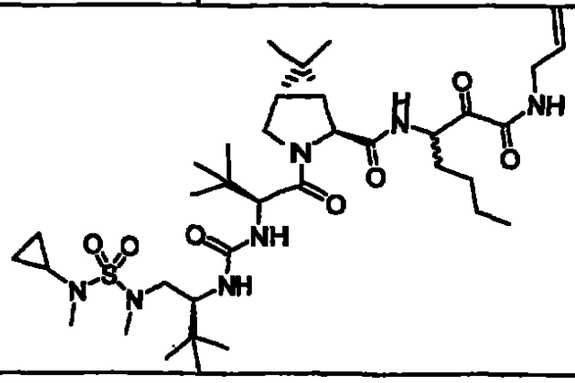
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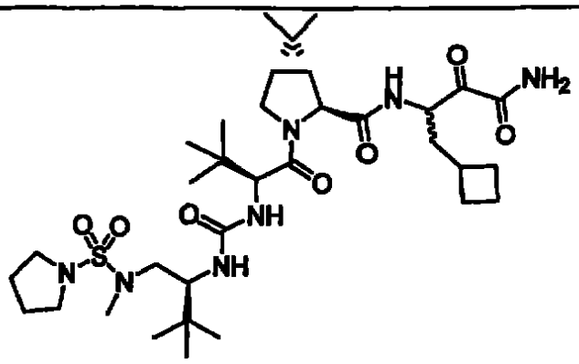
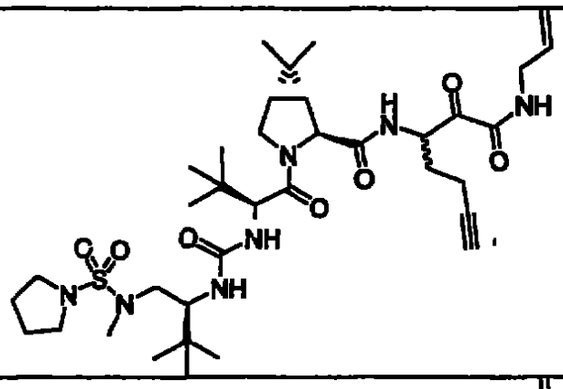
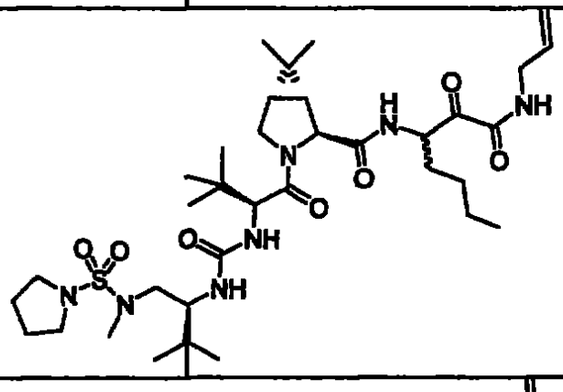
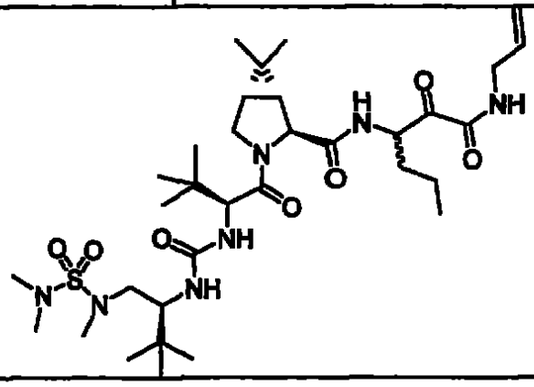
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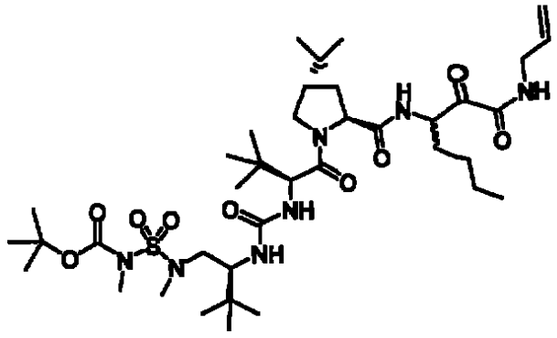
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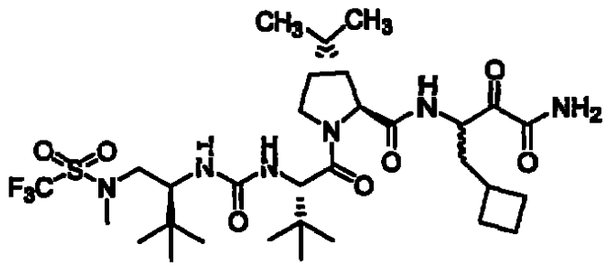
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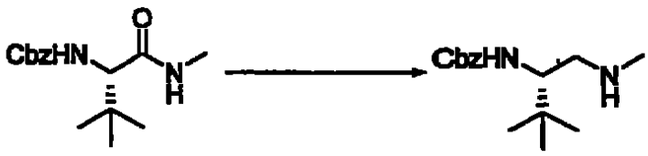
10101		A

Example-6 Synthesis of compound of Formula 11001



11001

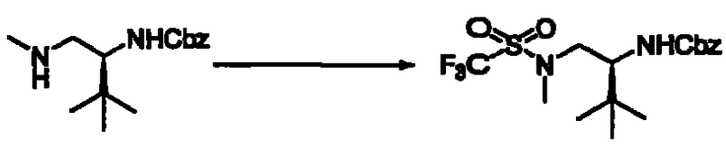
Step A.



11001a **11001b**

A solution of amide **11001a** (Obtained by Cbz protection of *tert*-butylglycine –N-methyl amide obtained from commercial source TCI-Japan) 18 g, 64 67 mmol) in toluene (200 mL) was treated with BH_3•DMS (2 M soln in THF, 65 mL, 130 mmol) and heated at 80° C for 3 h The reaction mixture was cooled to rt. and treated carefully with aq NaOH (2 M solution) and extracted into CH_2Cl_2 (3x200 mL) The combined organic layers were extracted with aq saturated $NaHCO_3$ (3x300 mL), brine (300 mL), dried ($MgSO_4$) and purified by chromatography (SiO_2, ammoniacal methanol (7M)/CH_2Cl_2 1 20) to yield **11001b** as a colorless oil

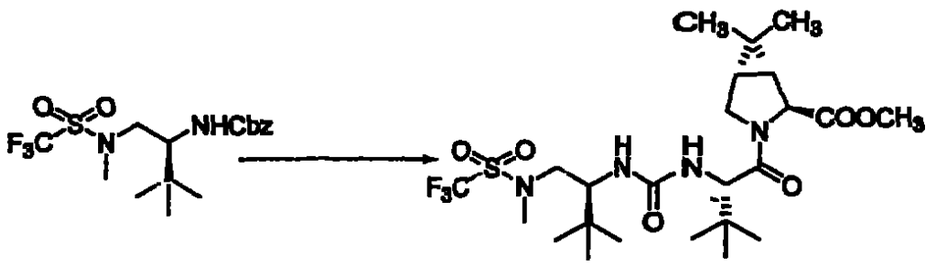
Step B



11001b **11001c**

A solution of amine **11001b** (900 mg, 3.40 mmol) in CH_2Cl_2 at 0 °C was treated with NMM (511 mg, 5 10 mmol) and triflic anhydride (585 mg, 5 10 mmol) and stirred at 0 °C for 12 h The reaction mixture was diluted with CH_2Cl_2 (300 mL) and washed with excess aq HCl (1M, 500 mL) The organic layer was dried ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, Hex/EtOAc 1·9-1 1) to yield trifluoromethane sulfonamide ***11001c.***

Step C

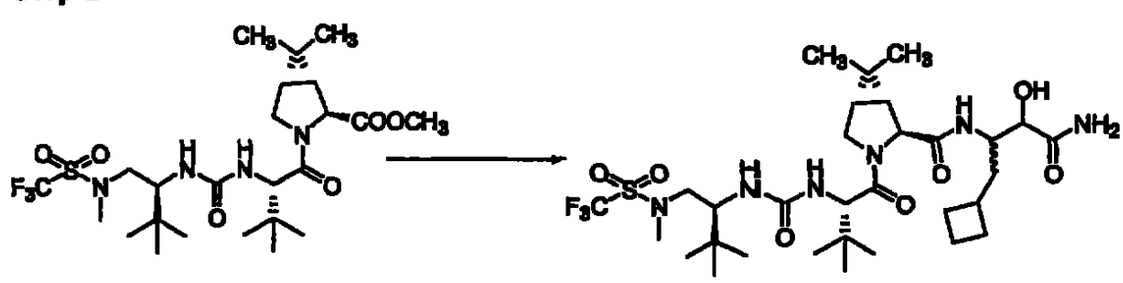


11001c **1 1001d**

A solution of **11001c** (1 28 g, 3 22 mmol) in methanol (30 mL) was treated with palladium hydroxide (200 mg, 10% wt/C) and hydrogenated at 60 psi for 3 h The reaction mixture was filtered through a plug of celite® and the filtrate was concentrated in *vacuo* The residue was directly used in further reaction without purification

A solution of deprotected amine (200 mg, 0 763 mmol) in DMF (3 mL), CH_2Cl_2 (3 mL) was treated with 4-nitrophenylcarbamate 1 16 (409 mg, 0 915 mmol), NMM (308 mg, 3 05 mmol) at 0 °C and stirred at rt. overnight. The reaction mixture was concentrated in *vacuo* diluted with CH_2Cl_2 (150 mL) and washed with aq HCl (1M, 2x125 mL), aq saturated $NaHCO_3$ (2x125 mL), brine (100 mL), dried ($MgSO_4$), filtered and purified by chromatography (SiO_2, CH_2Cl_2/EtOAc 1 19) to yield **11001d**

Step D



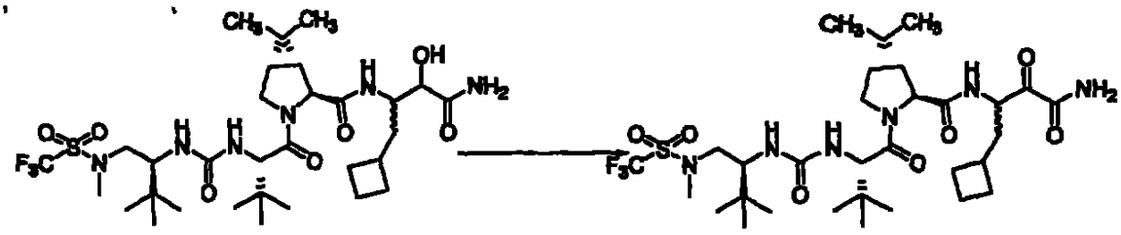
67

11001d 11001e

A solution of methyl ester 11001d (210 mg, 0.368 mmol) in dry THF (3 mL) was treated with H_2O (3 mL), methanol (3 mL) and treated with LiOH monohydrate (41 9 mg, 1 mmol) and stirred for 3 h at rt. The reaction mixture was acidified to pH~2 and extracted into CH_2Cl_2 (100 mL) The organic layer was washed with H_2O (100 mL), brine (100mL) dried ($MgSO_4$) filtered concentrated in *vacuo* to yield acid that was used as it is in the next reaction

A solution the acid (50 mg, 0 089 mmol) in dry CH_2Cl_2 (2 mL) and DMF (2 mL) was cooled to 0° C and treated with amine 10 11 (20 mg, 0 116 mmol) HATU (57 03 mg, 0 15 mmol) and NMM (40 4 mg, 0.40 mmol) The reaction was stirred at 0° C for 36 h and concentrated in *vacuo* The residue was dissolved in CH_2Cl_2 (100 mL) and washed with aq HCl (1 M, 2x 100 mL), aq saturated $NaHCO_3$ (2x100mL) brine (100 mL), dried ($MgSO_4$) filtered, concentrated in *vacuo* to yield 11001e that was used in the next reaction without further purification

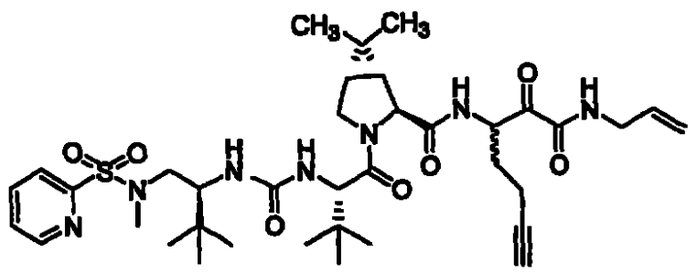
Step E



11001e 11001

A solution of 11001e (50 mg, 0 075 mmol) in toluene (3 mL) and DMSO (3 mL) was treated with EDCI (134 mg, 0 703 mmol), and dichloroacetic acid (45 3 mg, 0 351 mmol, 30µL) and stirred at rt. for 3 h The reaction mixture was diluted with CH_2Cl_2 (60 mL) and washed with aq saturated $NaHCO_3$ (30 mL), aq HCl (1 M, 30 mL), brine (30 mL), dried ($MgSO_4$) filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/Hexanes 20-50% linear gradient) to yield 11001.

Example-7, Synthesis of compound of Formula 11002



11002

Step A.

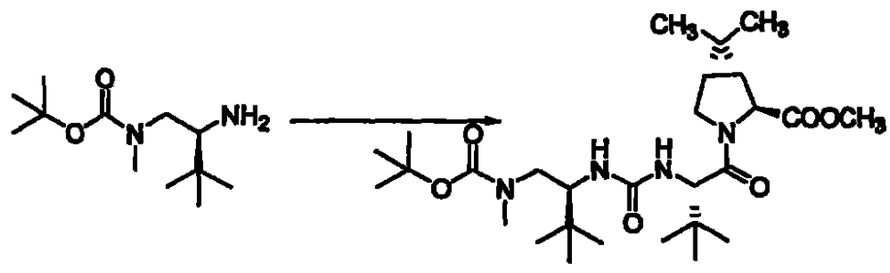


11001b 11002a

A solution of amine **11001b** (4 0 g, 15 14 mmol) in CH_2Cl_2 (100 mL) was treated with di-*tert*-butyldicarbonate (4 13 g, 18 91 mmol) and stirred at rt. for 12 h The reaction mixture was concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hexanes 1 5) to yield Boc protected amine.

A solution of the Boc protected compound in methanol was treated with palladium hydroxide and hydrogenated at 60 psi for 12 h The reaction mixture was filtered through a plug of celite® and the filtrate was concentrated in *vacuo* The residue **11002a** was used in subsequent steps without further purification

Step B

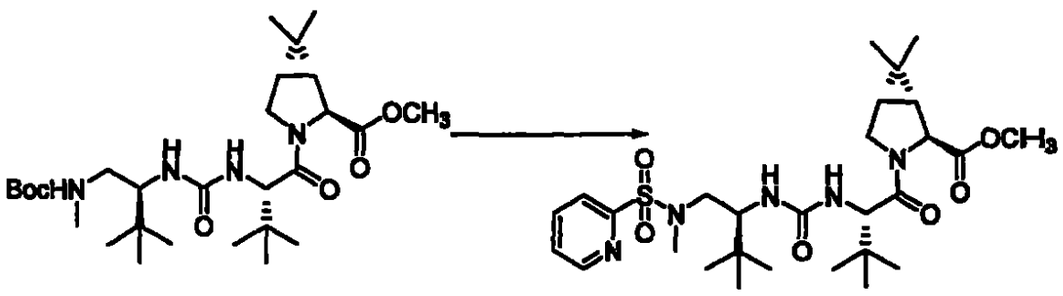


11002a 11002b

A solution of amine **11002a** (134 mg, 0 58 mmol) in acetonitrile (20 mL) was treated with 4-nitrophenylcarbamate 1 16 (260 mg, 0 58 mmol), NMM (177 mg, 1 74 mmol) at 0° C and stirred at rt. overnight The reaction mixture was concentrated in *vacuo*, diluted with CH_2Cl_2 (250 mL) and washed with aq HCl (1M, 2x125 mL), aq saturated $NaHCO_3$ (2x125 mL), brine (100 mL), dried

(MgSO$_4$) filtered and purified by chromatography (SiO$_2$, CH$_2$Cl$_2$/EtOAc 1 1 9) to yield **11002b** (279 mg)

Step C

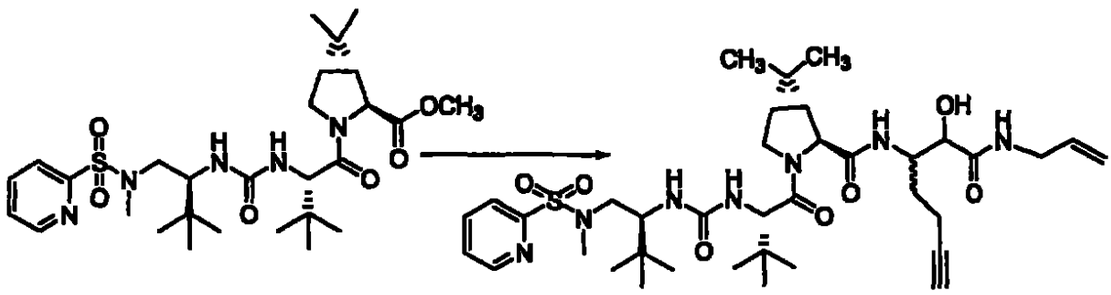


11002b **11002c**

A solution of **11002b** (279 mg, 0 52 mmol) in 4 M HCl dioxane was stirred at rt for 2 h and concentrated in *vacuo* The residue was used in further reaction as it is

The ammonium salt (274 mg, 0 58 mmol) was dissolved in CH$_2$Cl$_2$ DMF (1 1) and cooled to 0 °C The reaction mixture was treated with 4 eq of Et$_3$N (233 mg, 2 33 mmol) and 2 eq of 2-pyridinesulfonyl chloride (248 mg, 1 2 mmol) and stirred at rt overnight. The reaction mixture was washed with saturated NaHCO$_3$, and the organic layer was extracted with CH$_2$Cl$_2$ The organic layer was dried with MgSO$_4$, filtered, and concentrated in *vacuo* The crude product was purified using silica gel chromatography using a Horizon HPFC system (30% –> 90% EtOAc/hexanes) to yield 240 mg of **11002c**

Step D



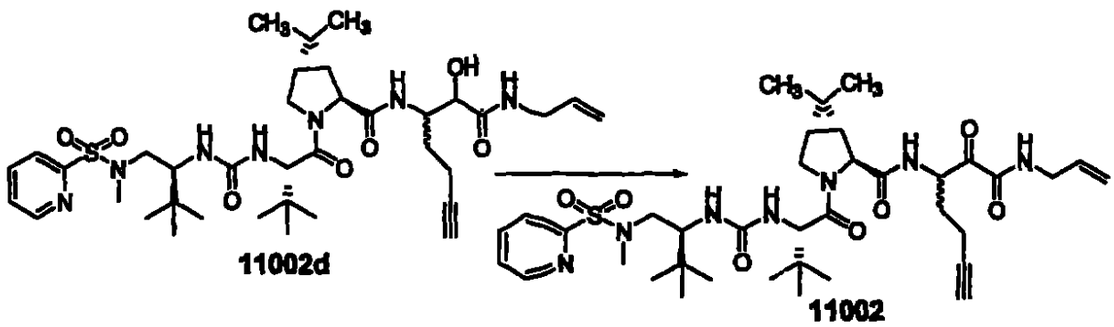
11002c **11002d**

11002c (240 mg, 0 41 mmol) was dissolved in THF and H$_2$O (3 1) and treated with 2 5 eq of LiOH•H$_2$O The reaction mixture was treated with

MeOH until the solution turns homogeneous The reaction mixture was stirred at rt for approximately 3 hr The reaction mixture was treated with 1 M aq HCl and concentrated in *vacuo* The aqueous layer was extracted with CH_2Cl_2, dried with $MgSO_4$, filtered, and concentrated in *vacuo* The crude was used in further couplings without any purification

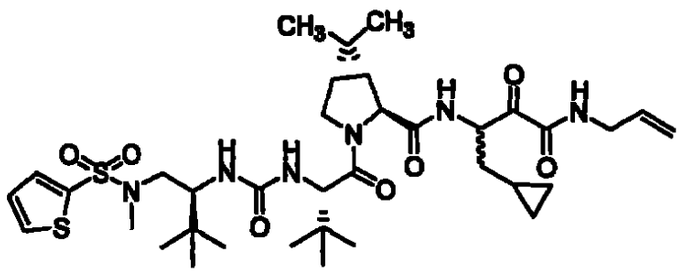
The acid (179 mg, 0 32 mmol) was dissolved in 1 1 CH_2Cl_2/DMF and cooled to 0°C The reaction mixture was treated with 1 3 eq of deprotected 11 01 (11 01 was deprotected by dissolving (200 mg, 0 61 mmol) in 10 mL of TFA and 3 mL of Me_2S and standing for 3h The reaction mixture was concentrated in *vacuo* and used as it is in further couplings) (238 mg, 0 41 mmol) 3 5 eq of NMM (112 mg 1 1 mmol), and 1 5 eq of HATU (180 mg, 0 47 mmol), and stored in the freezer (~ 0 °C) overnight. The reaction mixture was concentrated under high vacuum, and the residue was treated with saturated $NaHCO_3$ The aqueous layer was extracted with CH_2Cl_2, dried with $MgSO_4$, filtered, and concentrated in *vacuo*

Step E



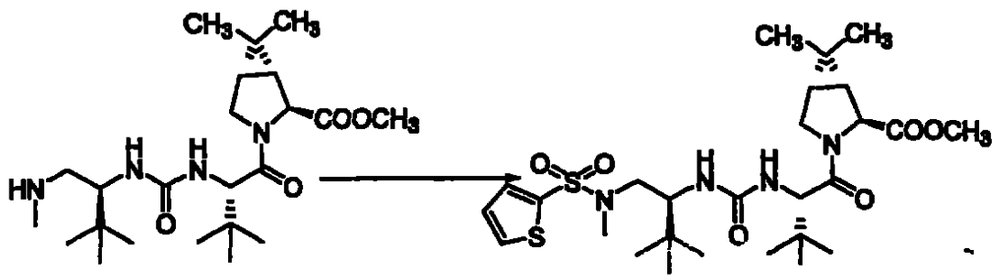
11002d (313 mg, 0 42 mmol) was dissolved in CH_2Cl_2 and treated with 3 eq of Dess-Martin periodinane (535 mg, 1 3 mmol) The reaction mixture was stirred at rt for approximately 2 hr The reaction mixture was diluted with 2 1 1 M $NaHSO_3$/saturated $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2 The organic layer was washed with 1 M $NaHSO_3$ and saturated $NaHCO_3$, dried with $MgSO_4$, filtered, and concentrated in *vacuo* The crude product was purified using silica gel chromatography with a Horizon HPFC system (20%—>60% acetone/hexanes) to yield 11002

Example-8 Synthesis of compound of Formula 11003



11003

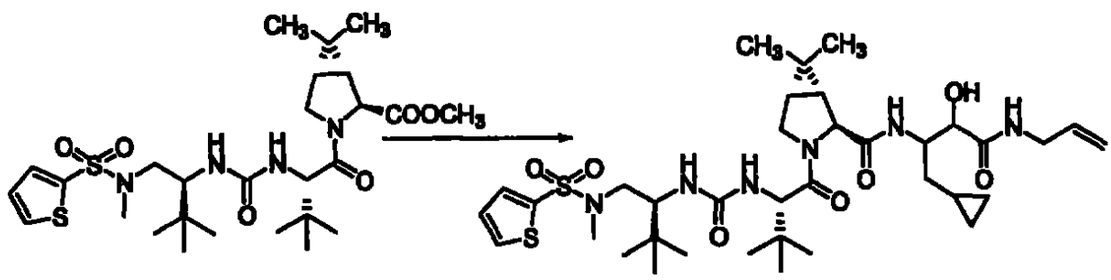
Step A.



11002c 11003a

A solution of ammonium salt **11002c** (880 mg, 1 86 mmol) in dry methylene chloride was cooled to 0 °C and treated with triethylamine (0 5 mL, 3 71 mmol) and 2-thiophenesulfonyl chloride (678 mg, 3 71 mmol) and stirred at 0 °C for 48 h The reaction mixture was taken in methylene chloride and the organic layer was washed with aq HCl (1 M soln), and brine The combined organic layers were dried ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/Hexanes 1 4) to yield 978 mg of **11003a** as a colorless solid

Step C

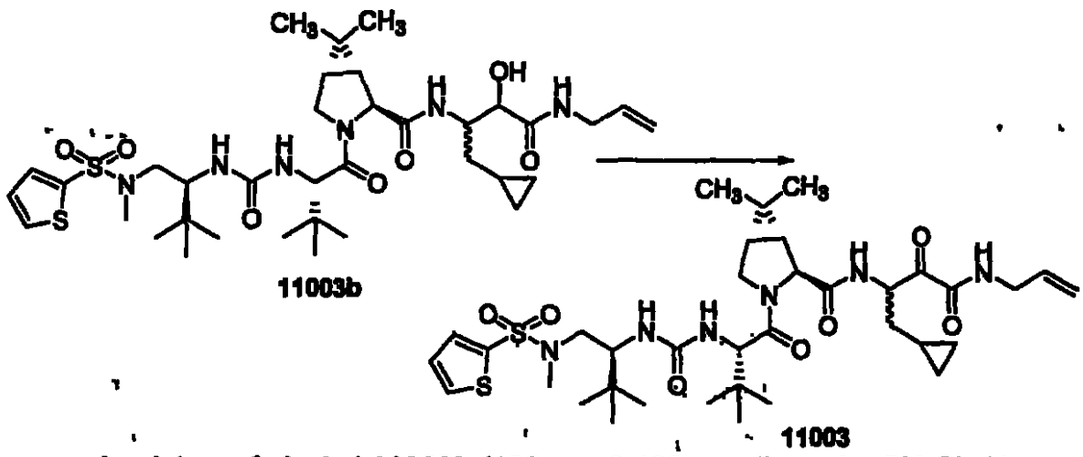


11003a **11003b**

A solution of <u>11003a</u> (1 2 g, 2 22 mmol) in THF/H_2O was treated with $LiOH \cdot H_2O$ and stirred at rt for 3 h The reaction mixture was acidified with 1 M aq HCl and extracted with CH_2Cl_2 The combined organic layers were dried ($MgSO_4$), filtered concentrated in *vacuo* and used as it is in the next step

A solution of acid (100 mg, 0 175 mmol) in dry CH_2Cl_2 (4 mL) and DMF (4 mL) was cooled to 0° C and treated with amine 12 04 (100 mg, 0 263 mmol) HATU (100 mg, 0 263 mmol) and NMM (70 4 mg, 0 704 mmol) The reaction was stirred at 0° C for 14 h and concentrated in *vacuo* The residue was dissolved in CH_2Cl_2 (100 mL) and washed with aq HCl (1 M, 2x 100 mL), aq saturated $NaHCO_3$ (2x100mL) brine (100 mL), dried ($MgSO_4$), filtered, concentrated in *vacuo* to yield 11003b that was used in the next reaction without further purification

Step D

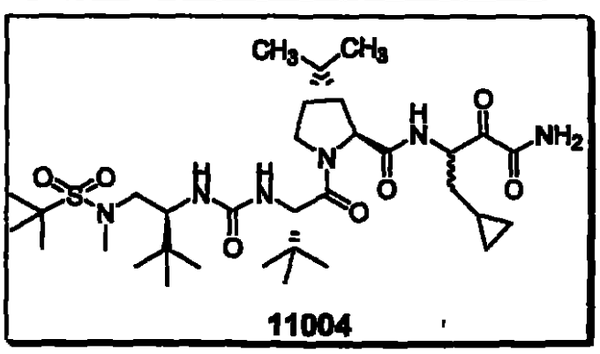


11003b

11003

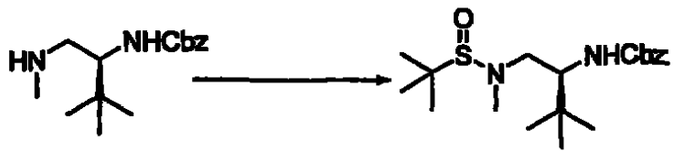
A solution of alcohol 11003b (100 mg, 0 133 mmol) in dry CH_2Cl_2 (4 mL) was treated with Dess-Martin reagent (Dess, D B , Martin, J C *J Am Chem Soc* **1991**, *113*, 7277) (150 mg, 0 345 mmol) and stirred at rt for 2 h The reaction mixture was diluted with aq $Na_2S_2O_3$ (5%, 30 mL) and aq saturated $NaHCO_3$ (30 mL) and stirred at rt for 15 min The reaction mixture was extracted with CH_2Cl_2 (100 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/Hexanes 20%-55% linear gradient) to yield 11003

Example-9 Synthesis of compound of Formula 11004



11004

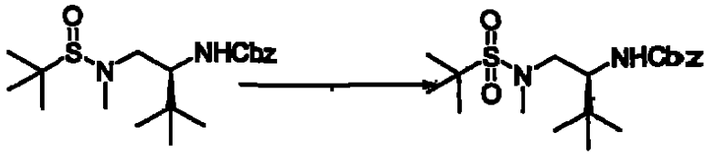
Step A



11001a 11004a

A solution of amine 11001a (150 mg, 0 567 mmol) in CH_2Cl_2 (5 mL) was cooled to 0° C and treated with NMM (100 mg, 100 mL) The reaction was treated with *tert*-butyl sulfenylchloride (Sun, P; Weinreb, S M , Shang, M *J Org Chem* 1997, *62*, 8604) (0 5 mL, 1 3 M soln in CH_2Cl_2) and stirred at rt. overnight. The reaction mixture was diluted with aq HCl (1M, 30 mL) and extracted with CH_2Cl_2 (3x30 mL) The combined organic layer was extracted with brine (30 mL) dried ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/Hexanes) to yield 11004a.

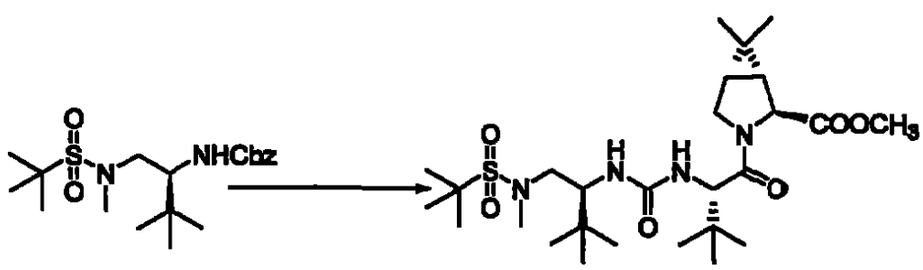
Step B



11004a 11004b

A solution of sulfenamide *11004a* (2 00 g, 5 43 mmol) in CH_2Cl_2 (60 mL) was treated with MCPBA (2 34 g, 8 145 mmol, 60%) and stirred at rt. for 1h The reaction mixture was diluted with aq $Na_2S_2O_3$ (10%, 50 mL) and aq $NaHCO_3$ (saturated, 100 mL) and stirred at rt. for 30 min The reaction mixture was extracted with CH_2Cl_2 (150 mL) and the combined organic layers were washed with water, brine, dried ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hex 1 9→1 1) to yield *11004b*

Step C

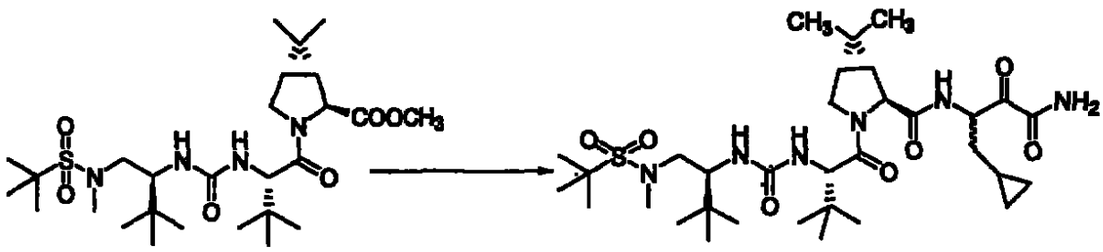


11004b 11004c

A solution of Cbz-protected compound ***11004b*** (1 5 g, 3 90 mmol) in methanol (25 mL) was treated with palladium hydroxide (10% on C) and hydrogenated at 60 psi for 1 h The reaction mixture was filtered through a plug of celite and concentrated in *vacuo* It was used for further reaction without any purification

A solution of deprotected amine (1 00 g, 4 00 mmol) in acetonitrile (20 mL) was treated with 4-nitrophenylcarbamate 1.16 (1 879 g, 4.20 mmol), NMM (1 062 g, 10 5 mmol) and stirred at rt. overnight. The reaction mixture was concentrated in *vacuo* diluted with CH_2Cl_2 (200 mL) and washed with aq HCl (1M, 2x125 mL), aq saturated $NaHCO_3$ (2x125 mL), brine (100 mL), dried ($MgSO_4$), filtered, and purified by chromatography (SiO_2, CH_2Cl_2/EtOAc 1 19) to yield ***11004c.***

Step D

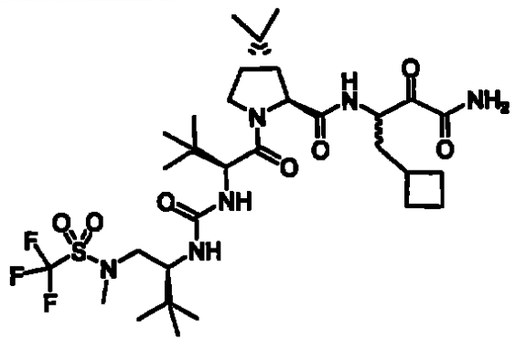
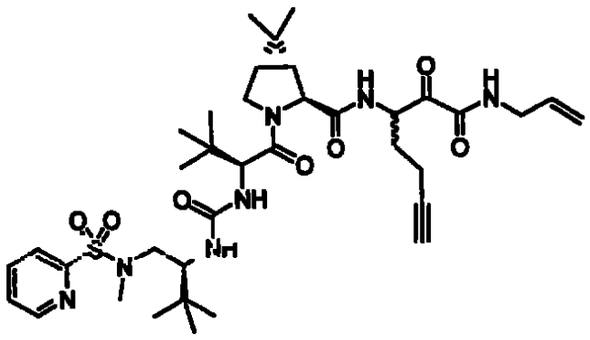
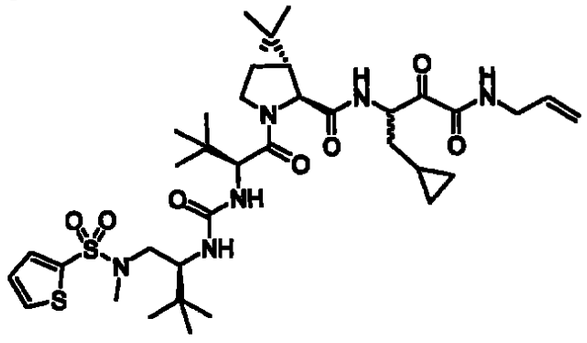
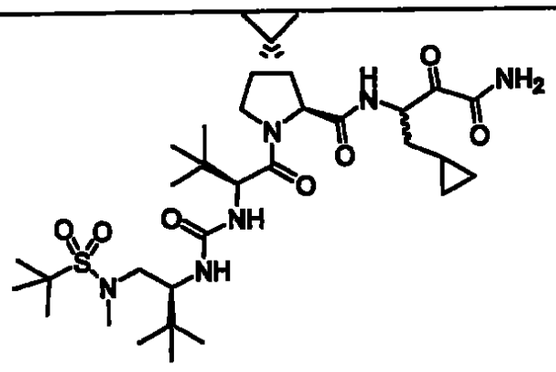


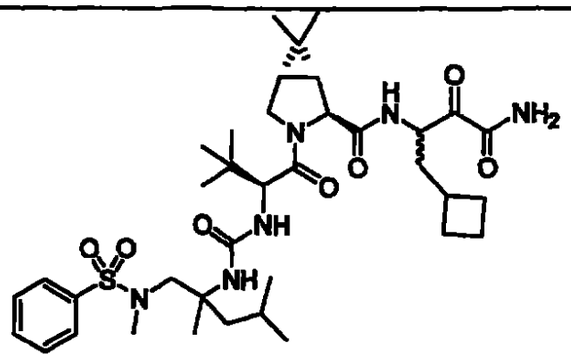
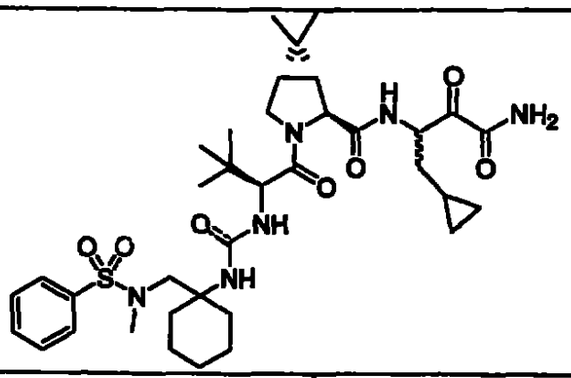
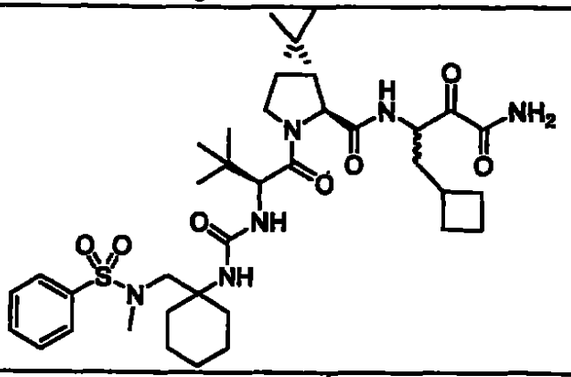
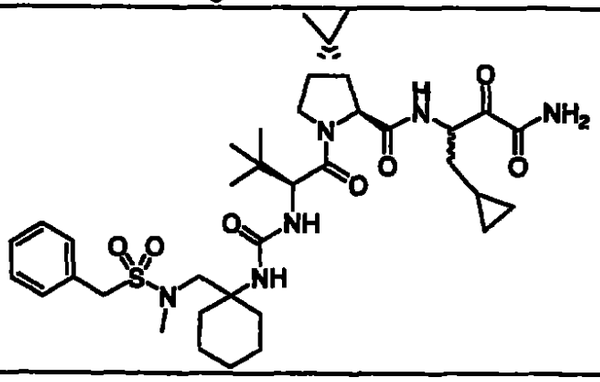
11004c **11004**

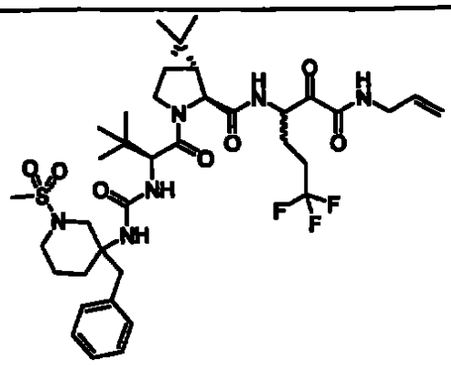
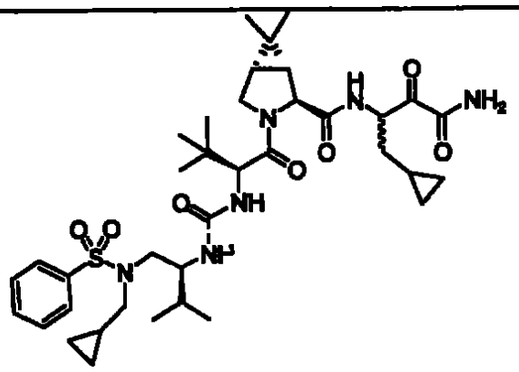
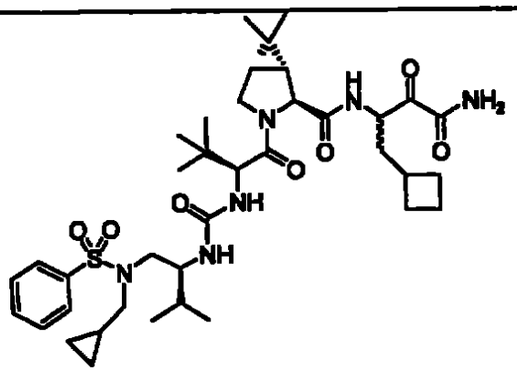
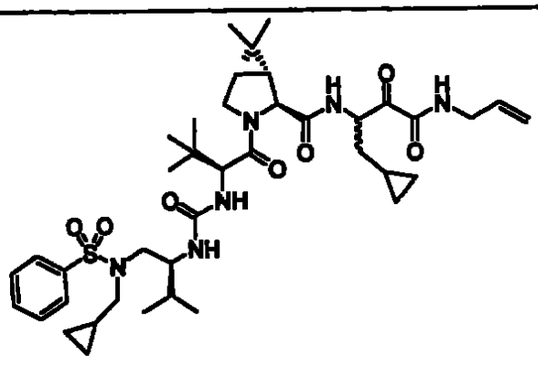
Intermediate **11004c** was converted to **11004** by coupling to intermediate **12 03** followed by Moffett oxidation identical to the procedures described in preparative example-6 of synthesis of **11001**, Step D and Step E Compounds shown in the following **Table 2** were synthesized using similar reactions as shown in Examples above Range of KI* indicated A≤75 nM, 75<B≤250 nM, C>250 nM

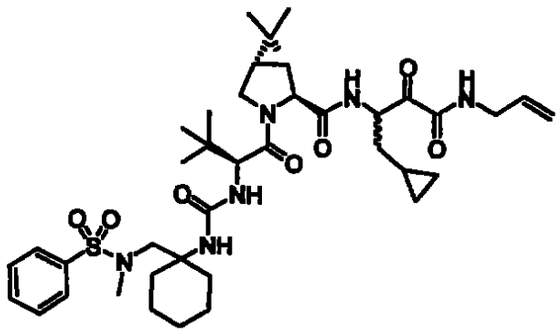
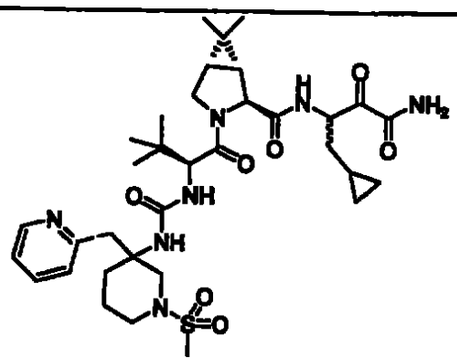
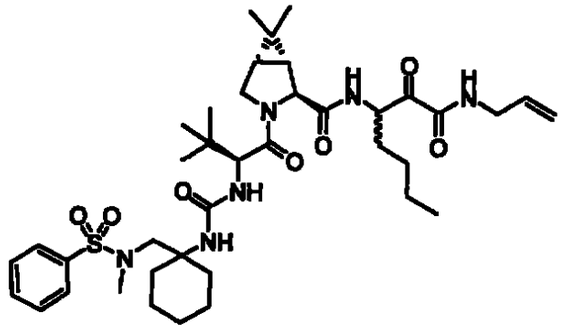
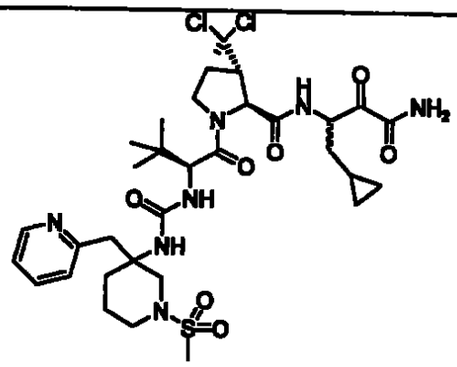
Table 2

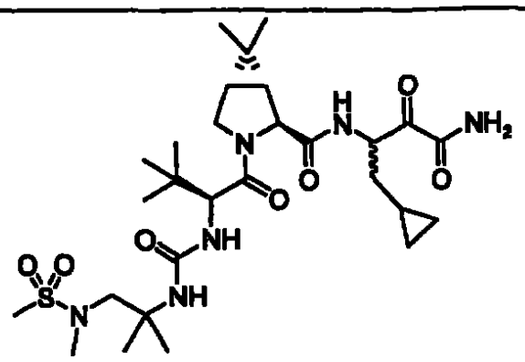
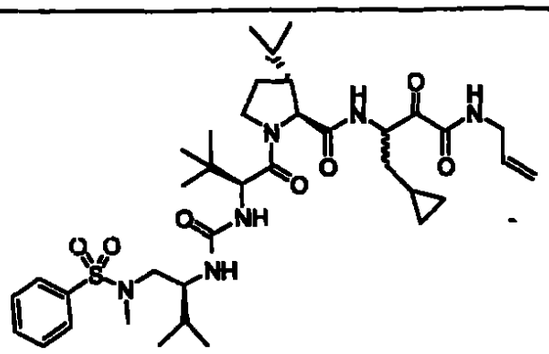
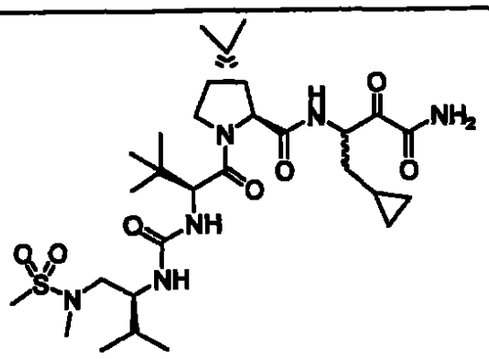
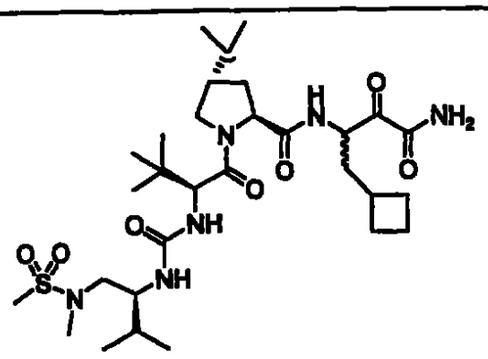
Entry	Structure	KI*

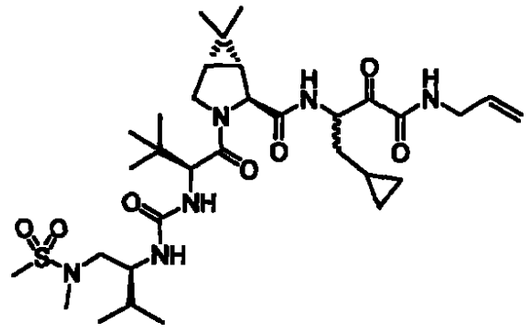
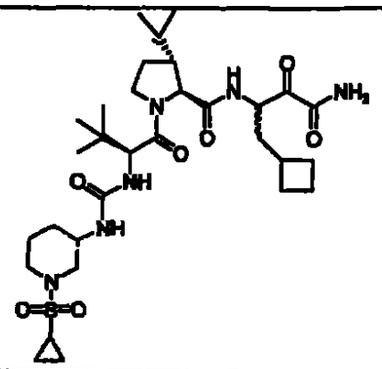
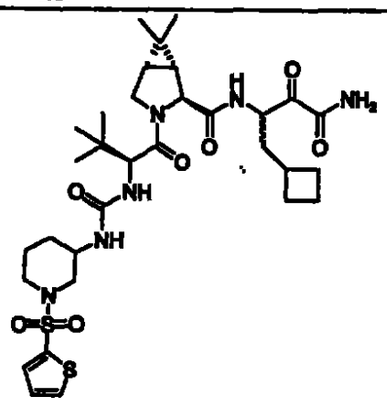
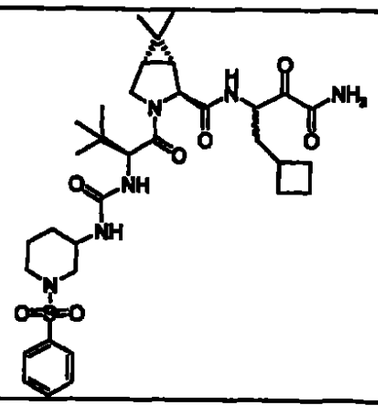
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11003		A
11004		A

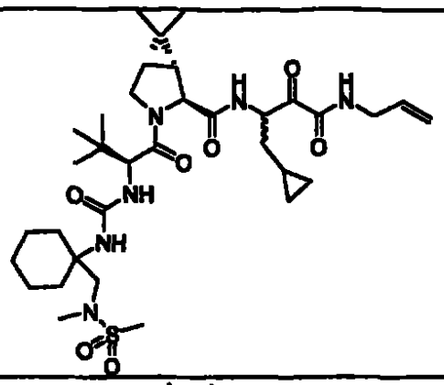
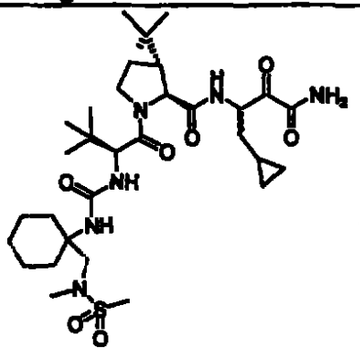
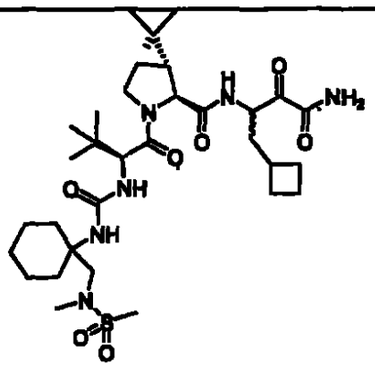
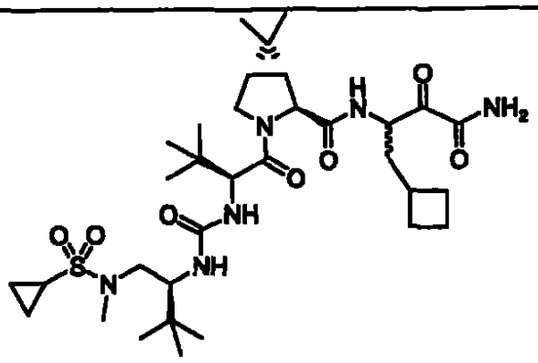
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11008		A

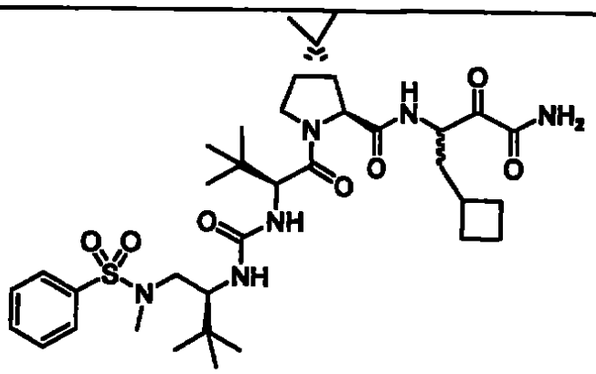
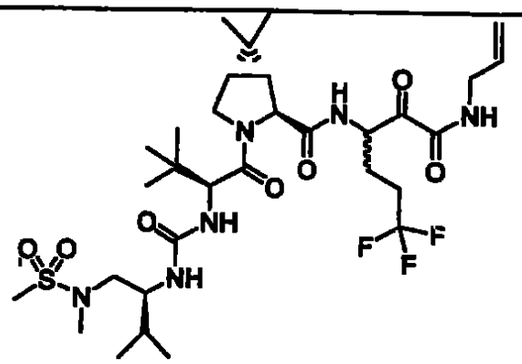
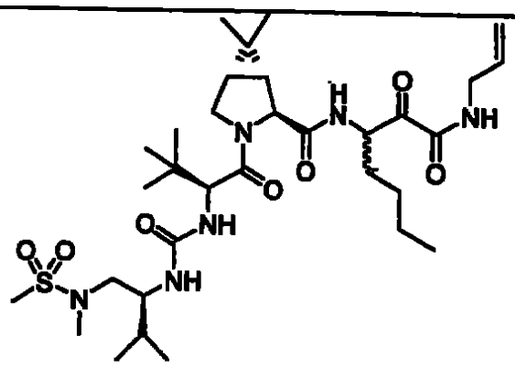
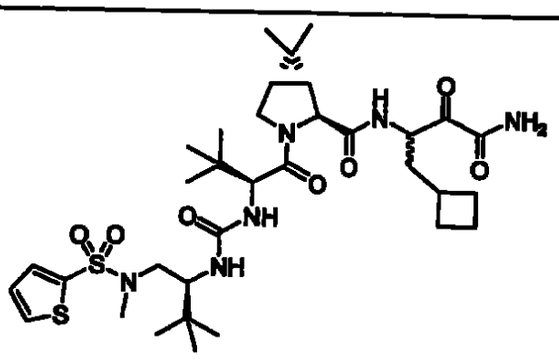
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11010		A
11011		A
11012		A

11013		A
11014		C
11015		A
11016		C

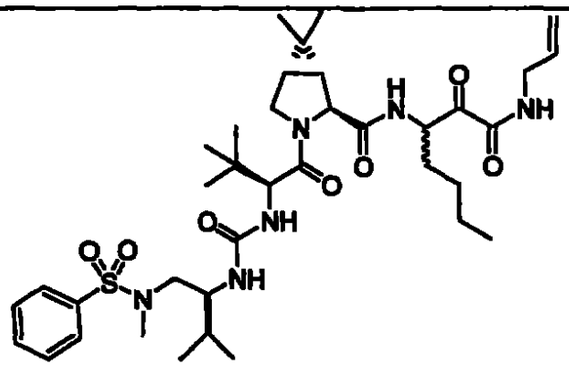
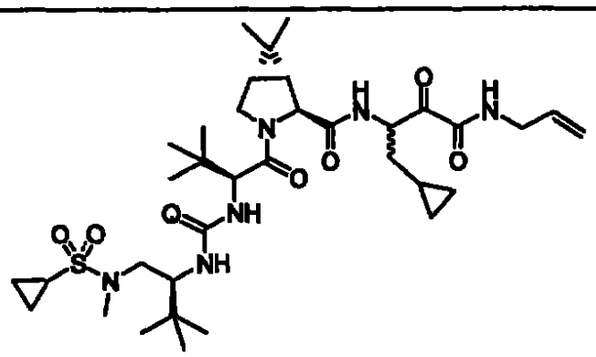
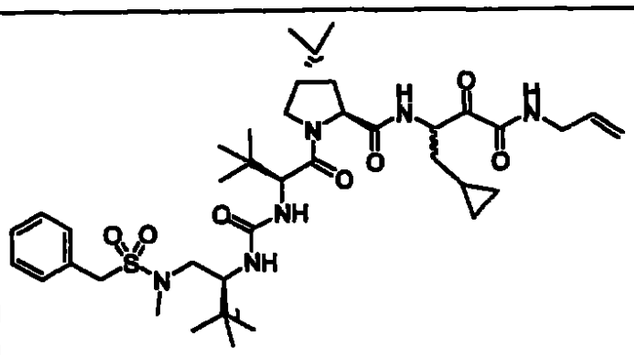
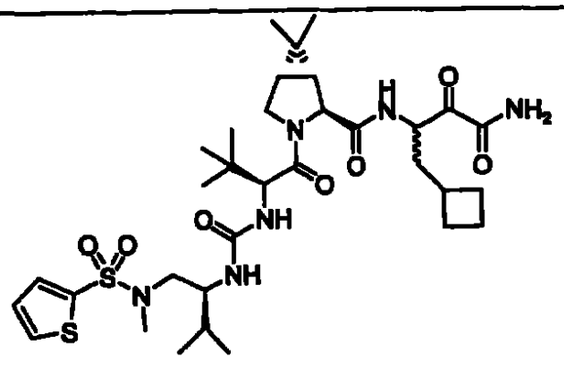
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11019		A
11020		A

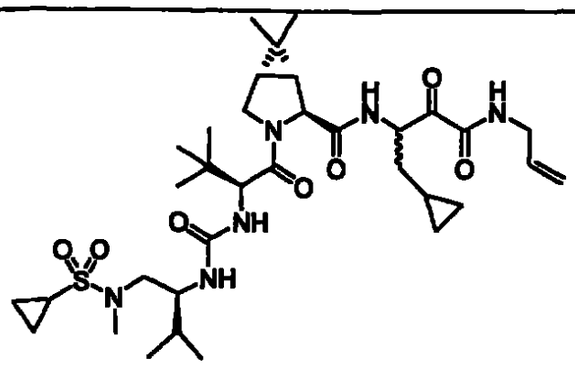
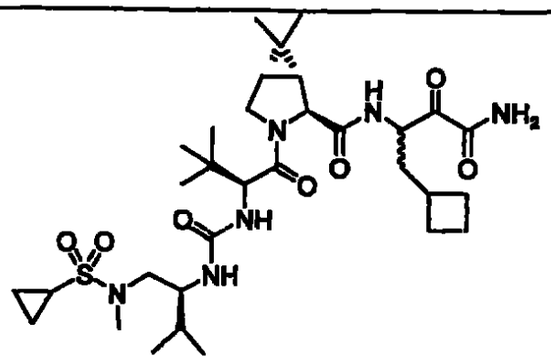
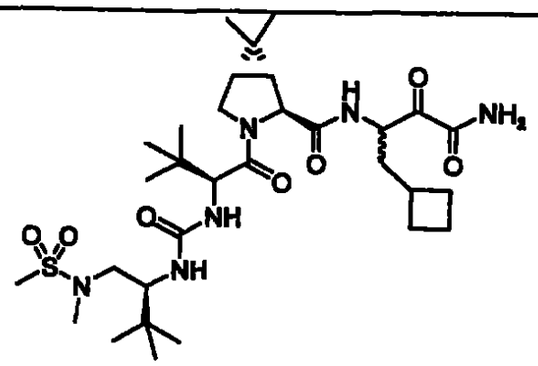
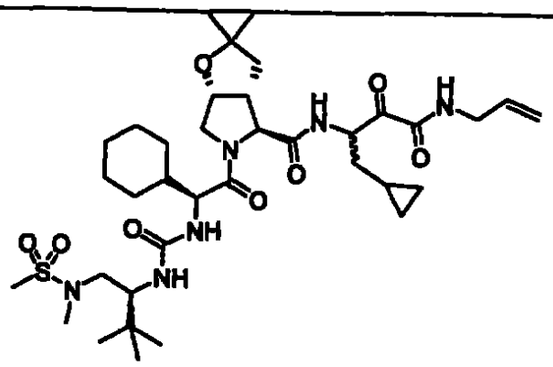
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11024		B

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11026		A
11027		A
11028		A

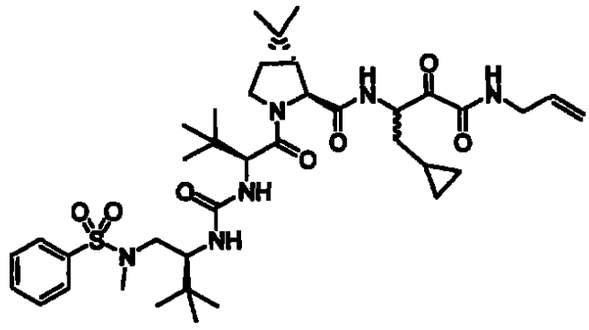
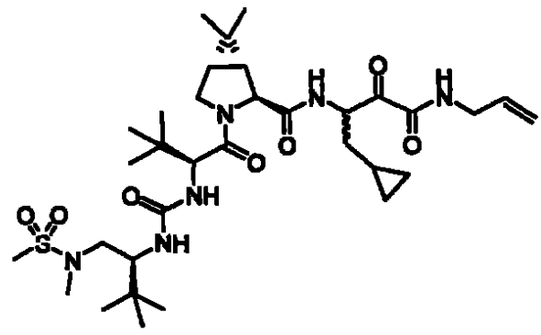
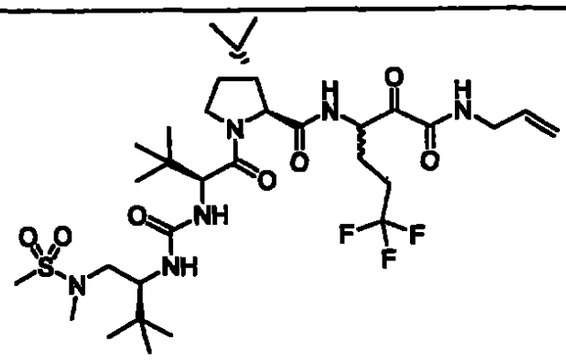
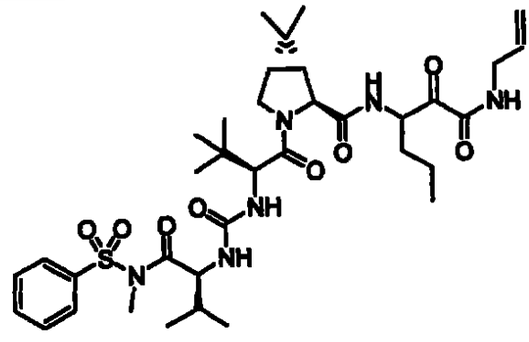
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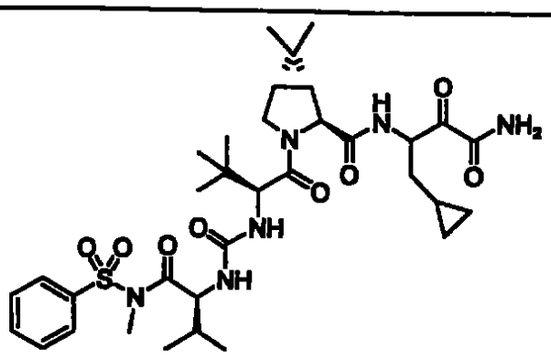
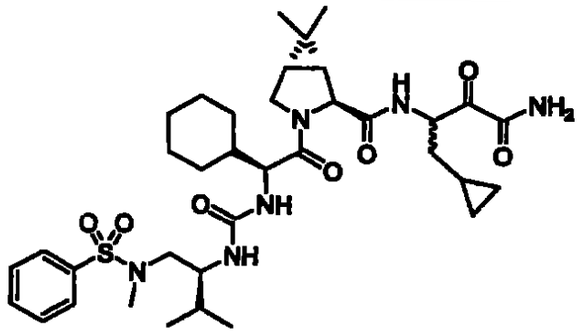
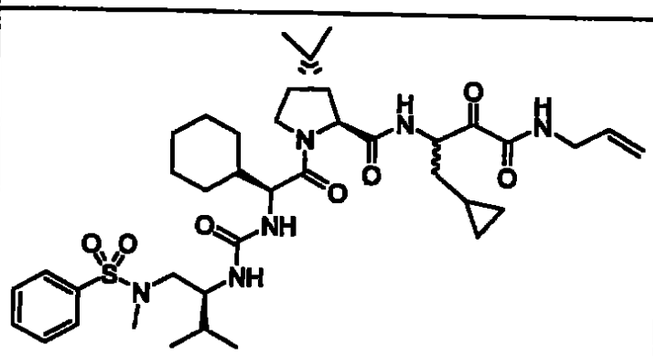
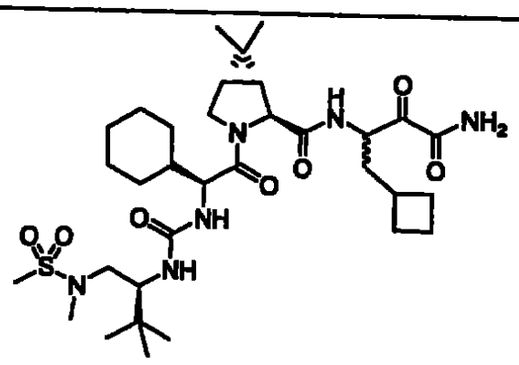
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75

11033		37
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11035		A
11036		A

11037		B
11038		A
11039		A
11040		B

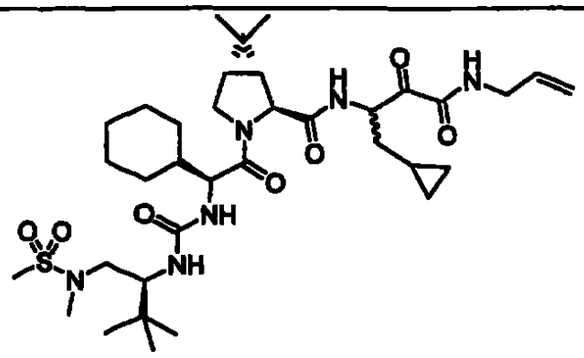
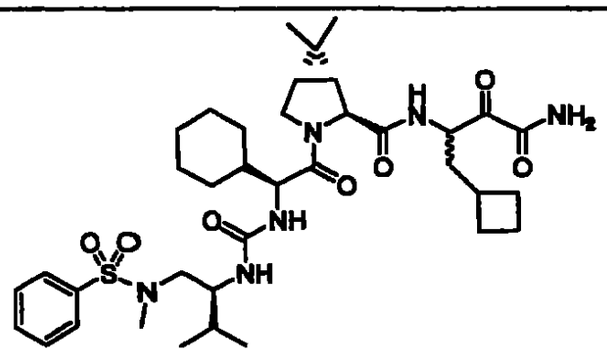
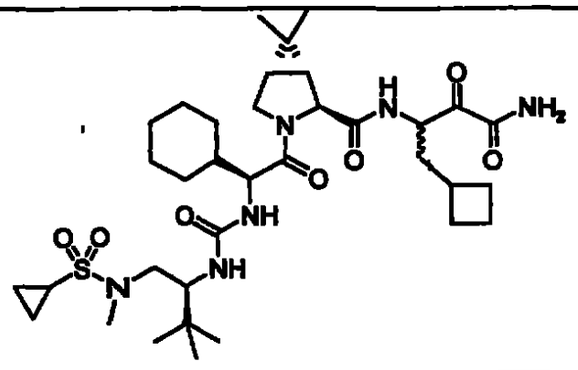
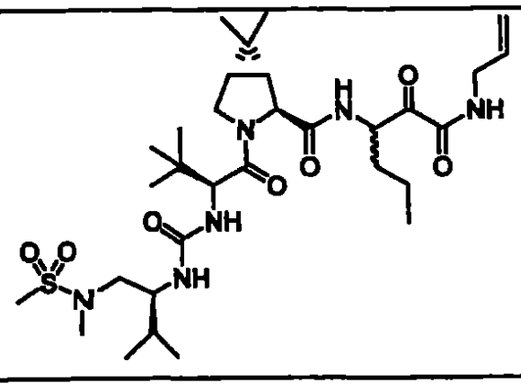
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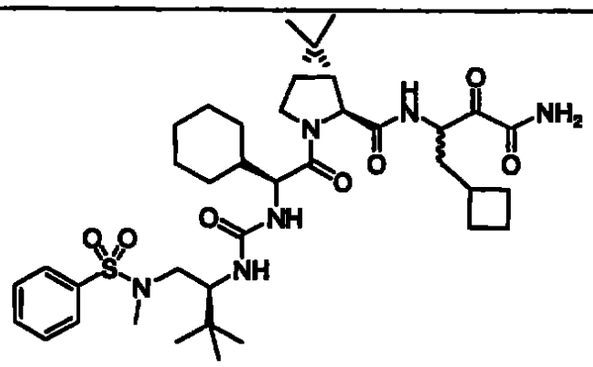
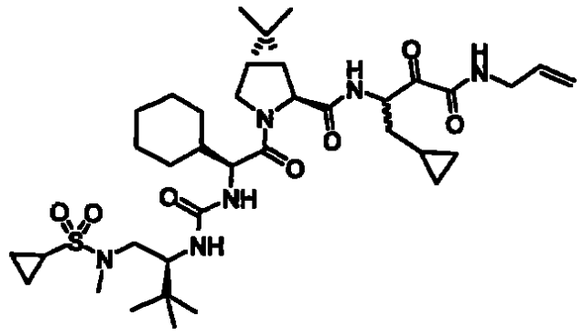
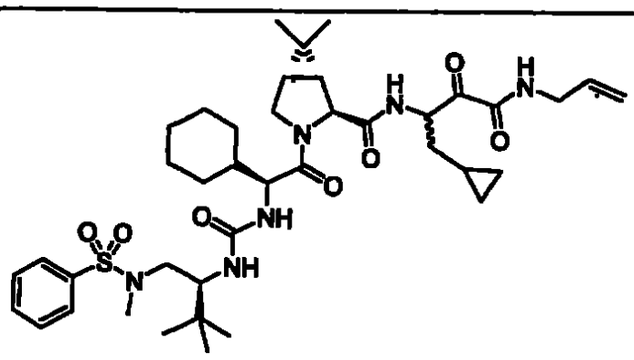
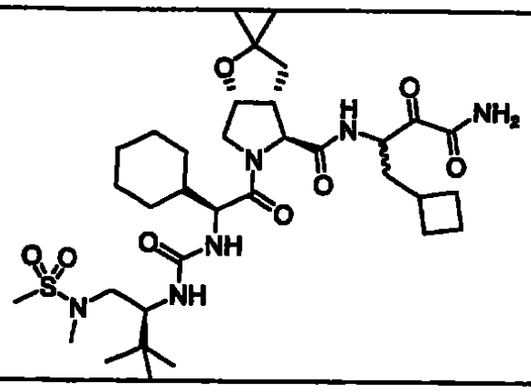
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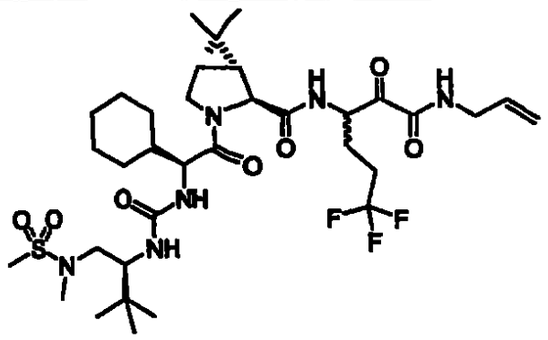
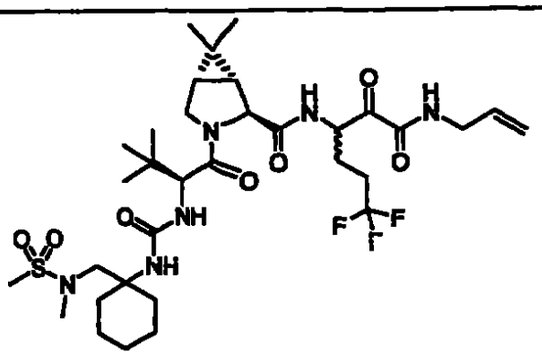
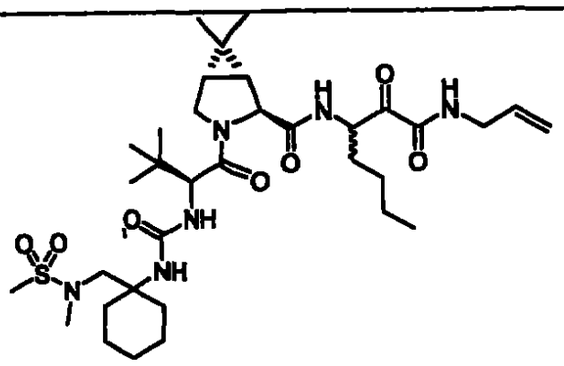
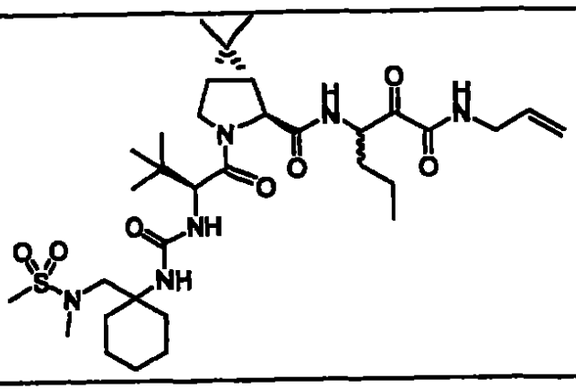
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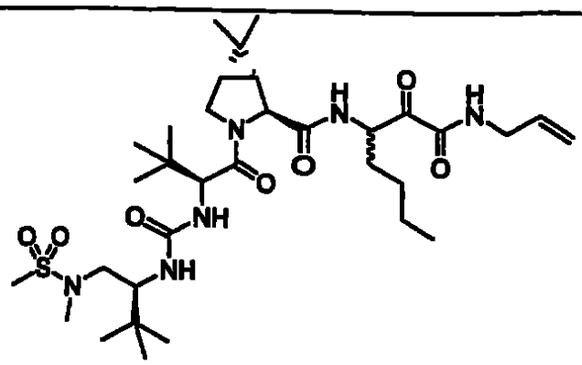
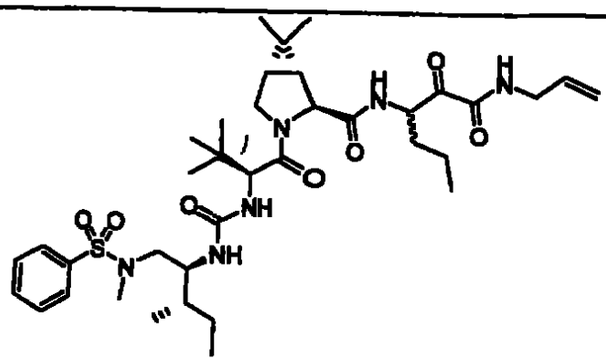
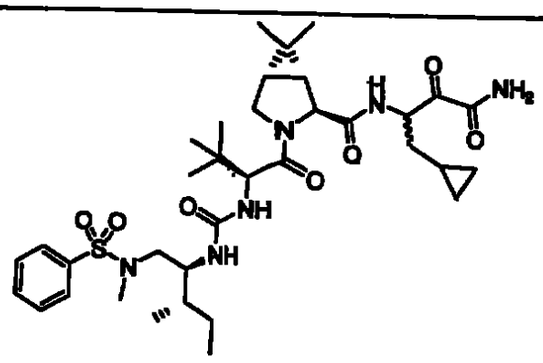
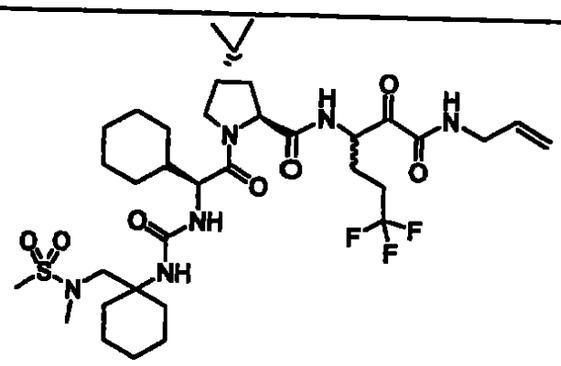
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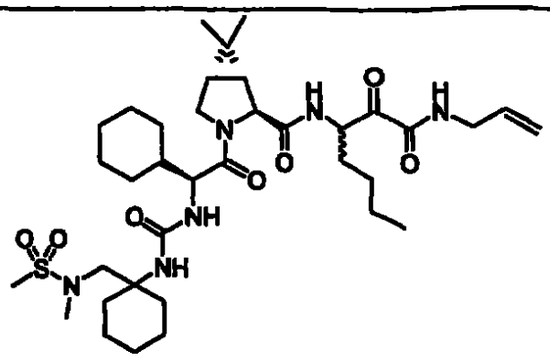
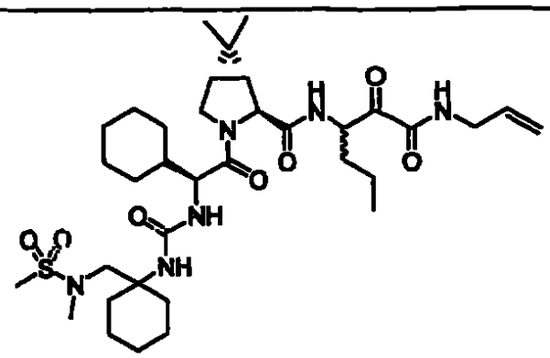
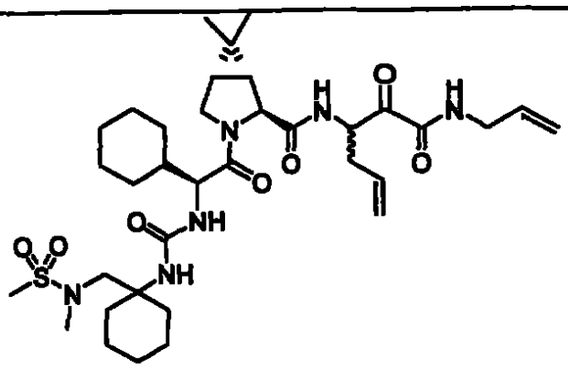
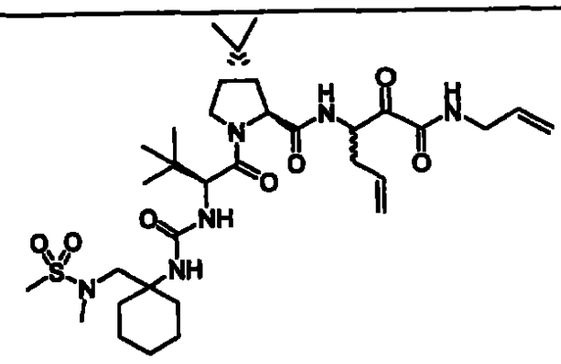
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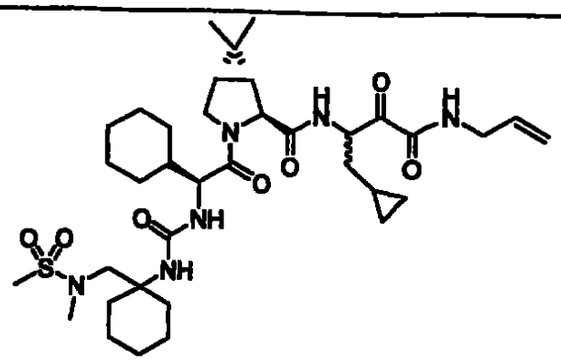
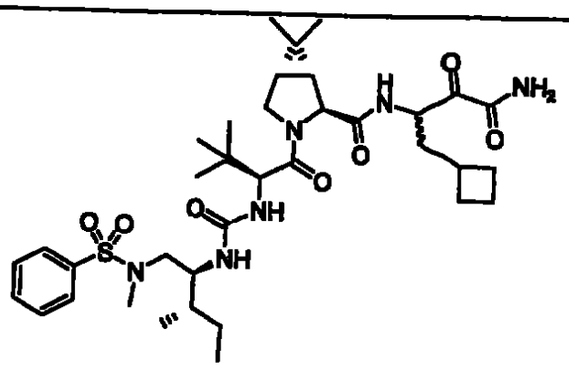
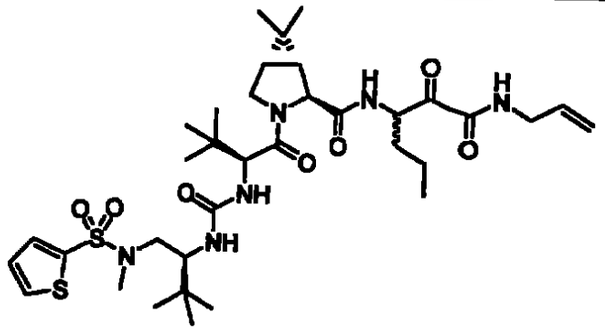
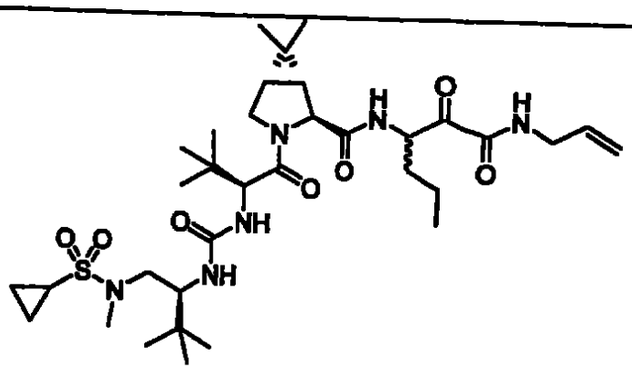
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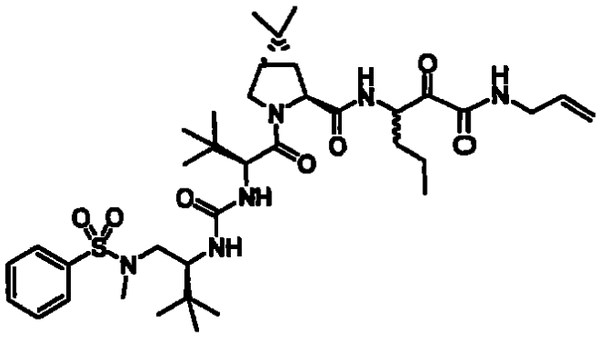
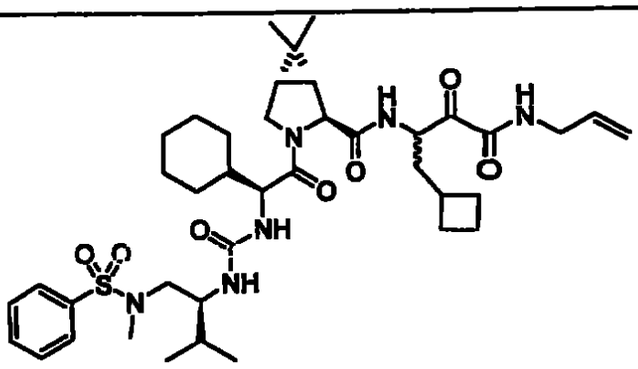
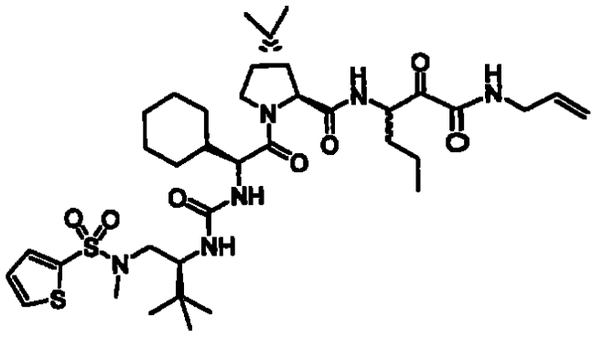
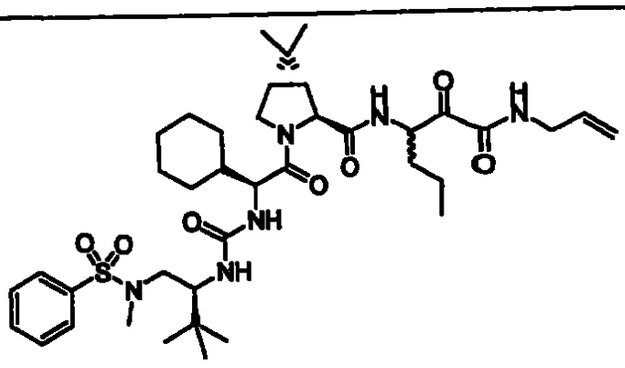
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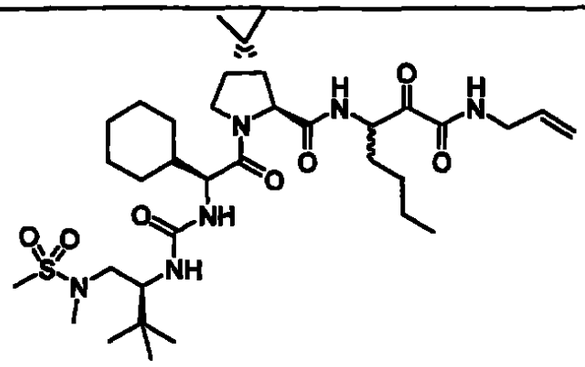
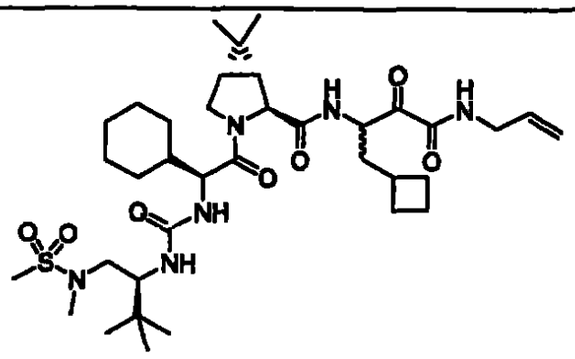
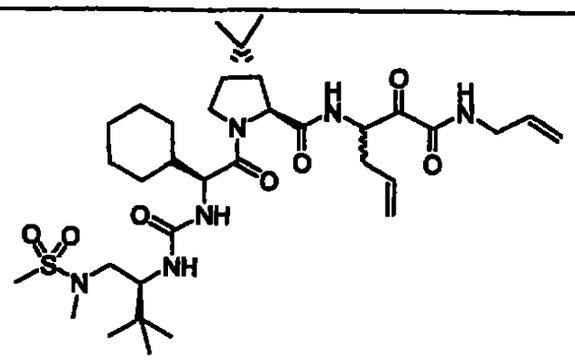
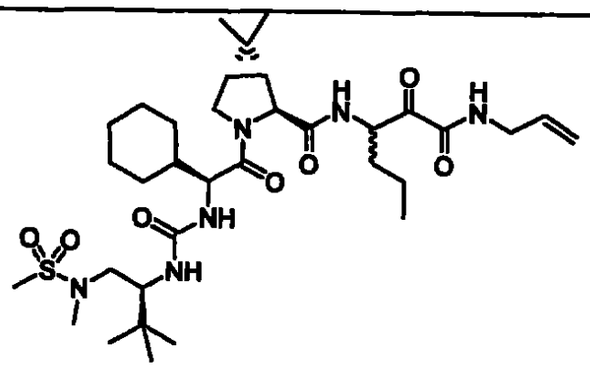
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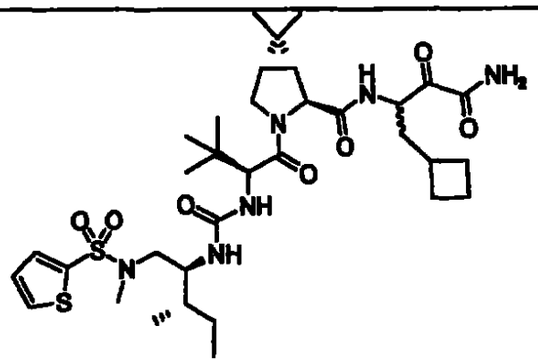
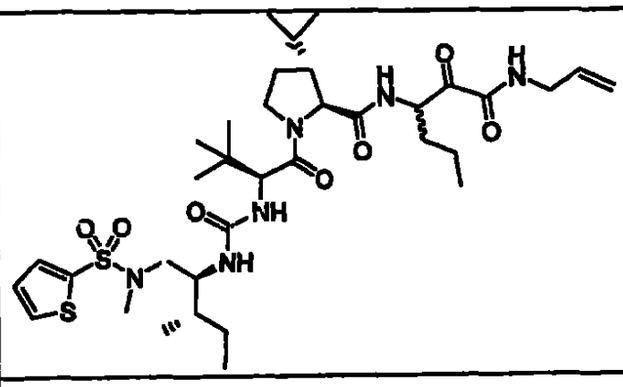
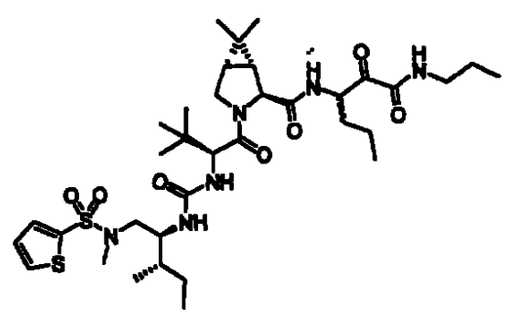
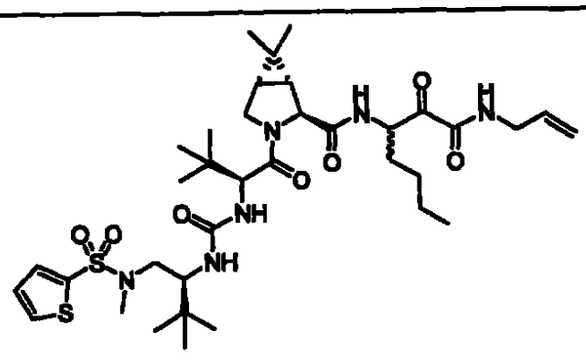
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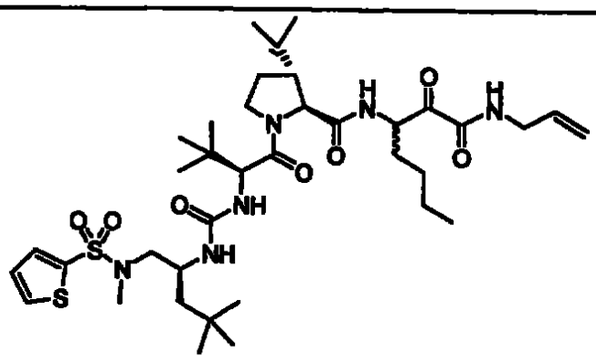
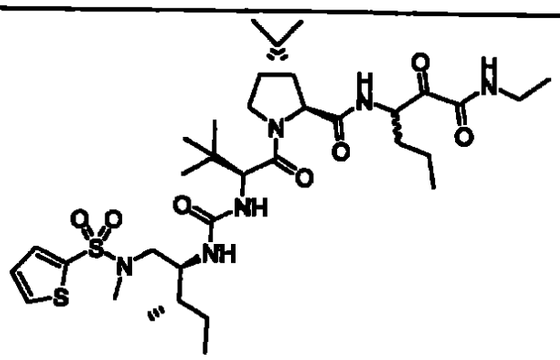
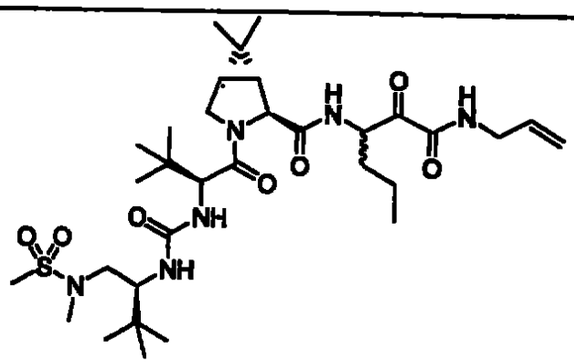
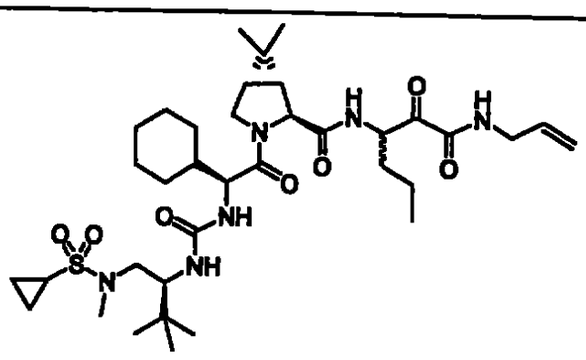
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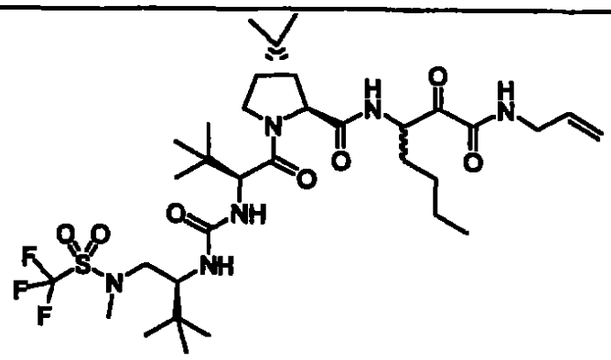
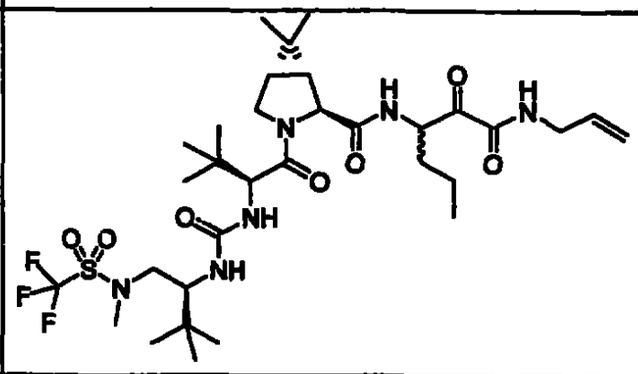
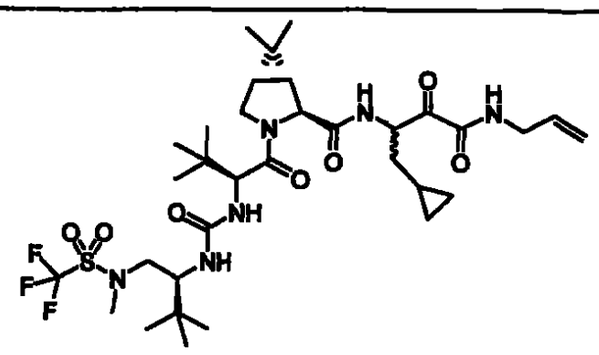
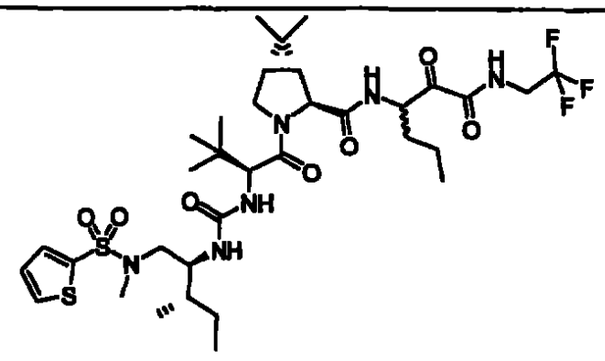
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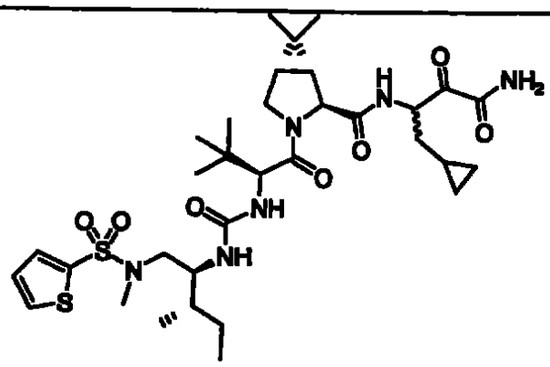
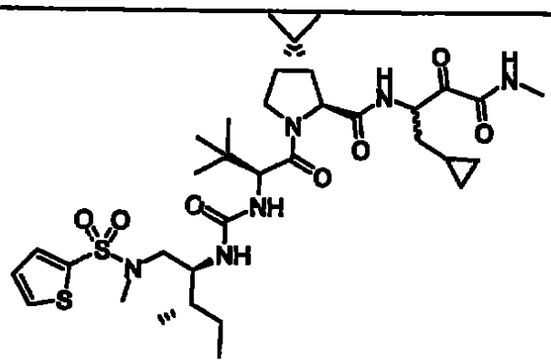
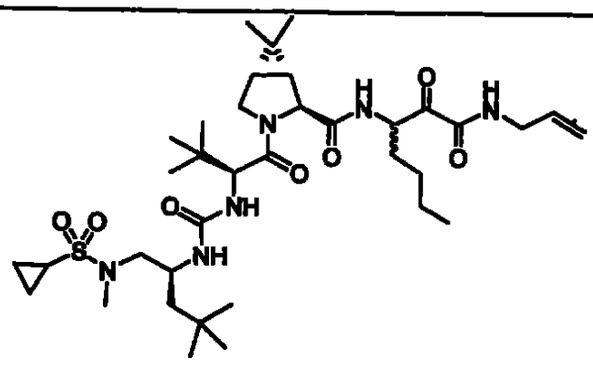
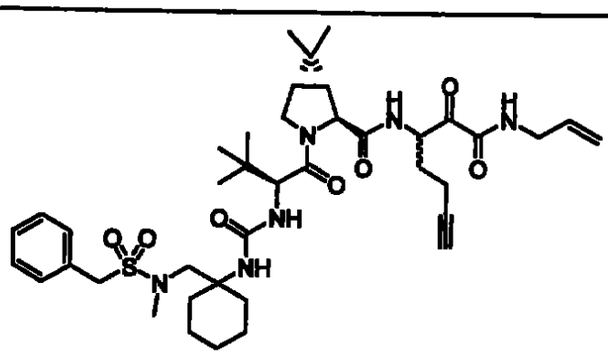
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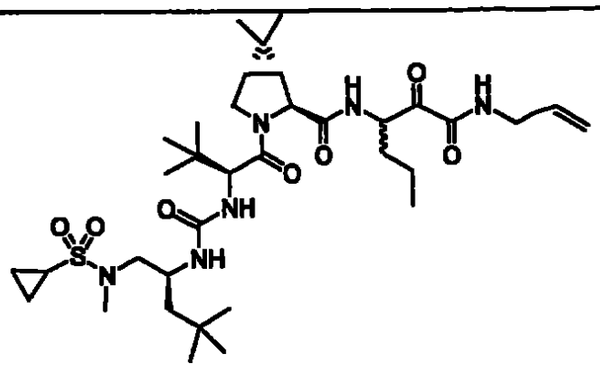
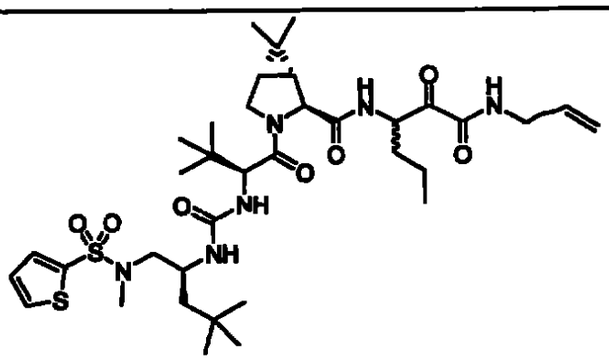
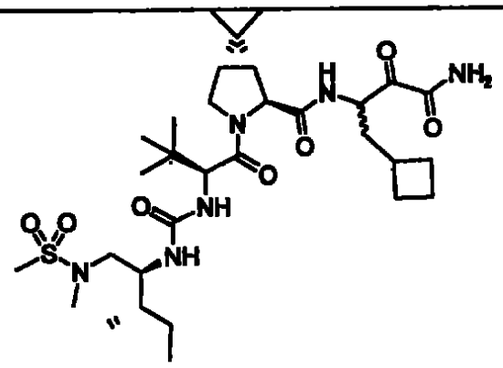
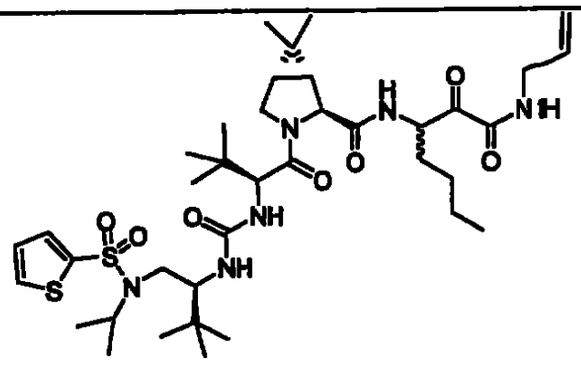
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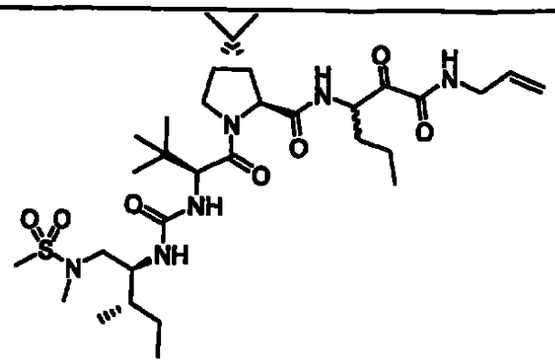
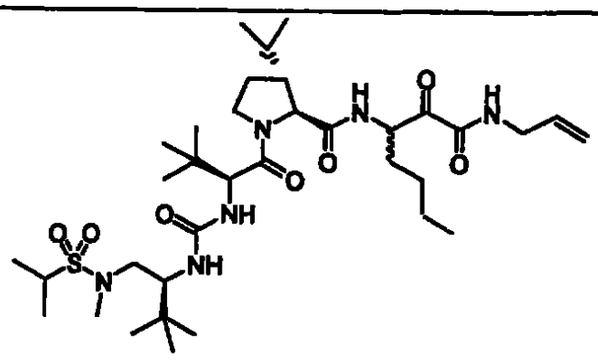
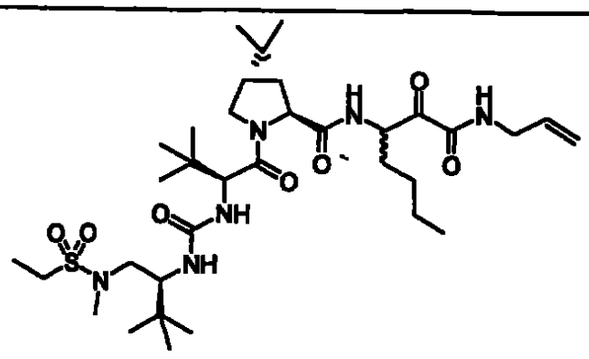
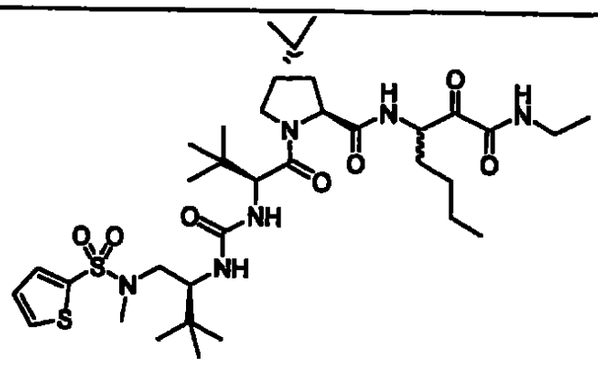
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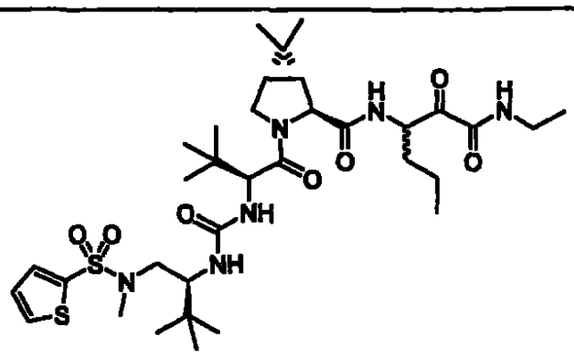
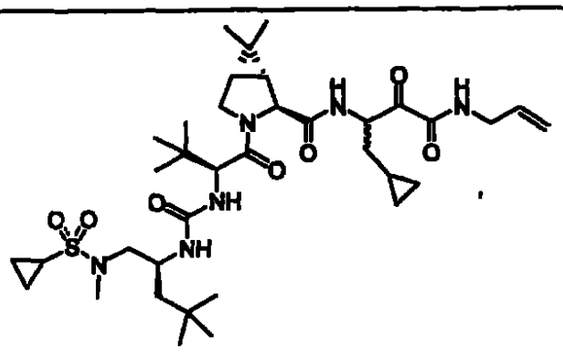
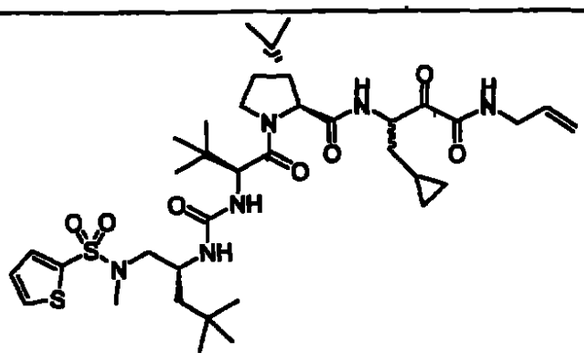
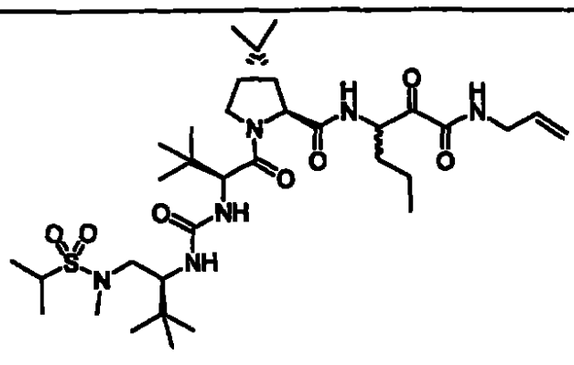
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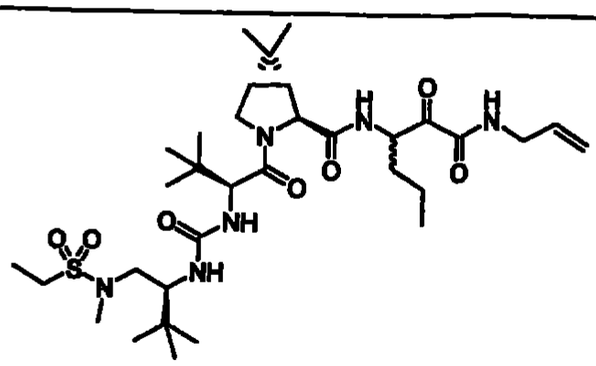
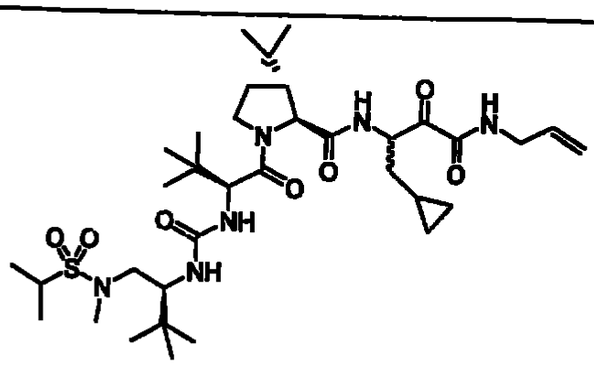
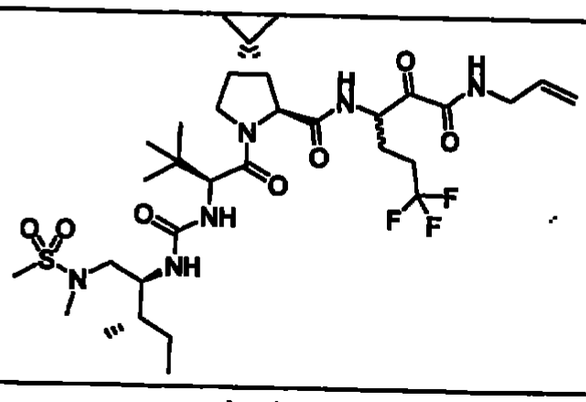
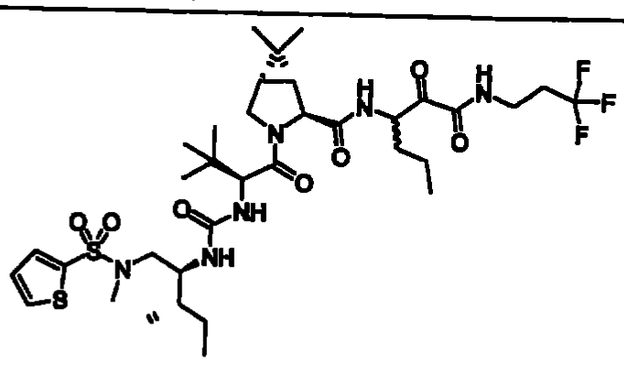
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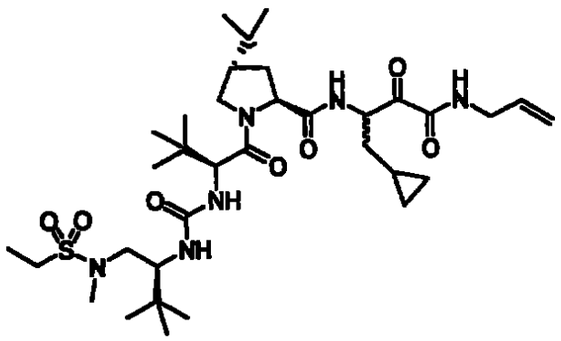
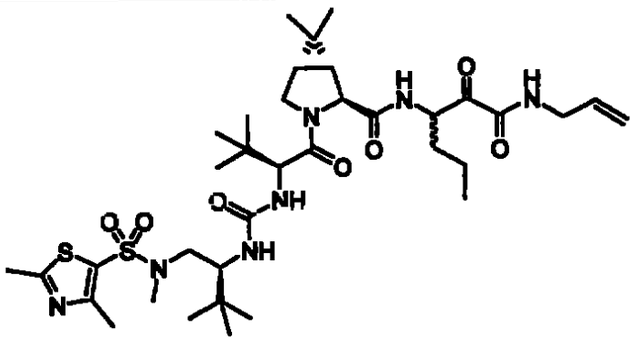
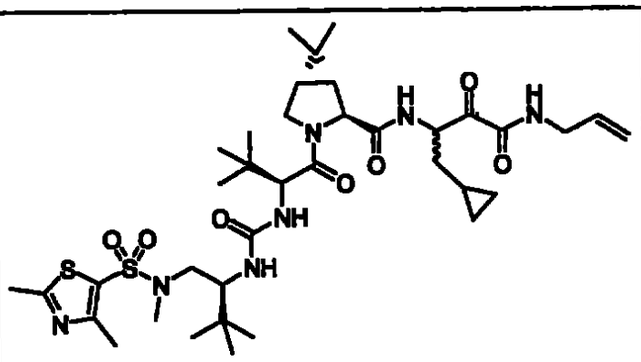
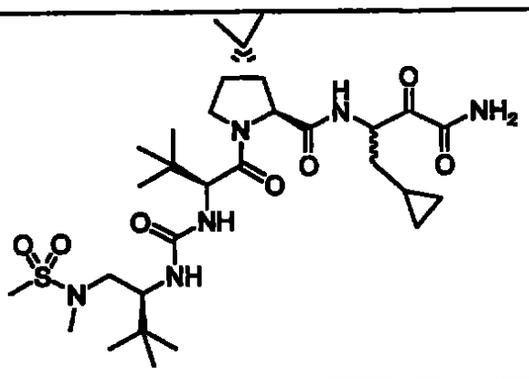
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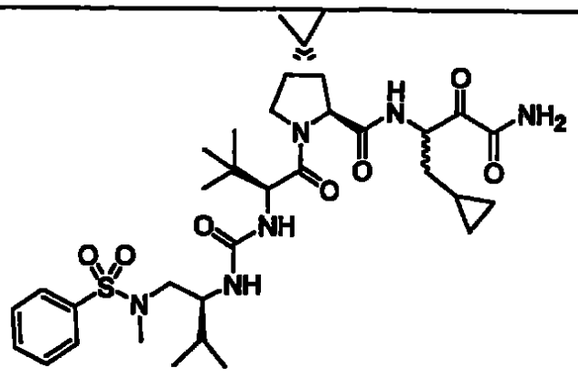
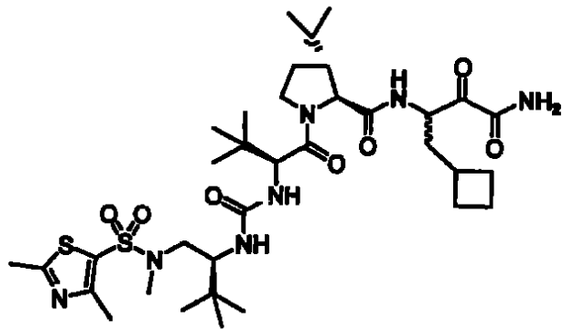
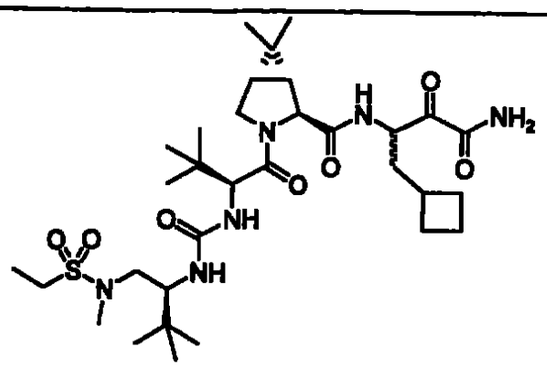
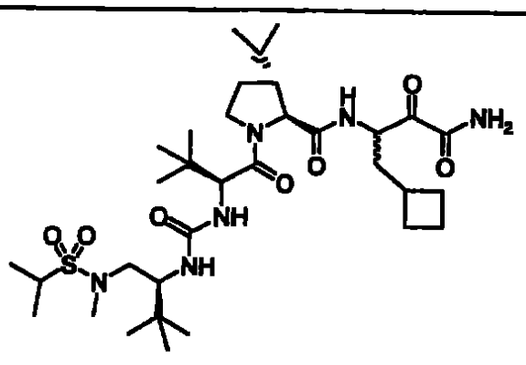
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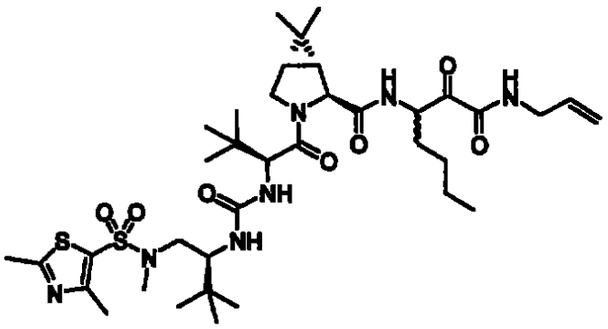
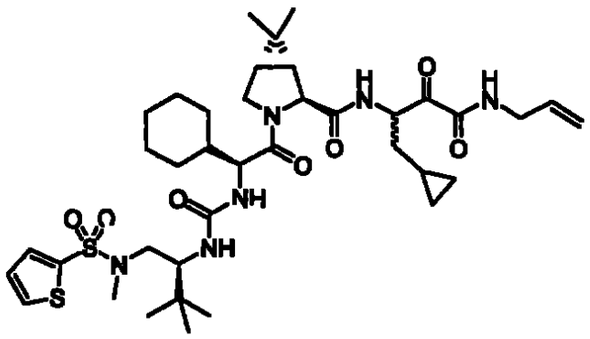
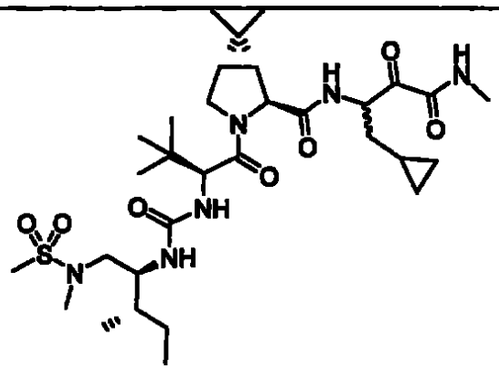
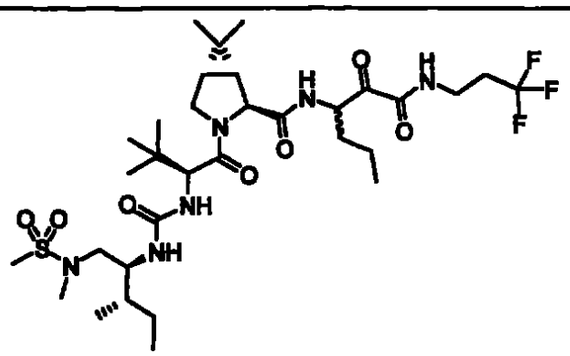
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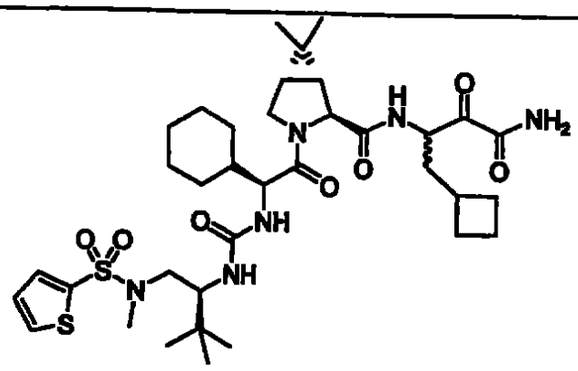
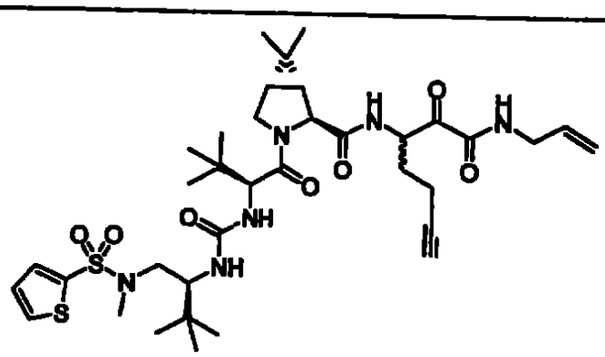
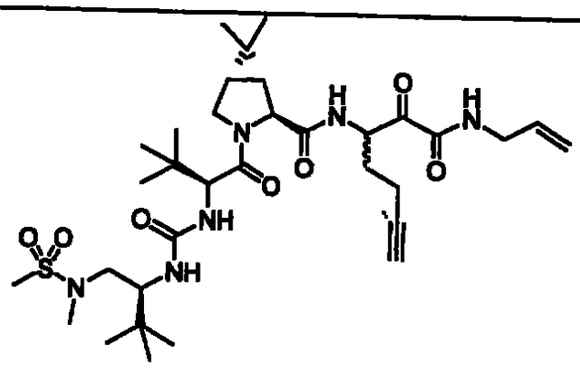
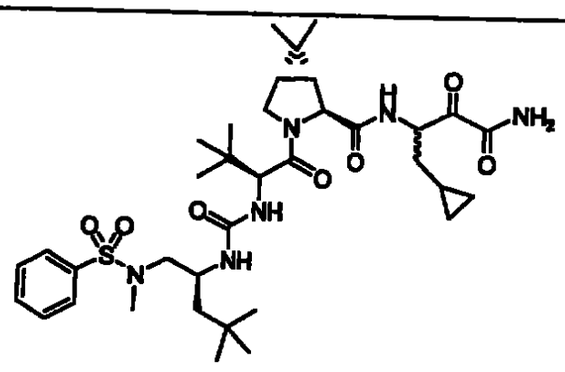
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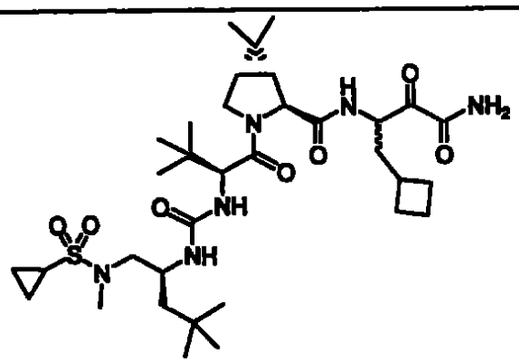
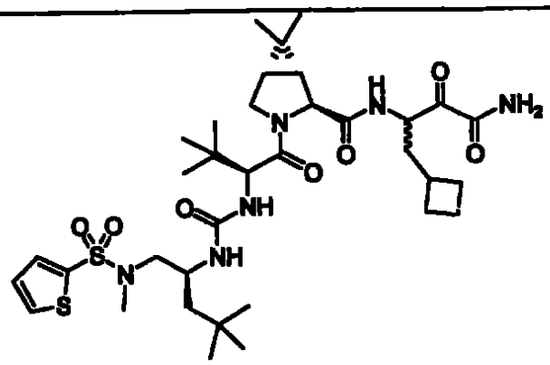
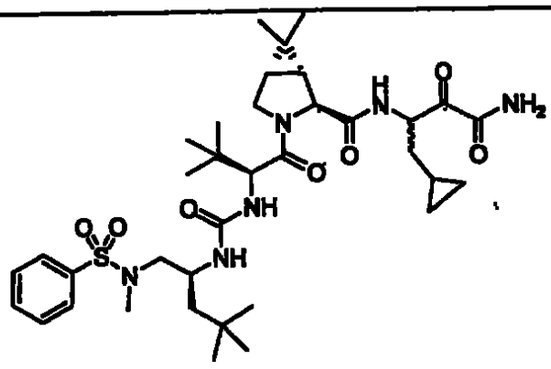
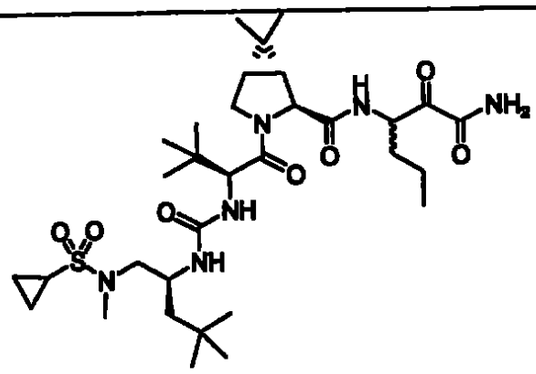
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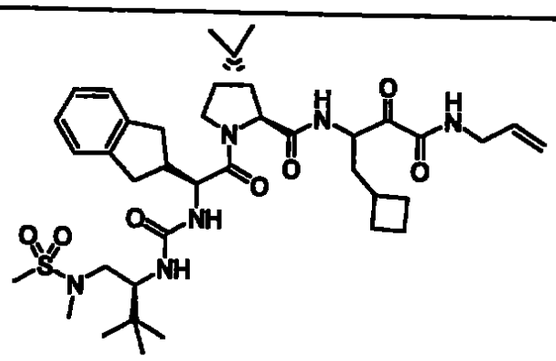
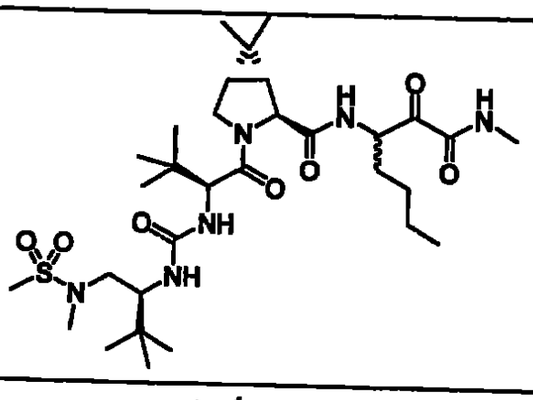
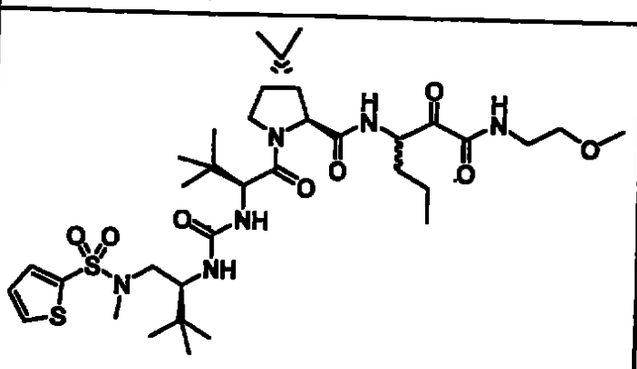
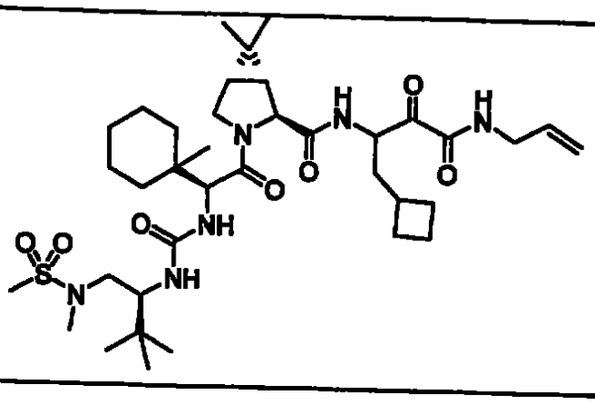
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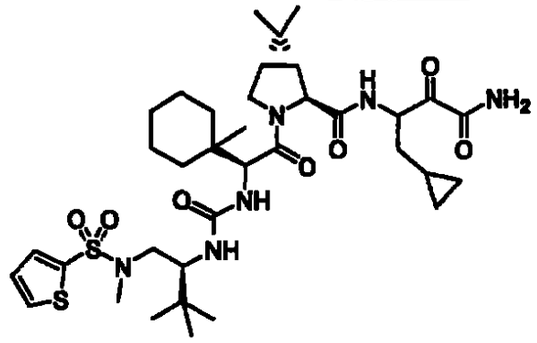
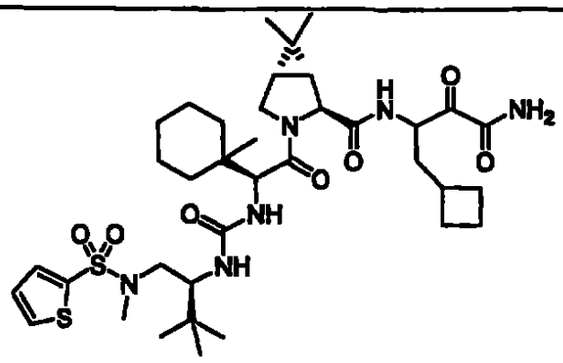
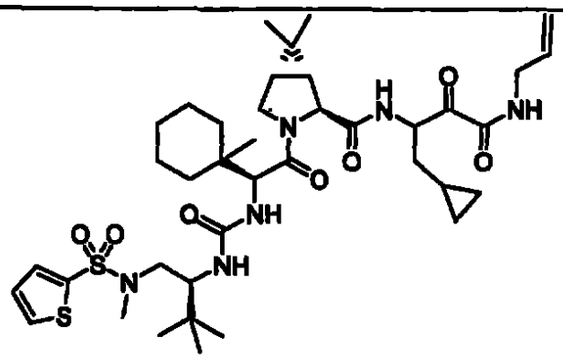
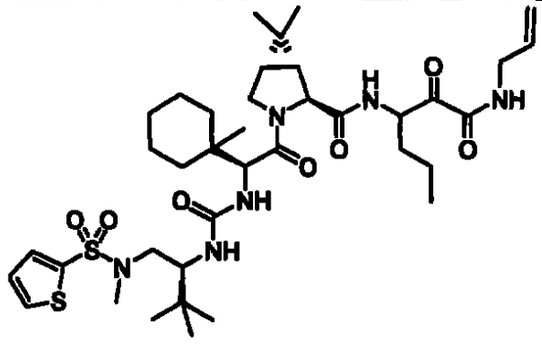
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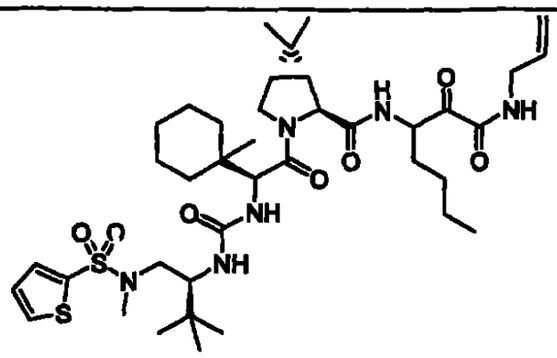
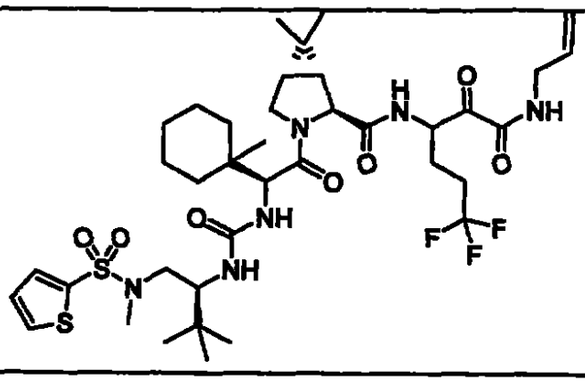
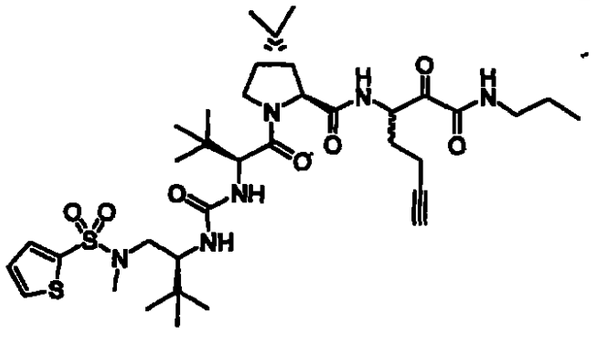
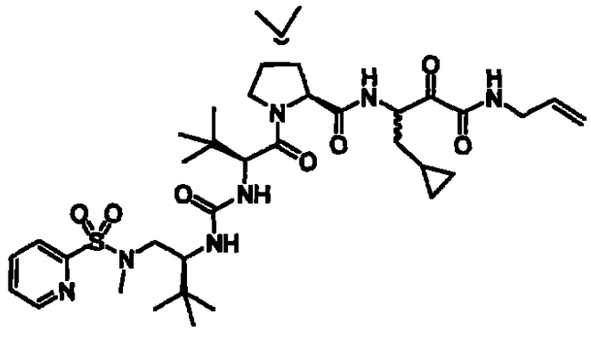
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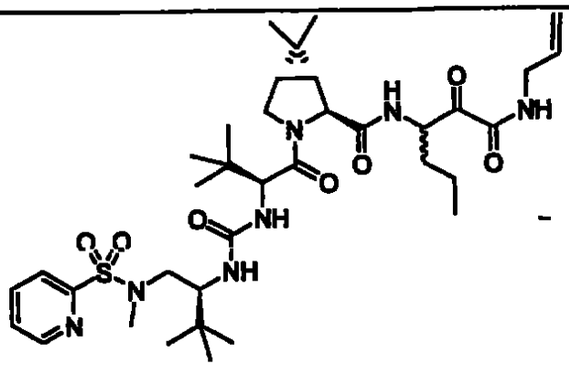
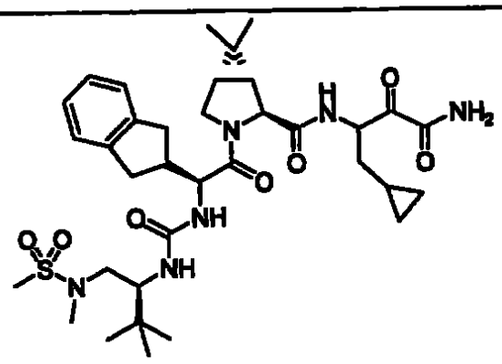
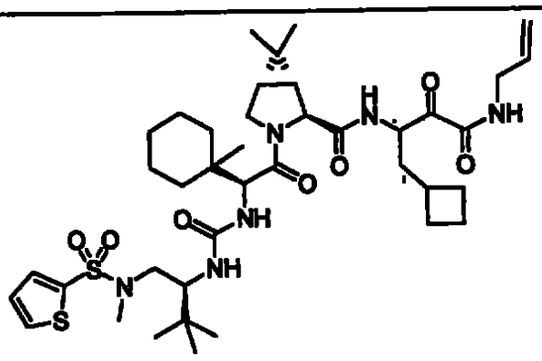
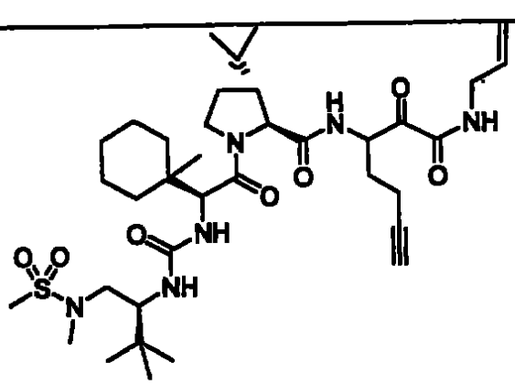
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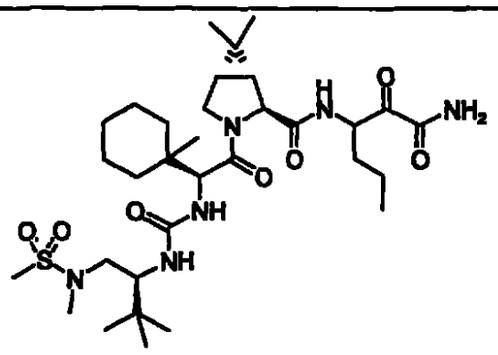
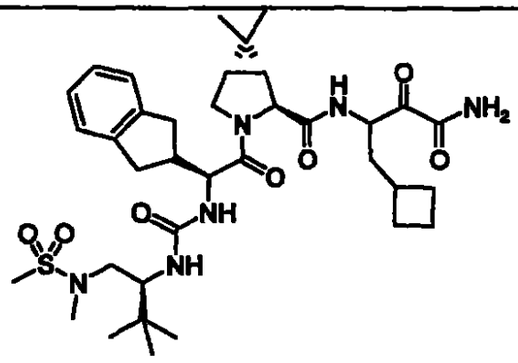
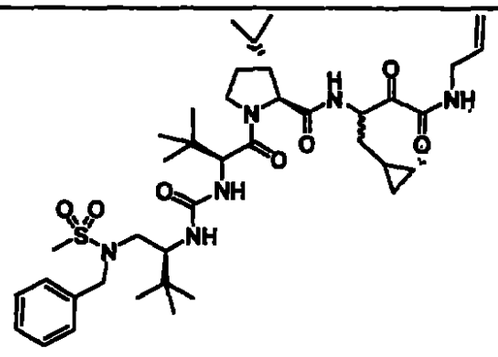
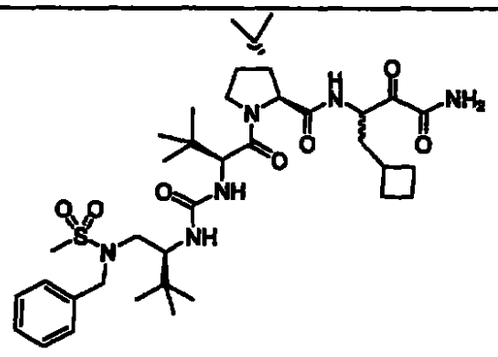
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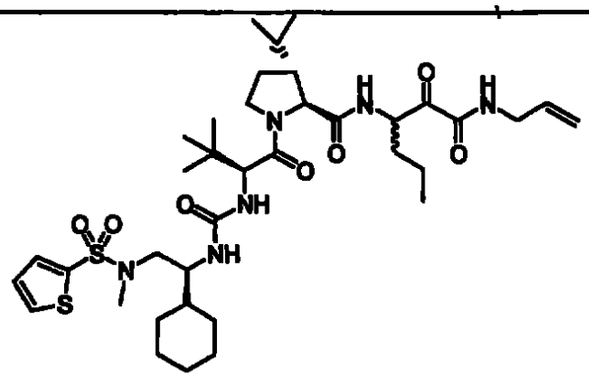
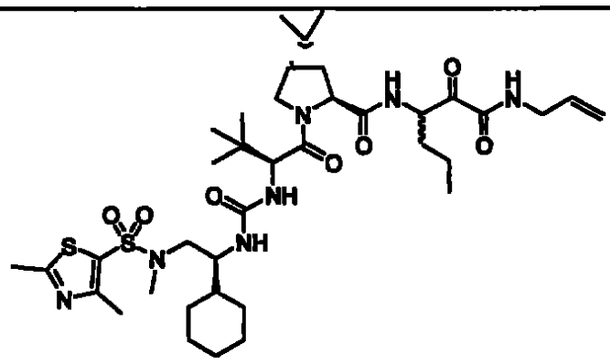
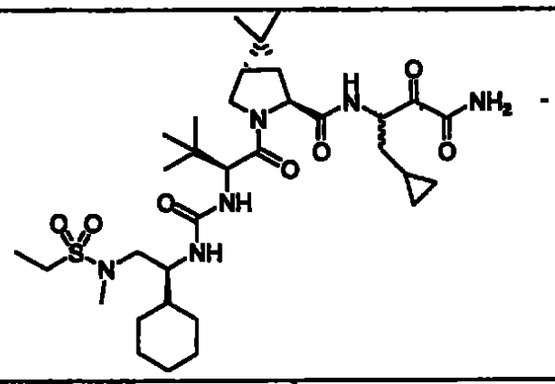
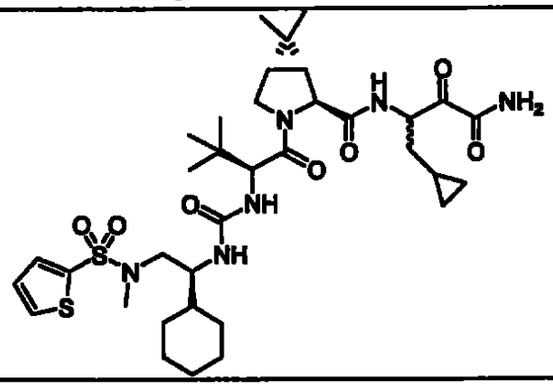
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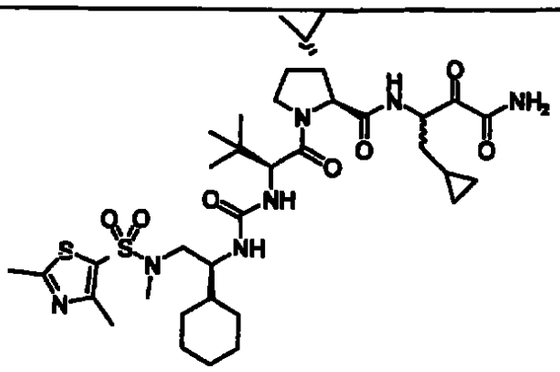
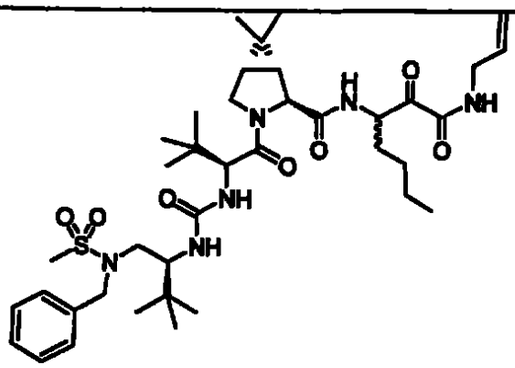
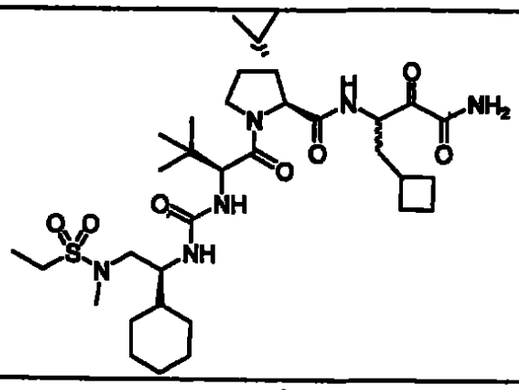
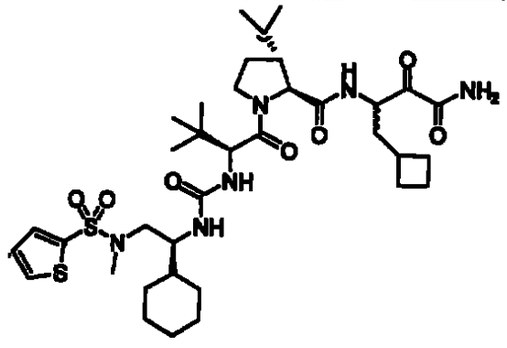
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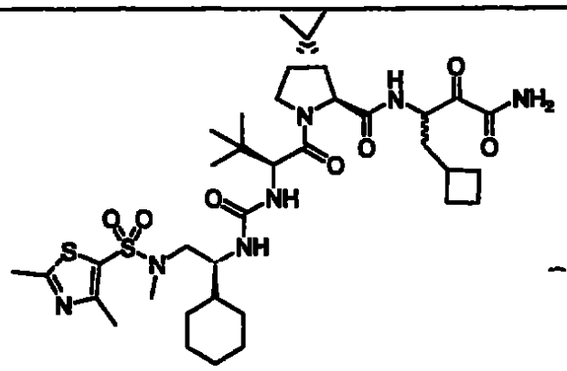
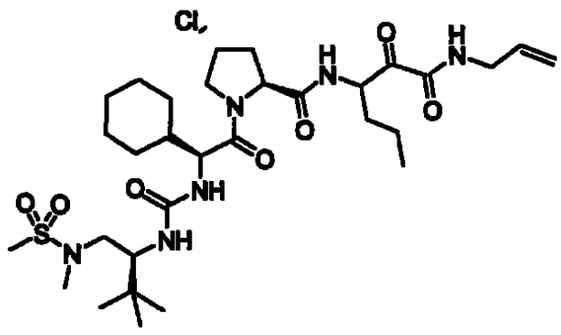
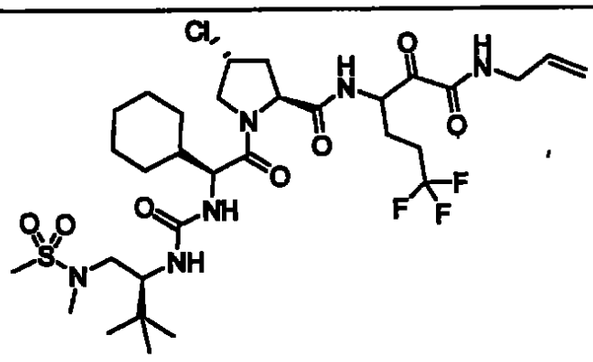
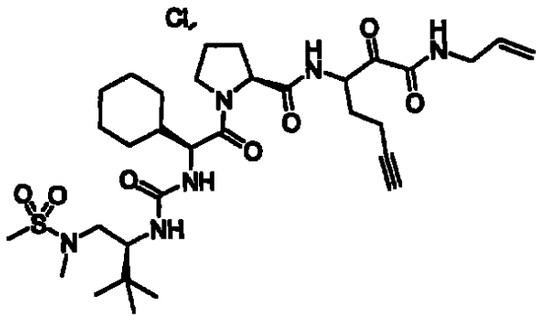
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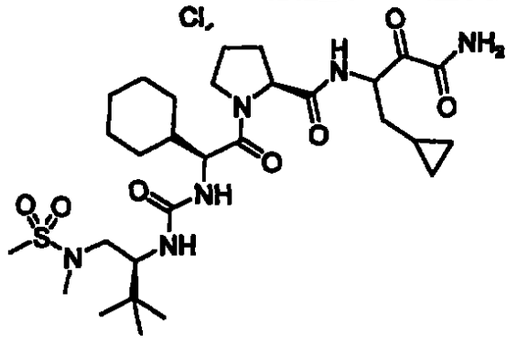
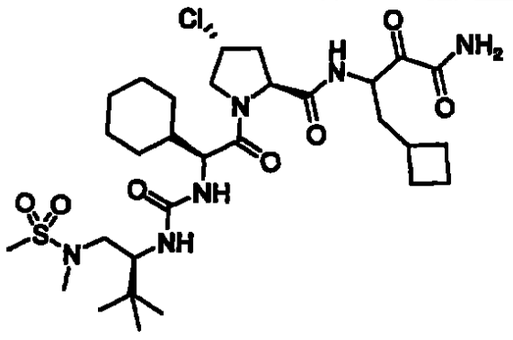
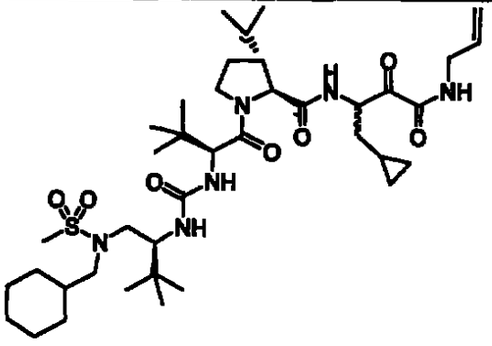
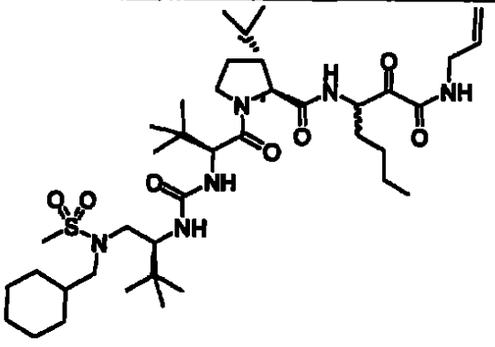
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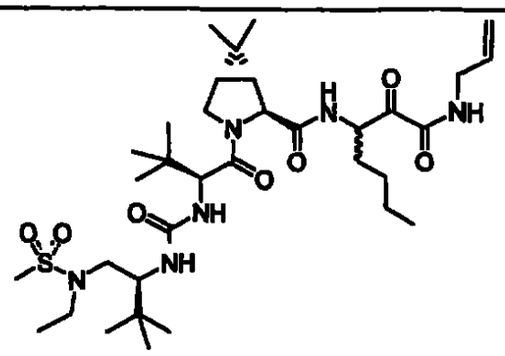
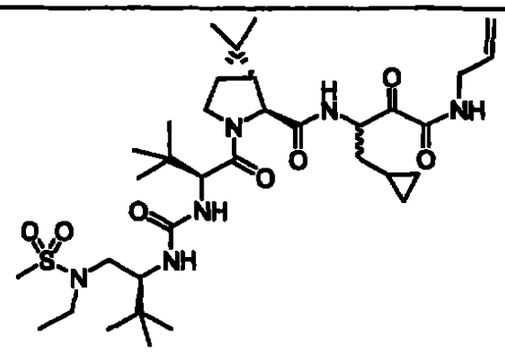
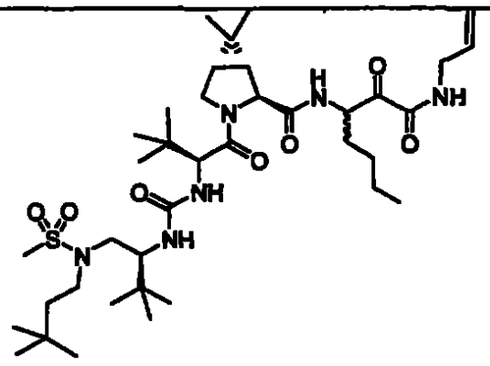
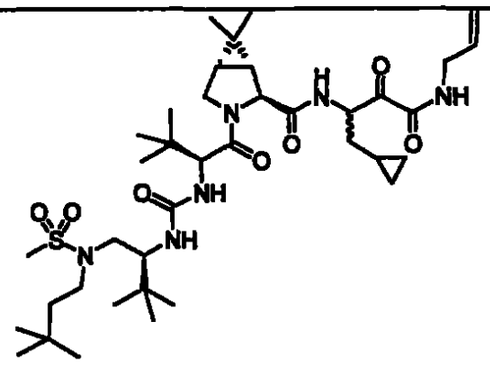
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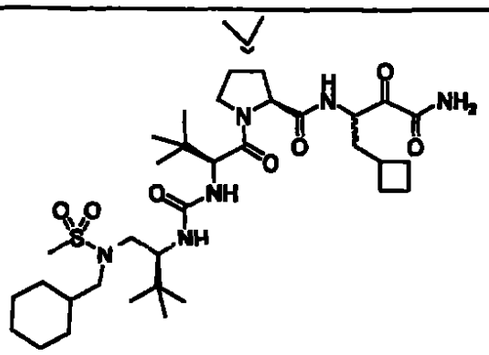
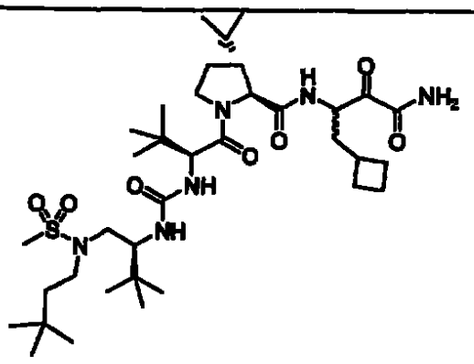
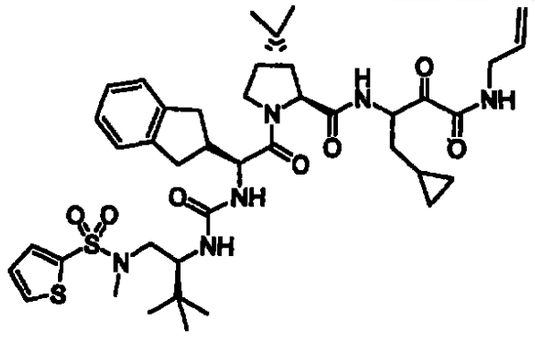
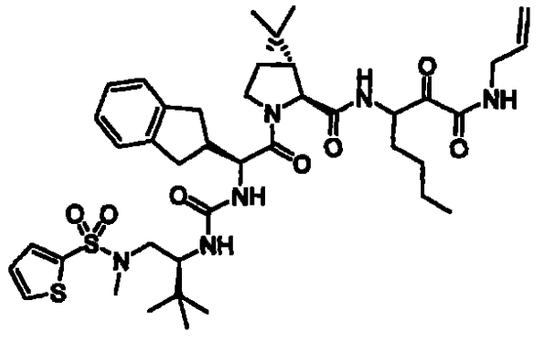
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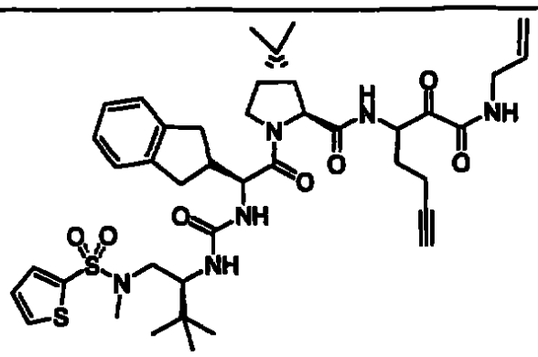
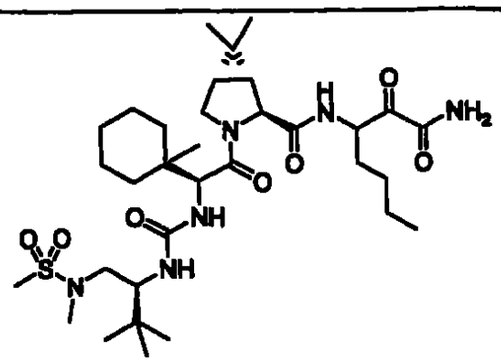
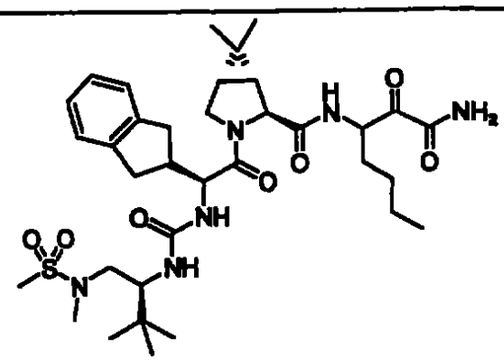
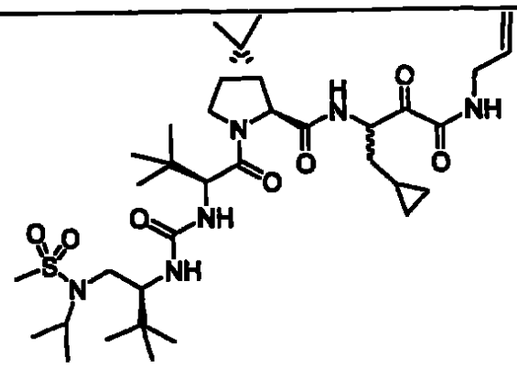
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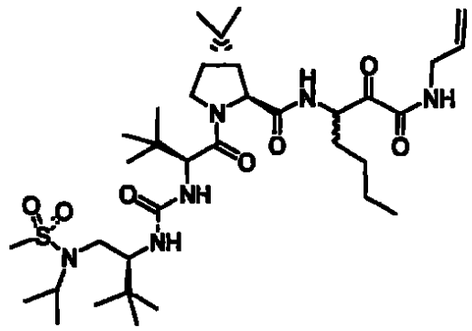
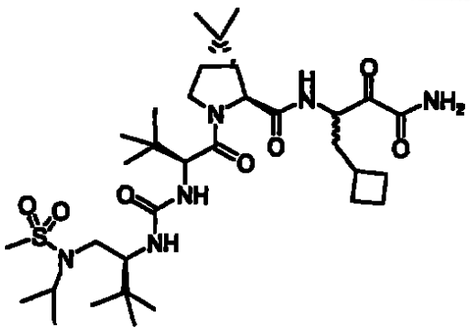
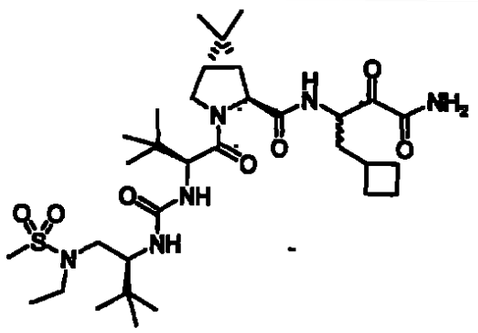
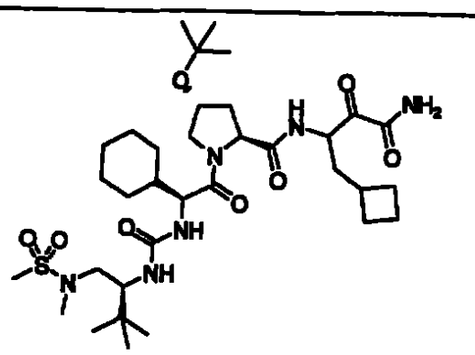
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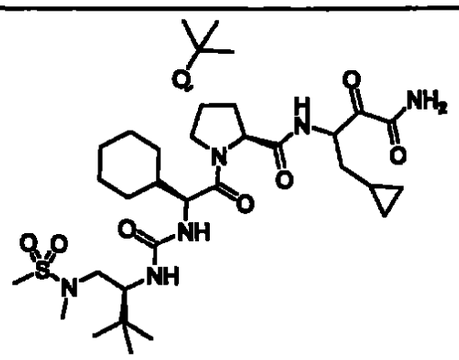
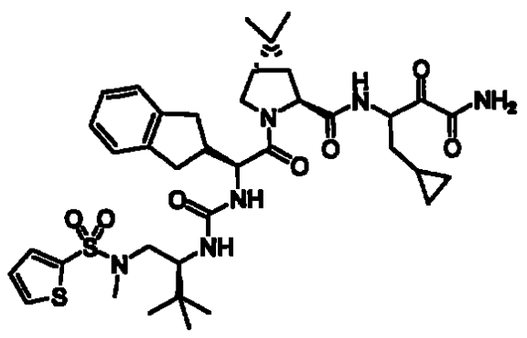
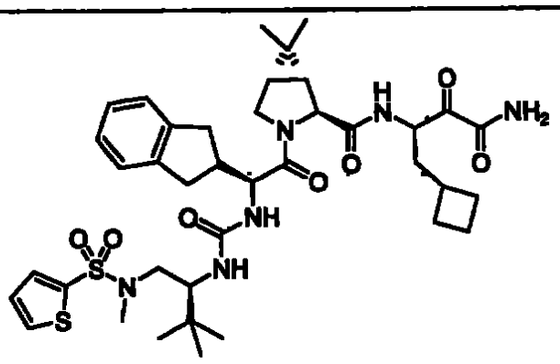
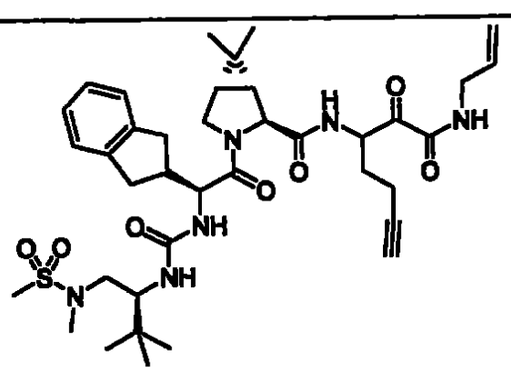
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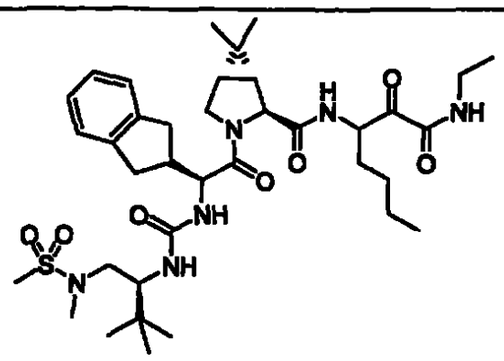
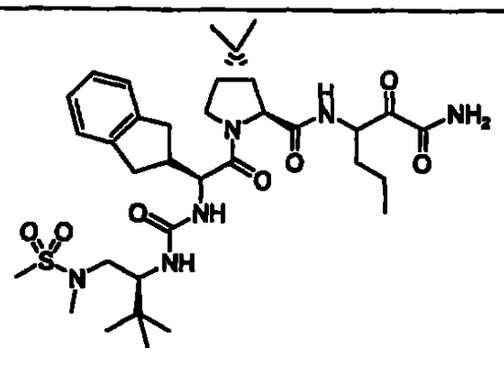
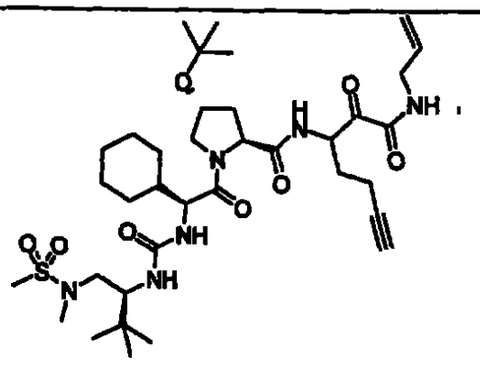
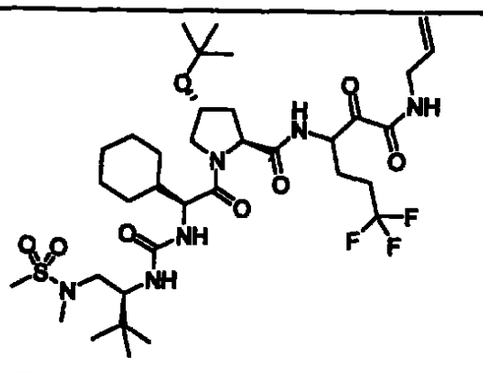
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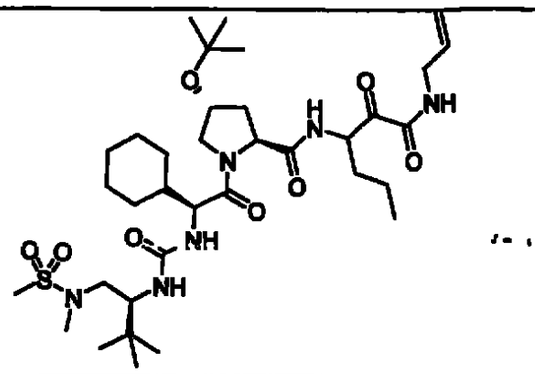
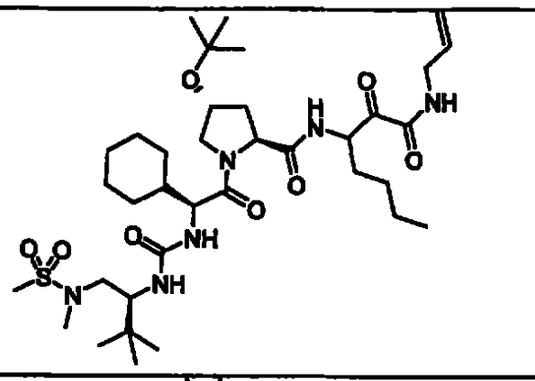
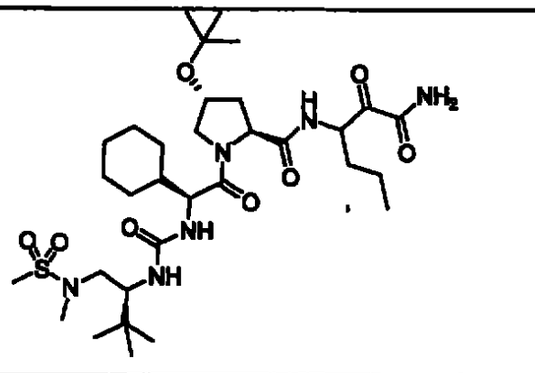
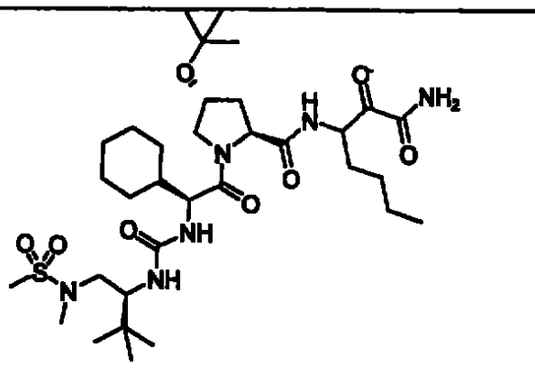
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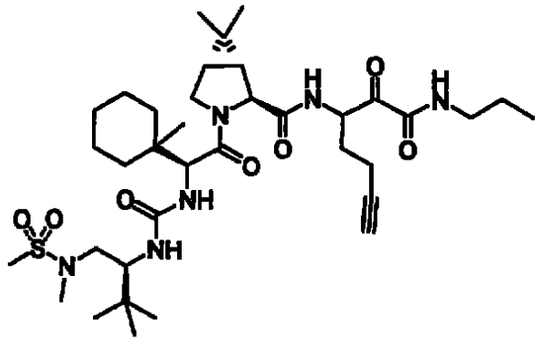
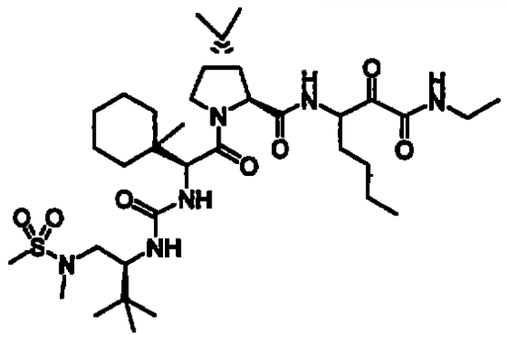
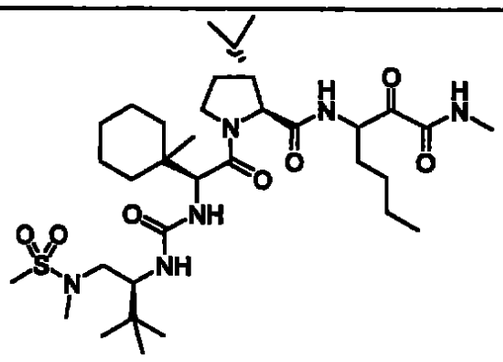
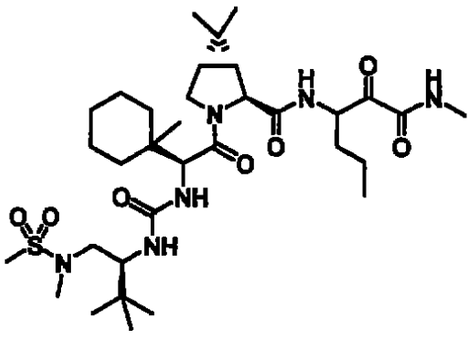
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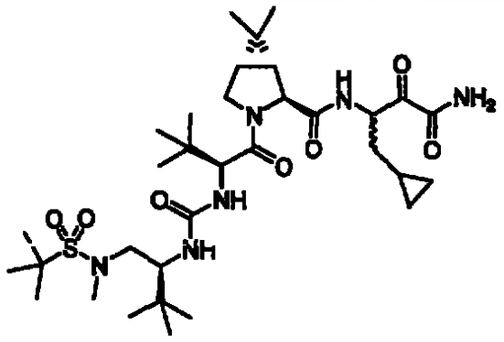
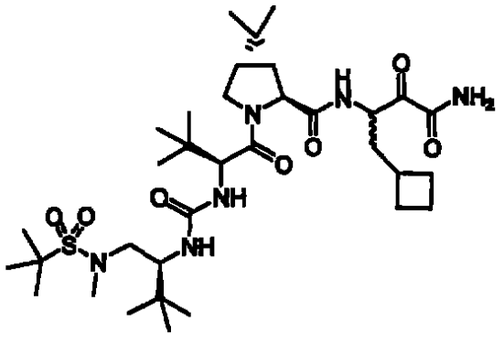
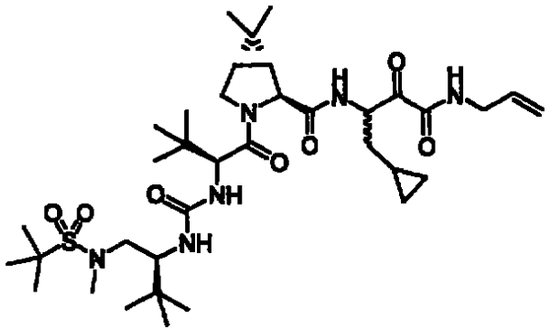
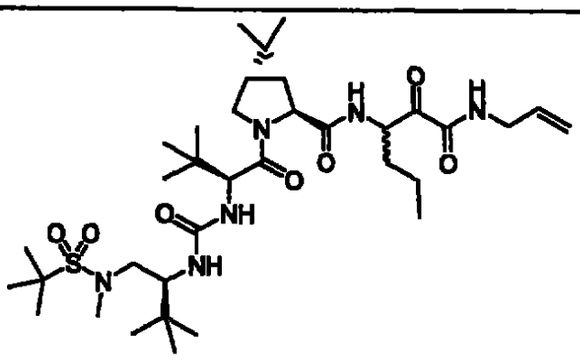
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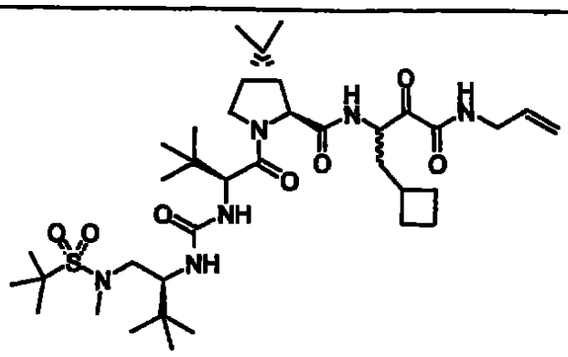
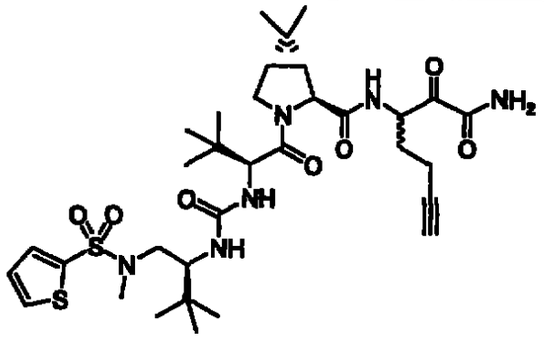
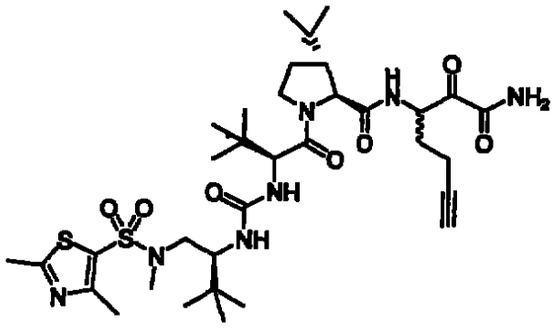
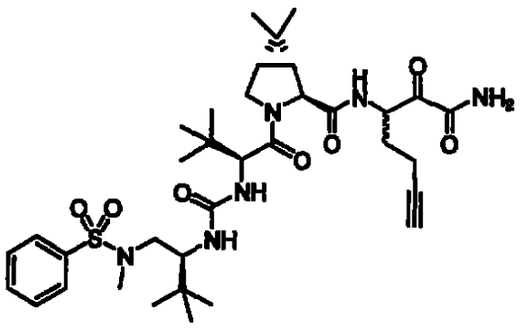
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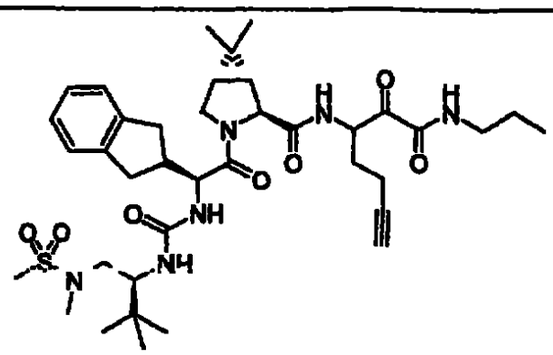
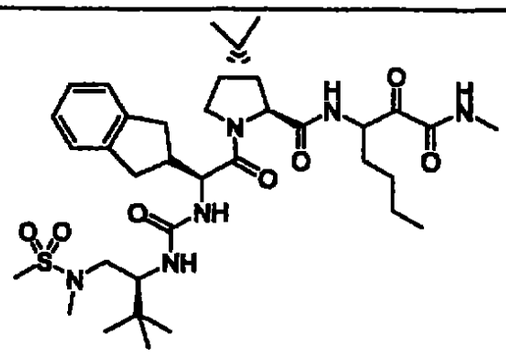
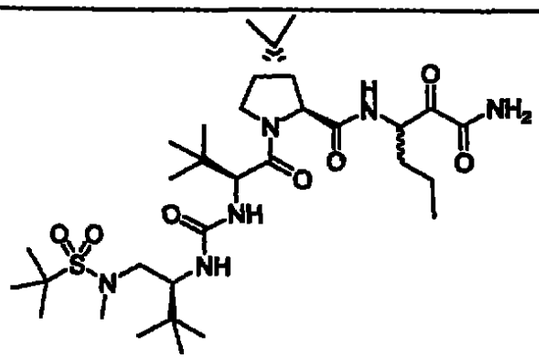
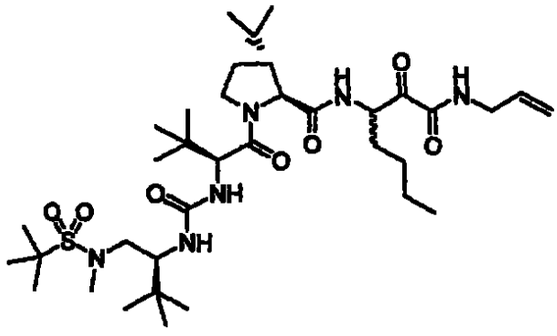
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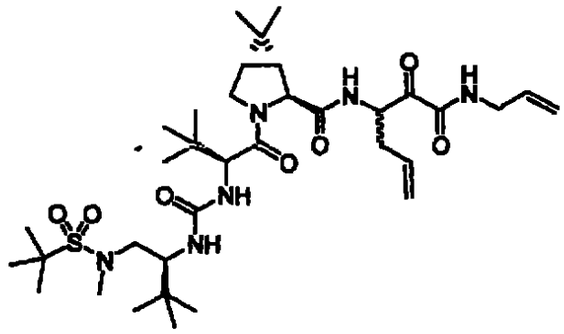
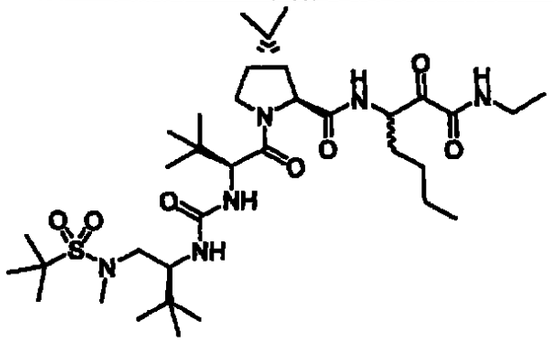
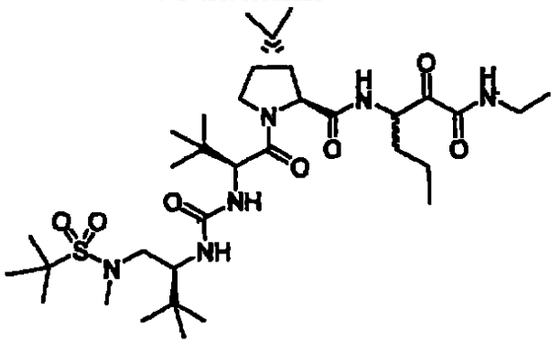
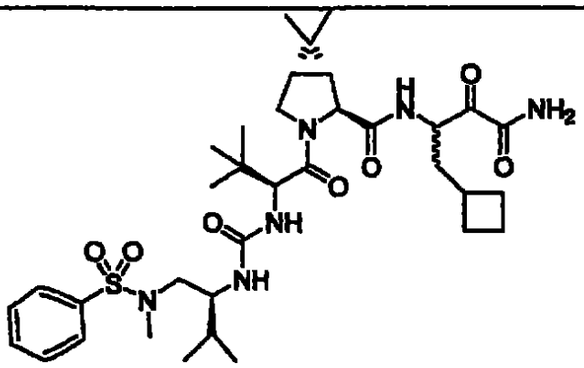
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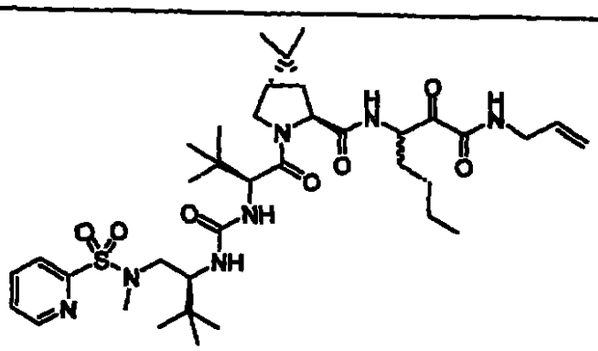
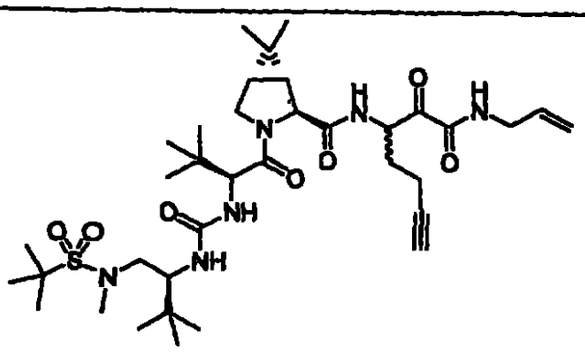
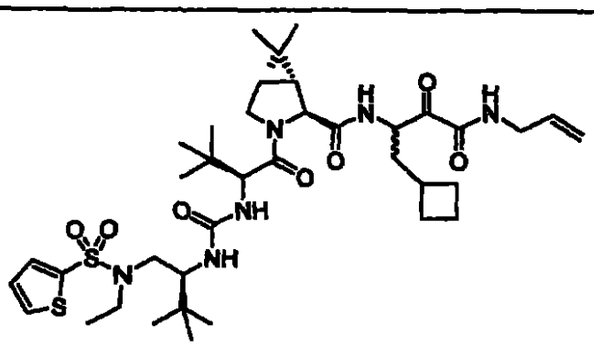
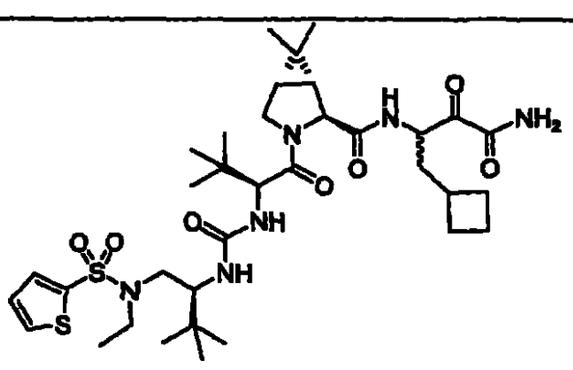
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11205		A

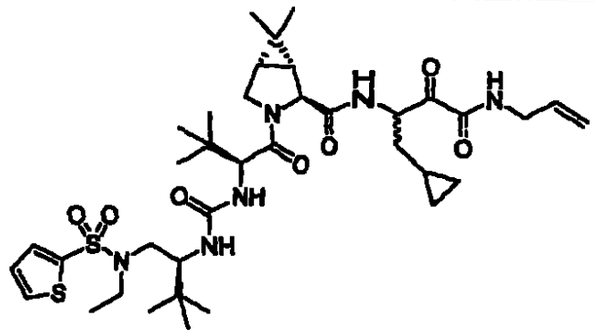
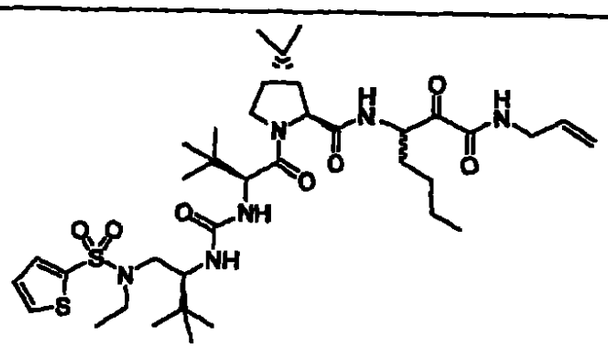
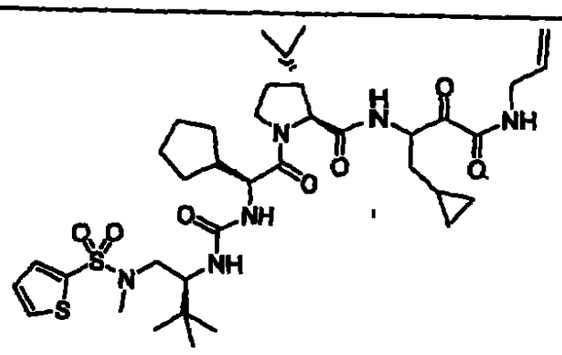
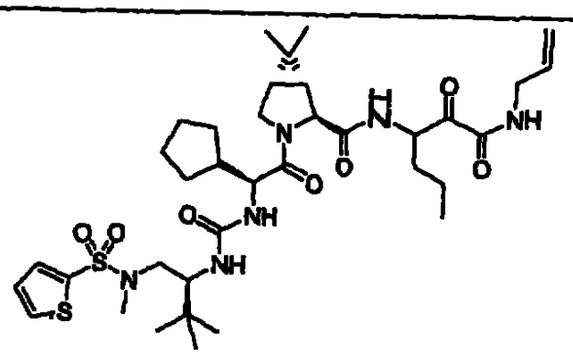
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11209		A

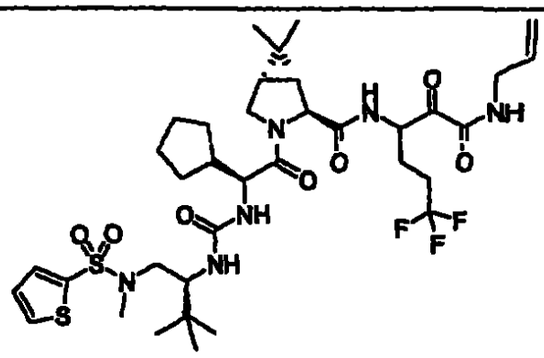
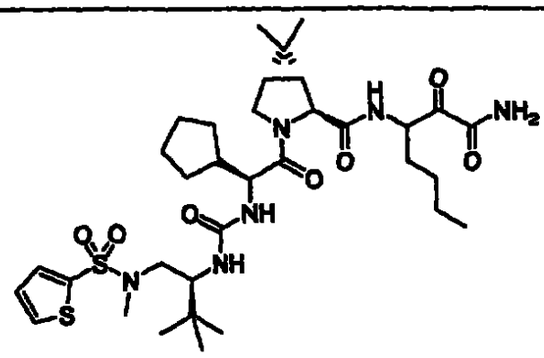
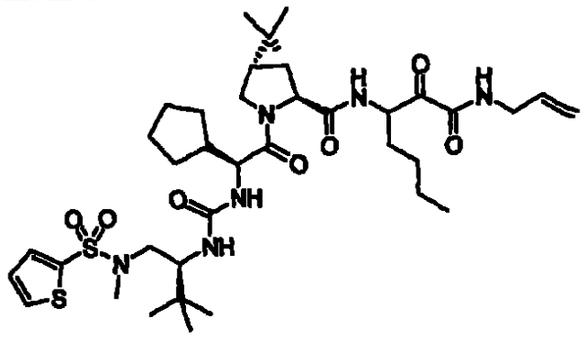
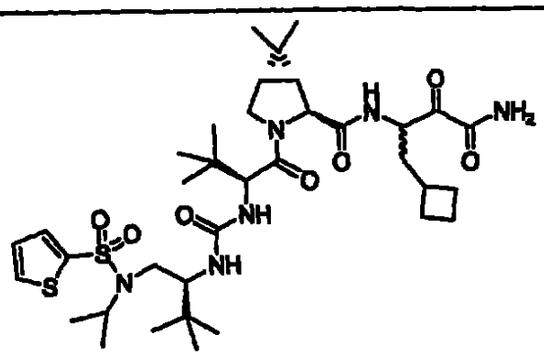
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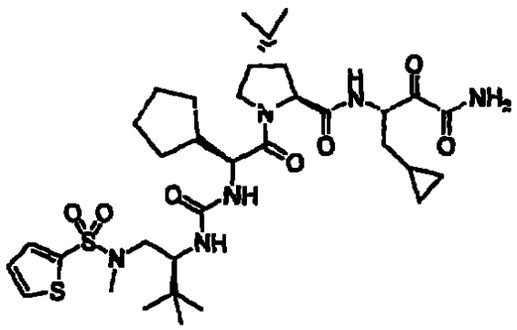
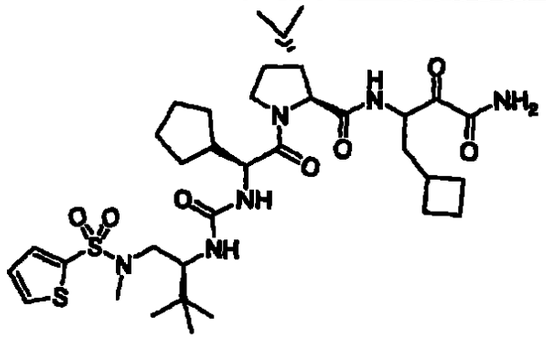
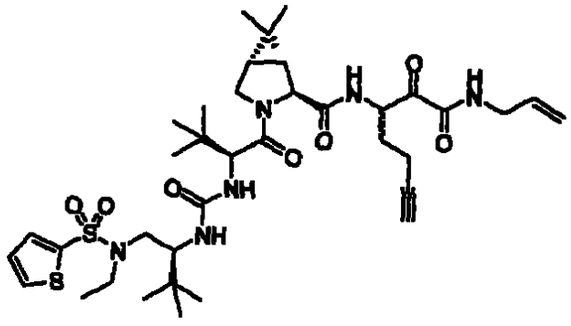
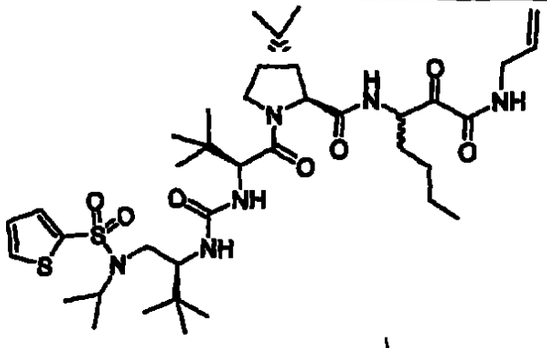
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11213		B

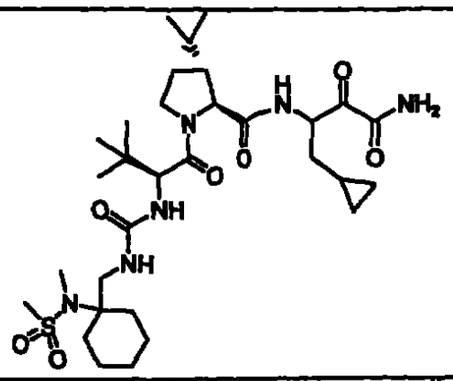
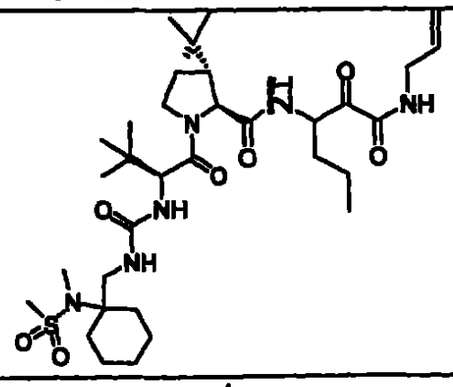
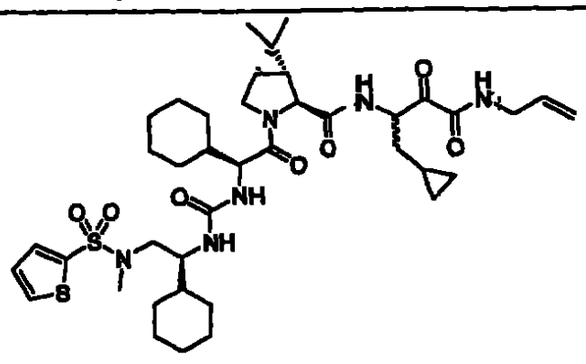
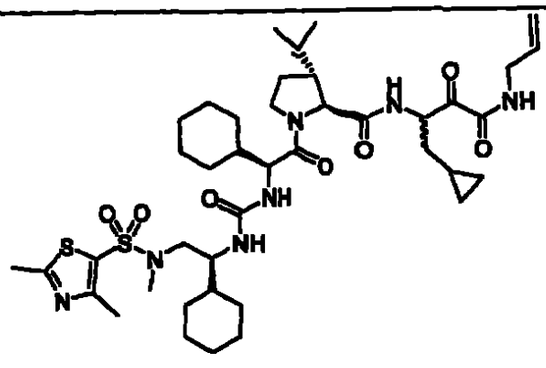
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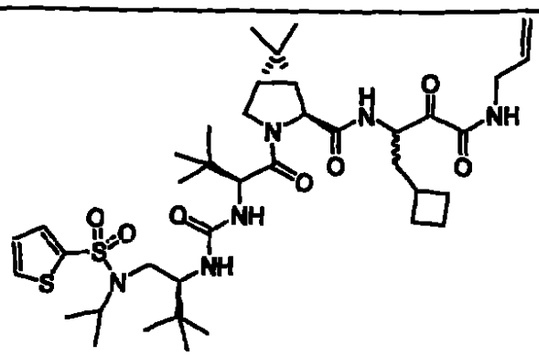
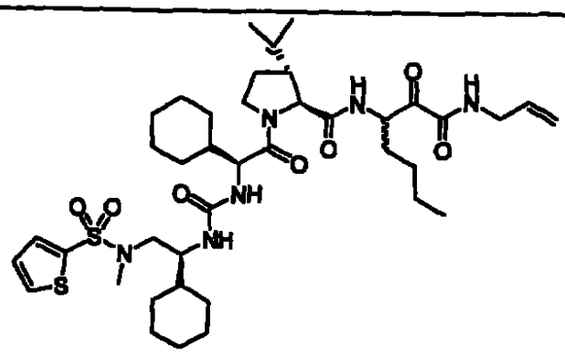
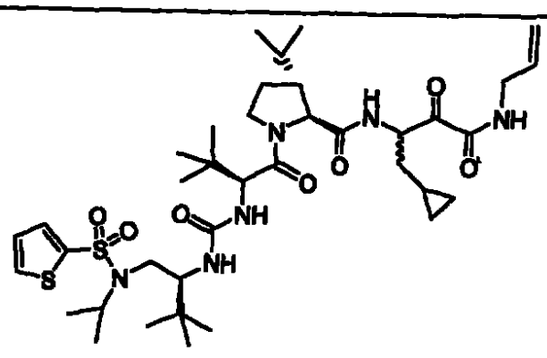
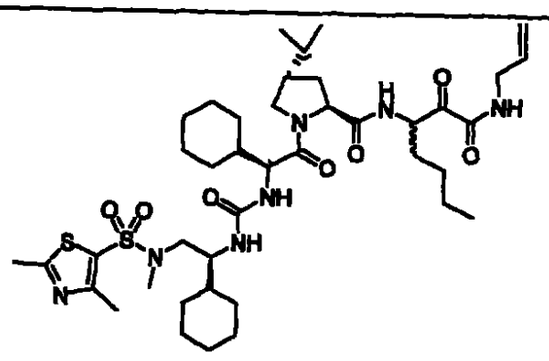
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11225		A

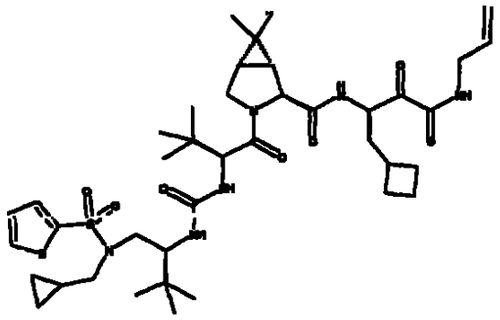
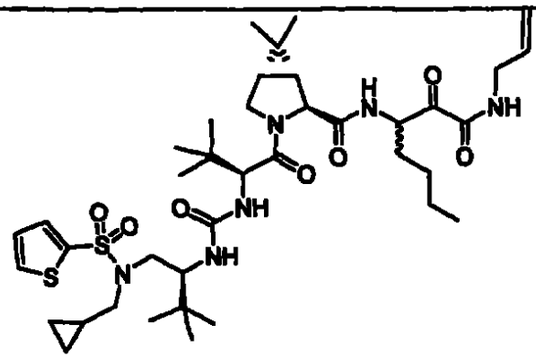
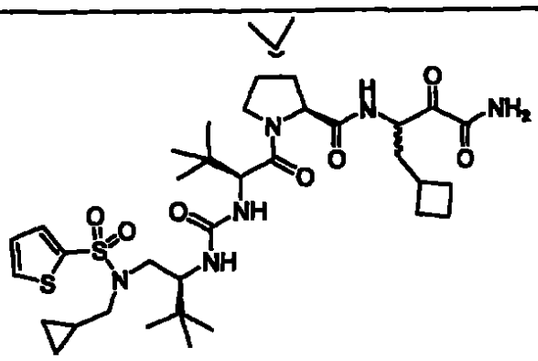
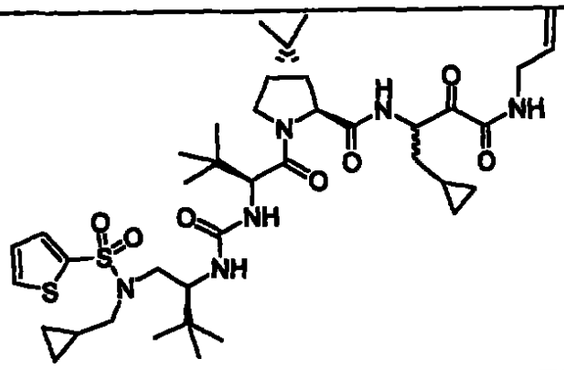
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11229		A

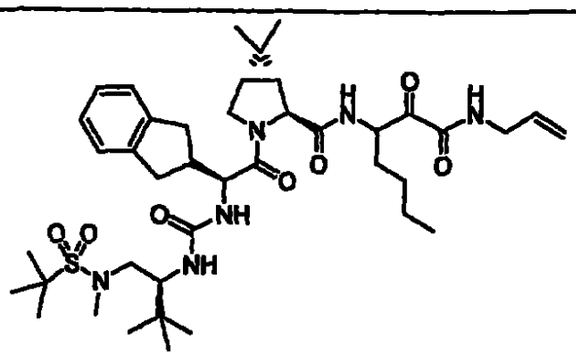
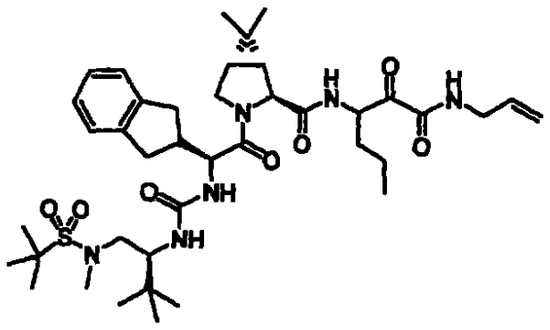
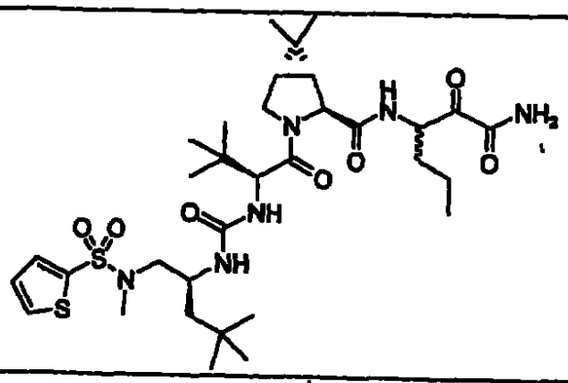
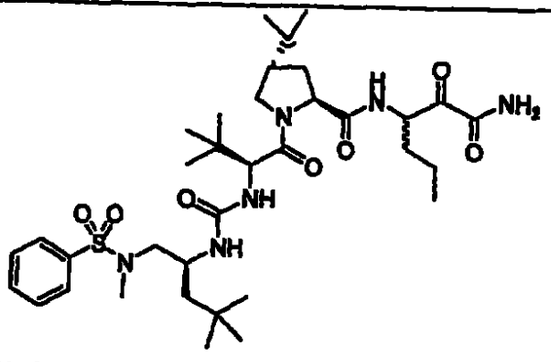
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11233		A

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11237		A

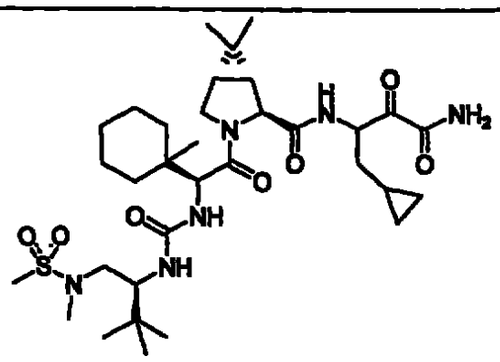
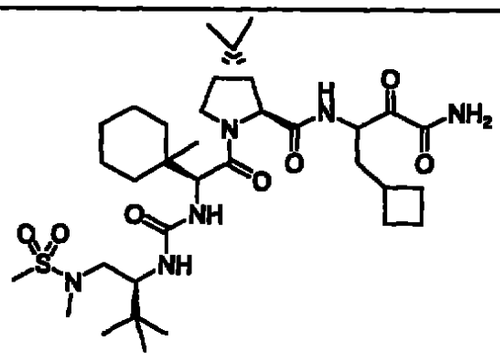
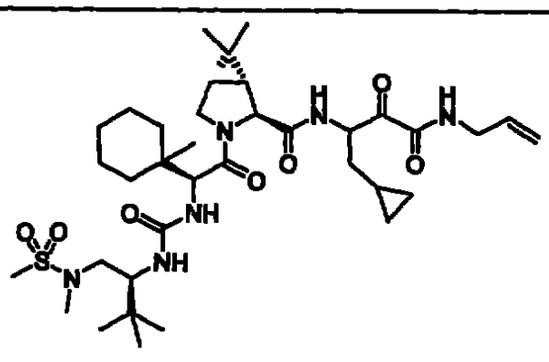
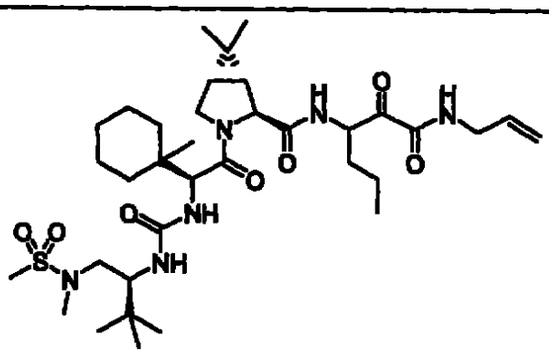
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11242		A

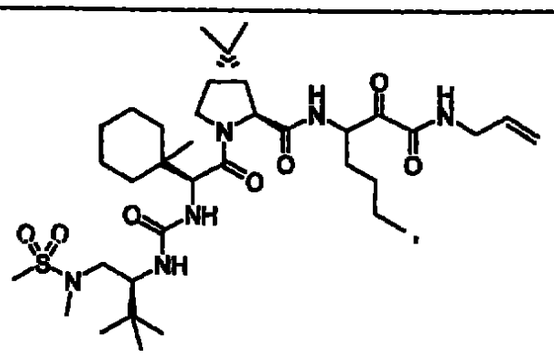
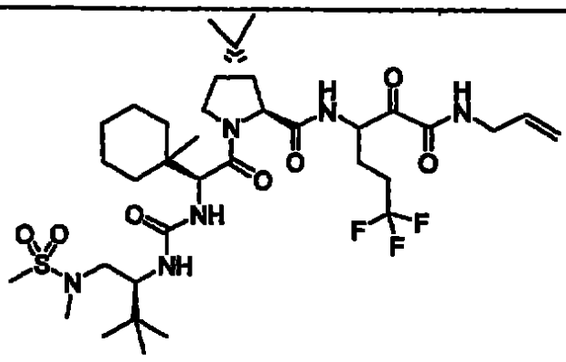
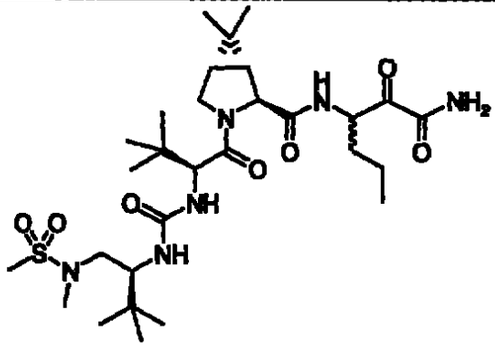
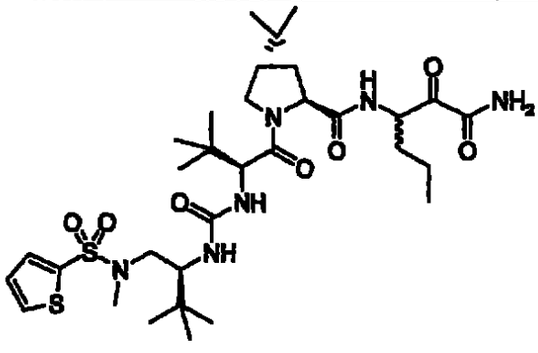
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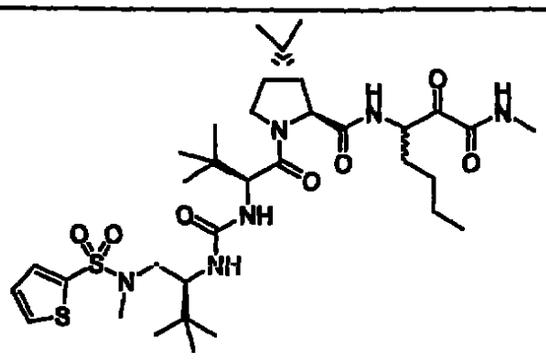
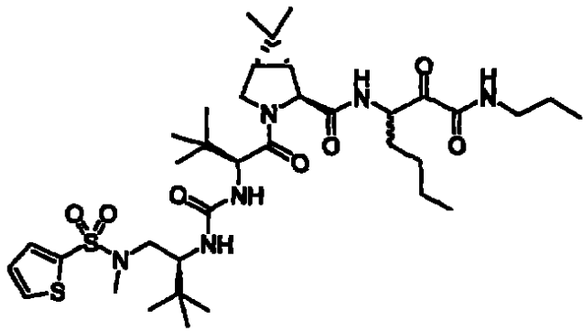
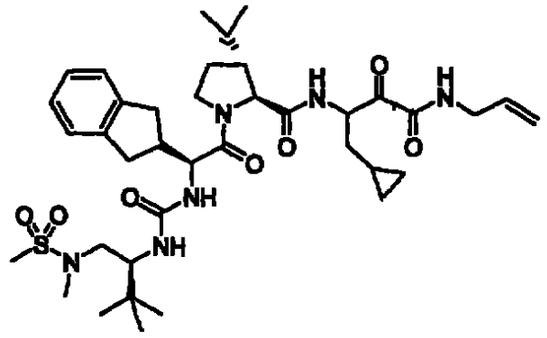
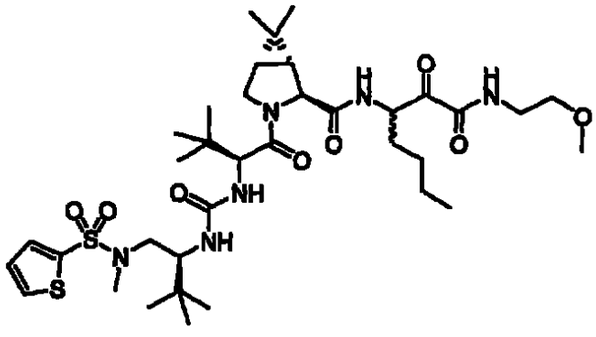
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11246		A

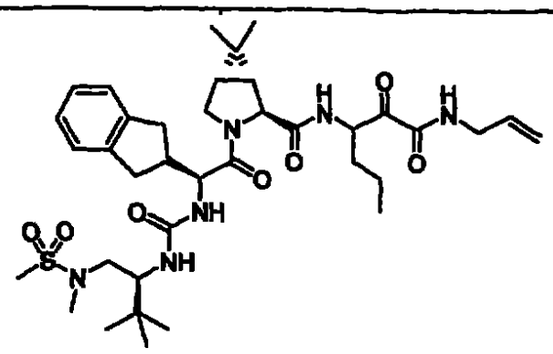
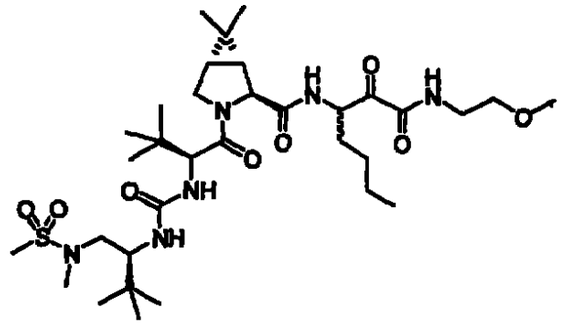
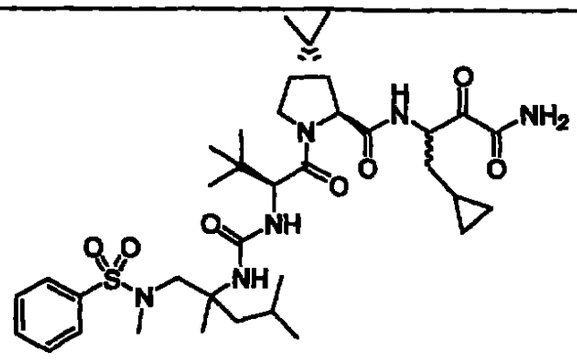
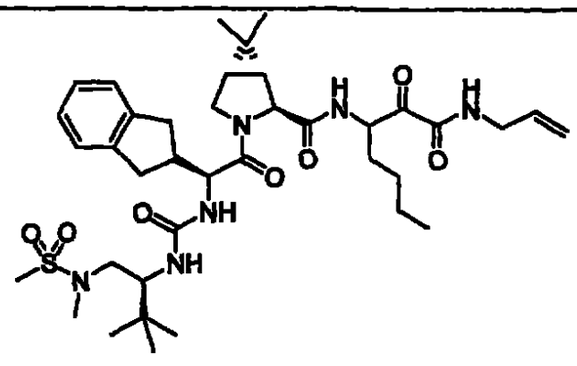
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11250		A

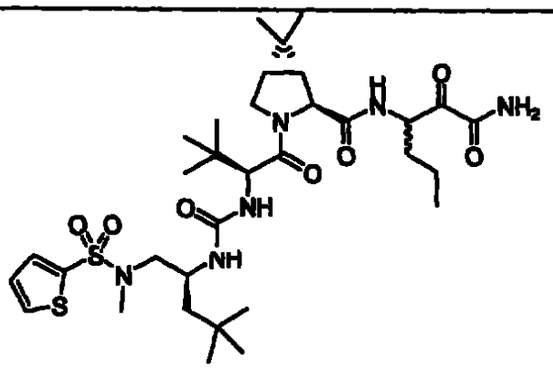
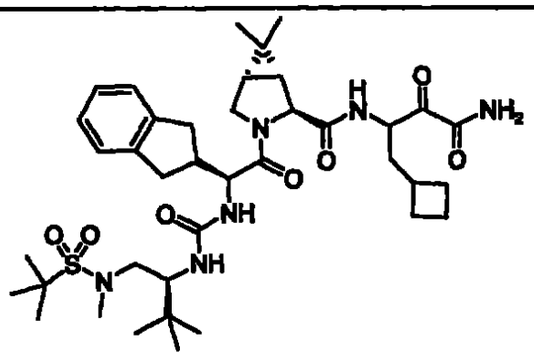
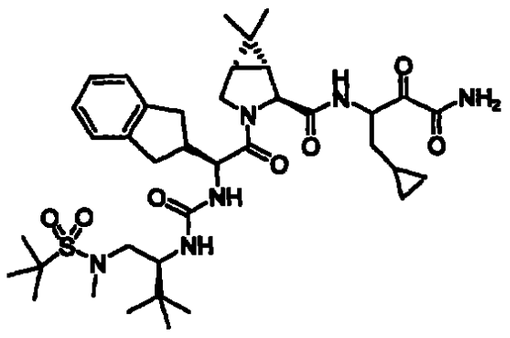
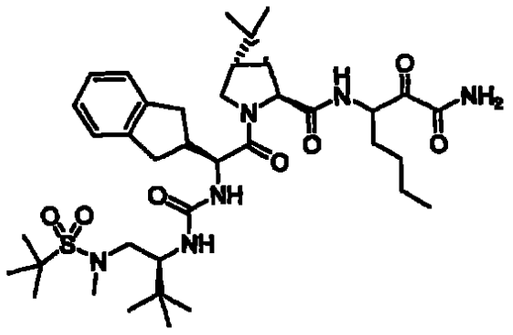
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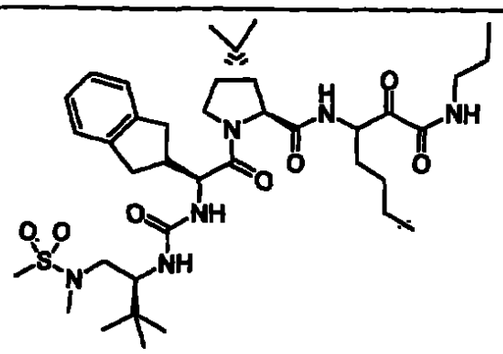
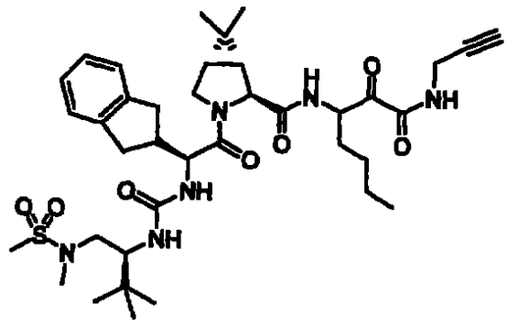
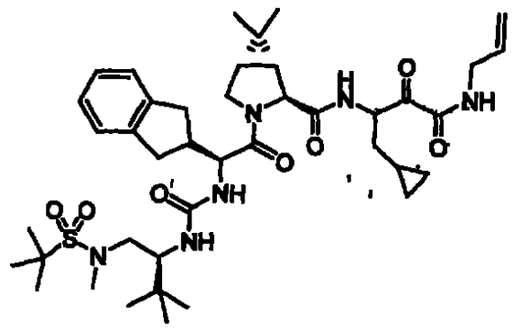
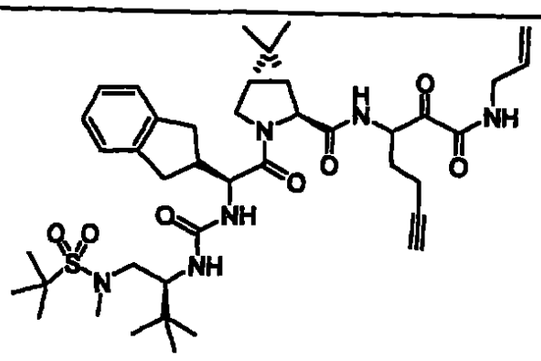
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11254		A

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11256		A
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11258		A

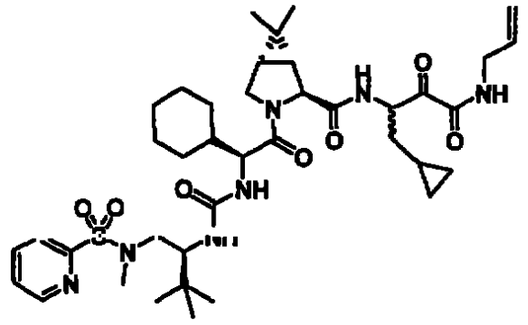
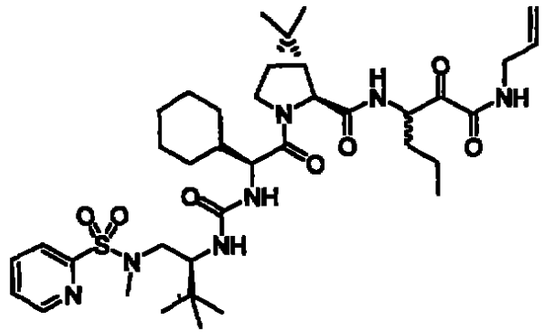
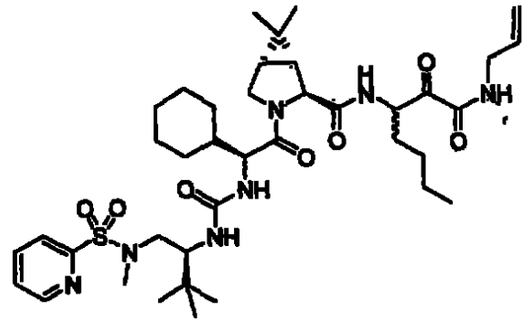
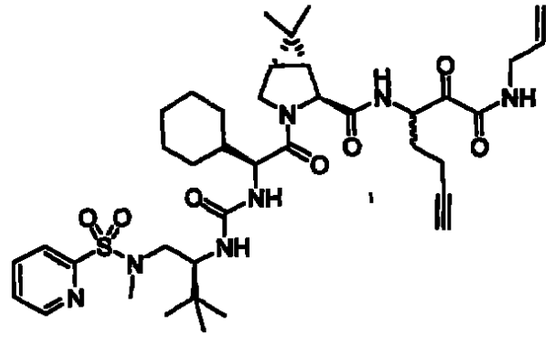
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11262		B

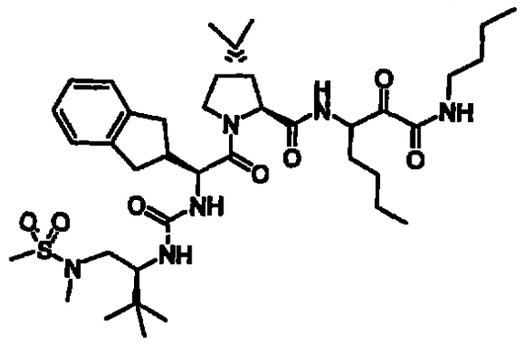
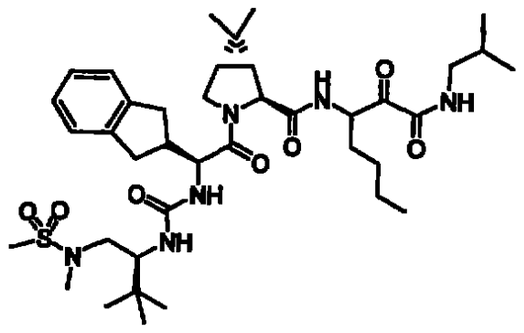
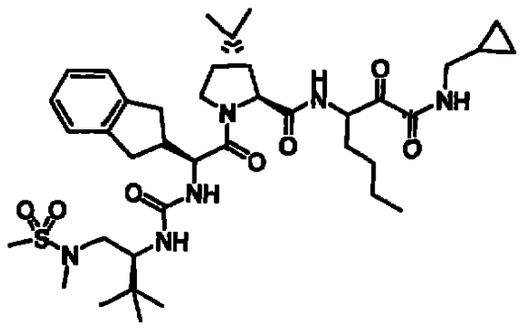
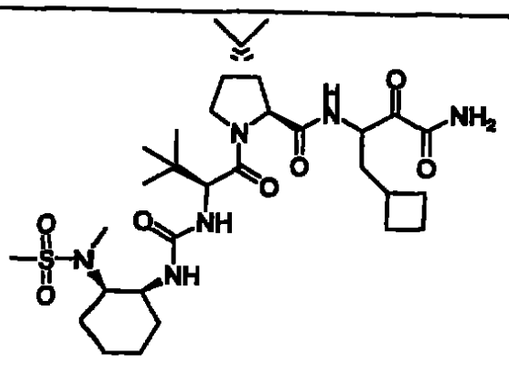
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11266		A

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11270		A

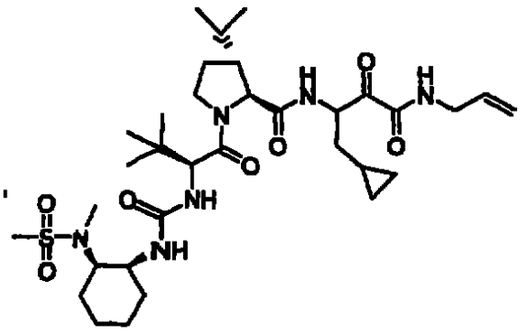
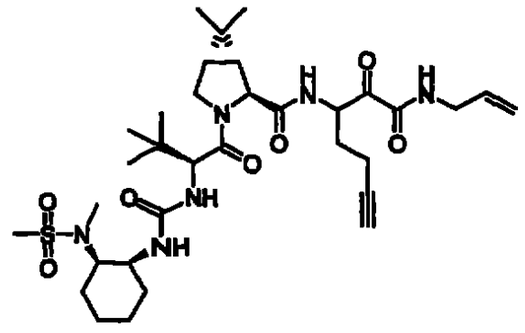
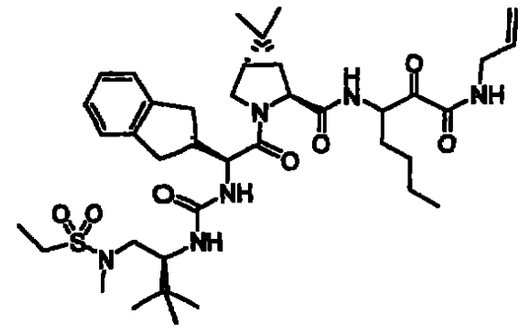
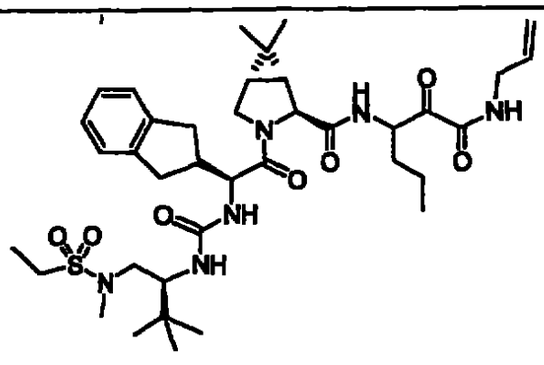
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11273		B
11274		A

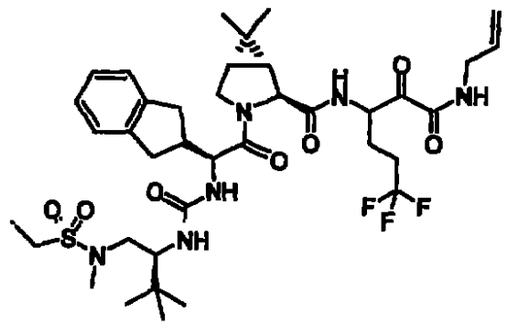
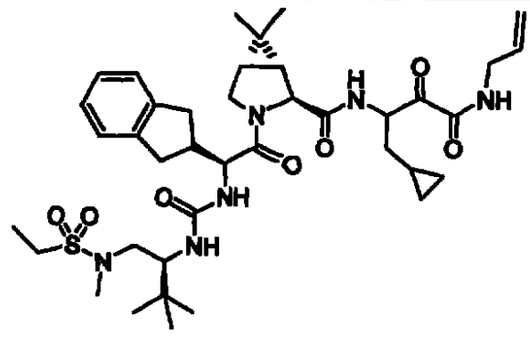
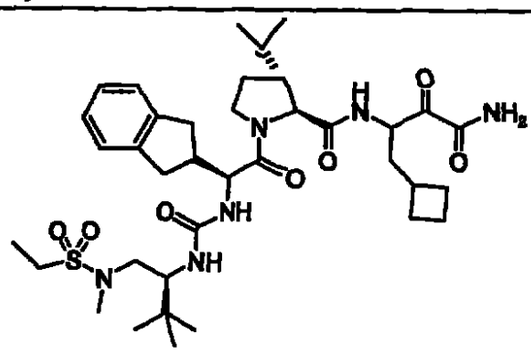
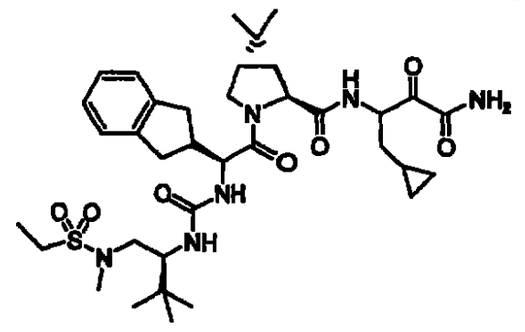
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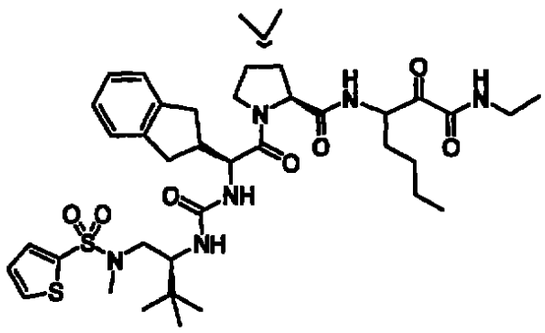
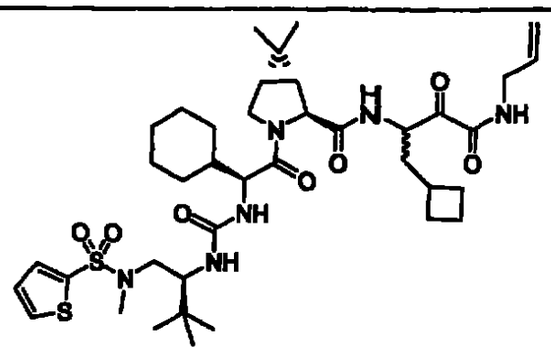
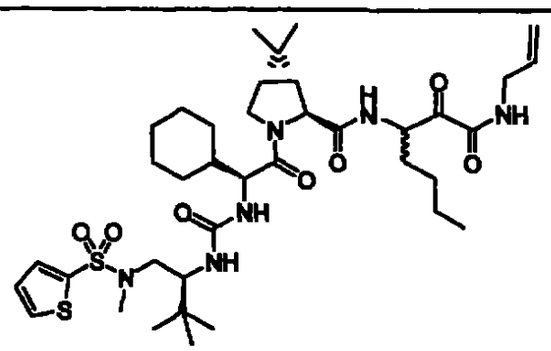
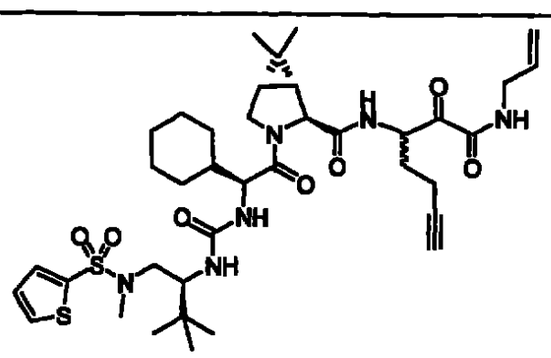
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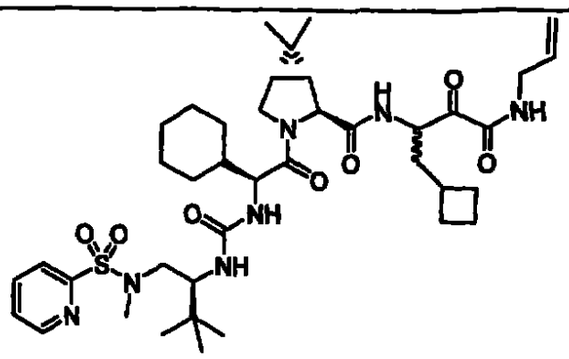
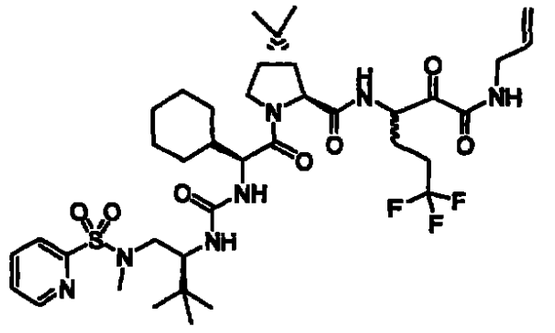
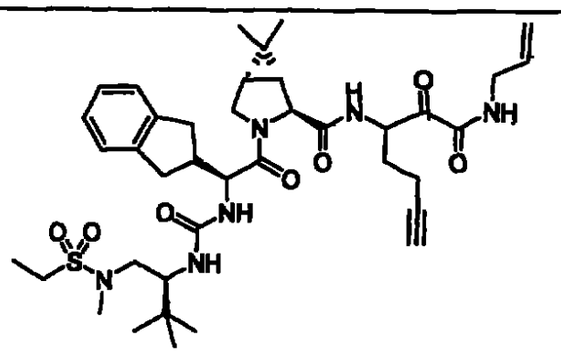
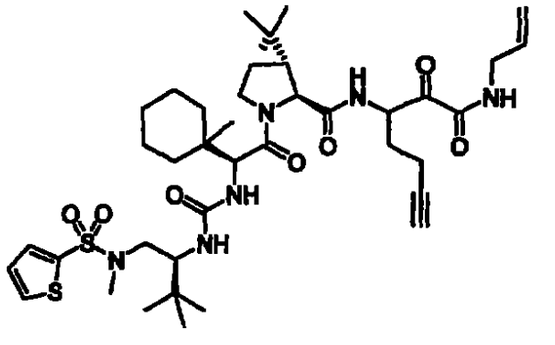
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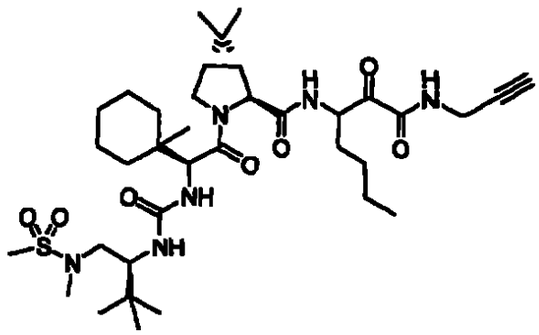
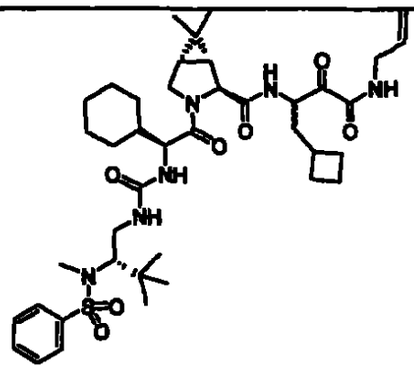
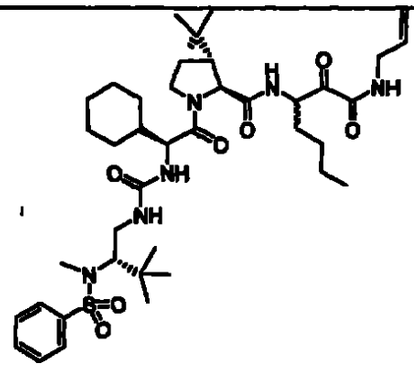
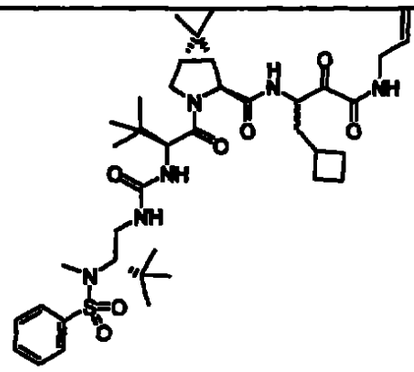
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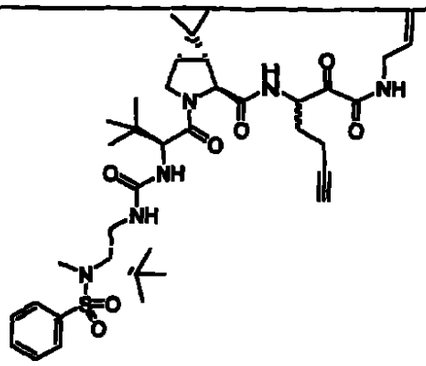
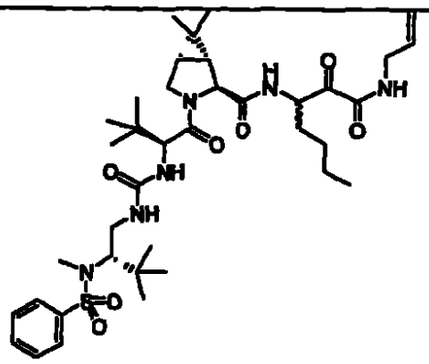
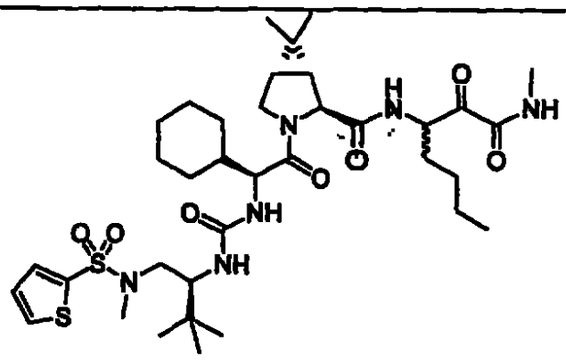
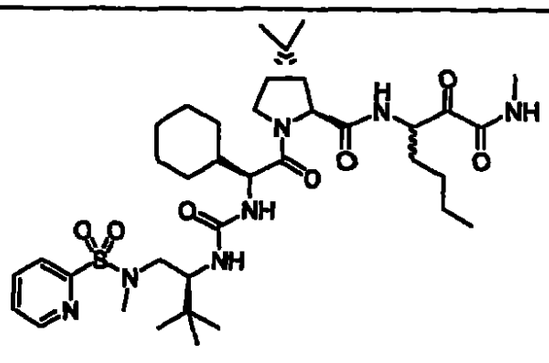
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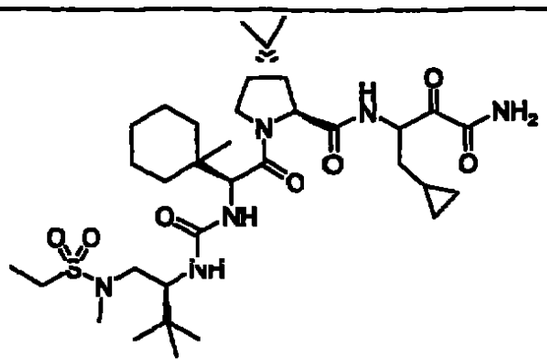
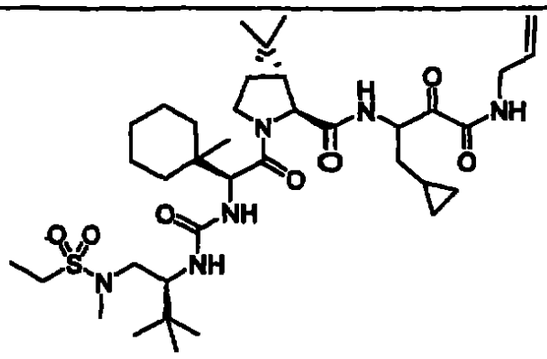
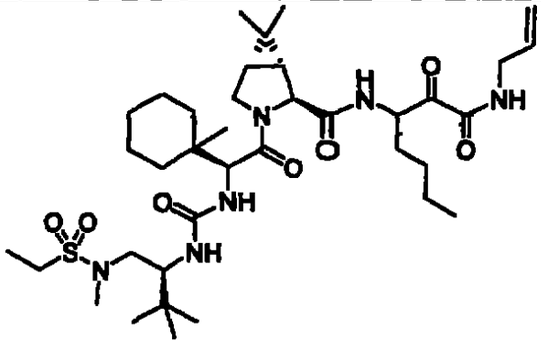
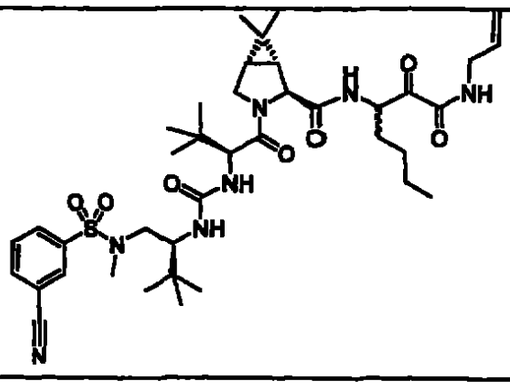
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11290		A

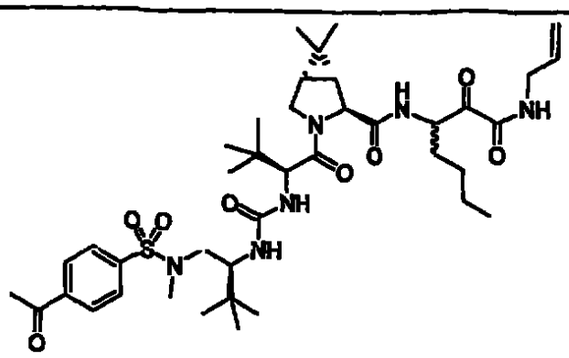
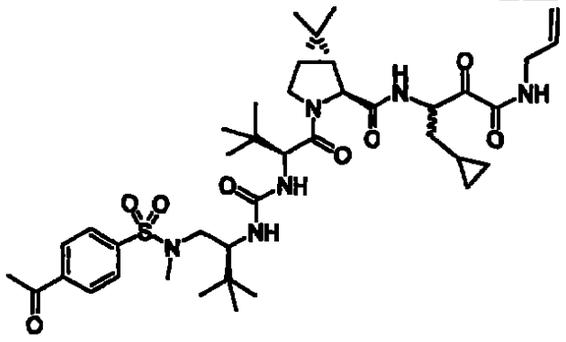
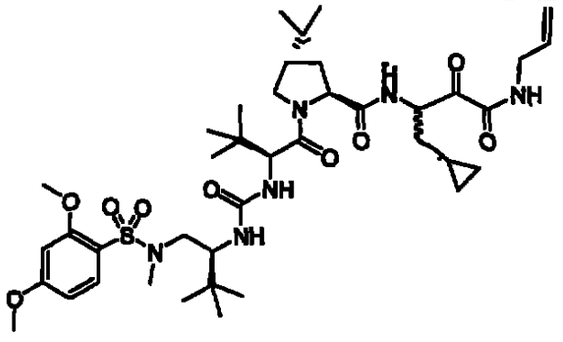
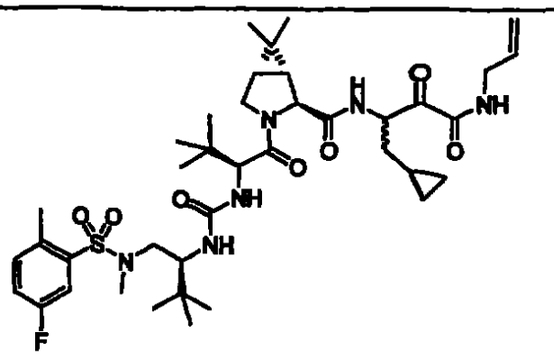
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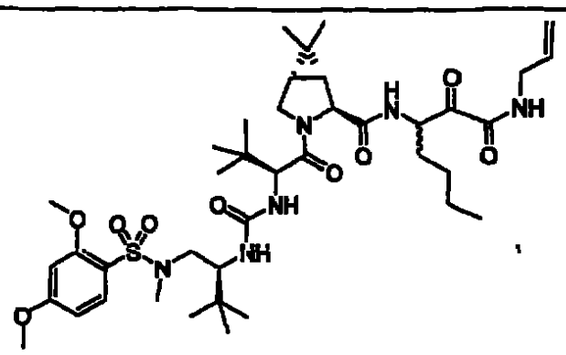
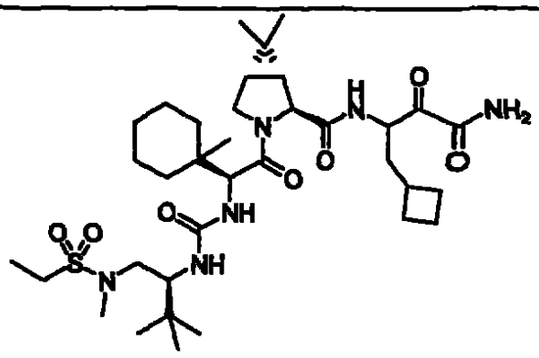
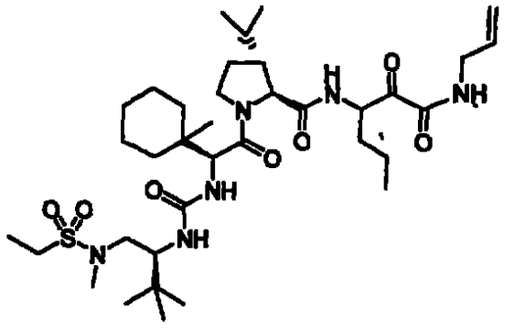
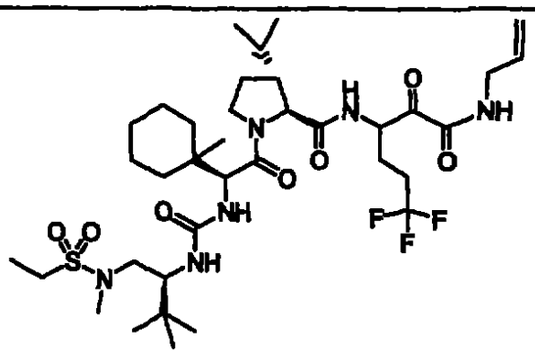
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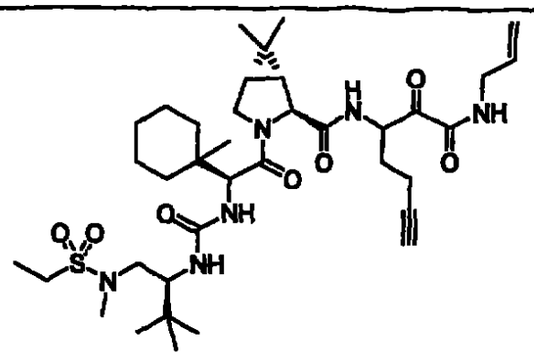
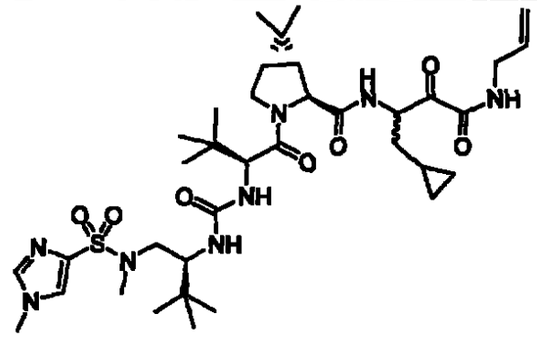
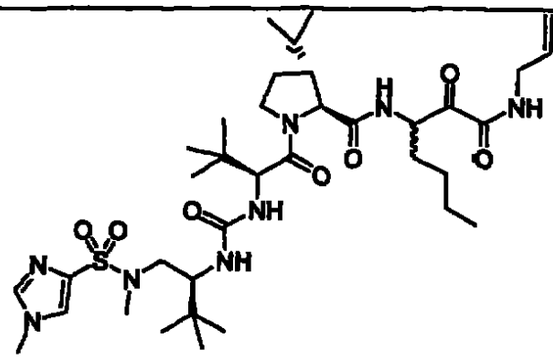
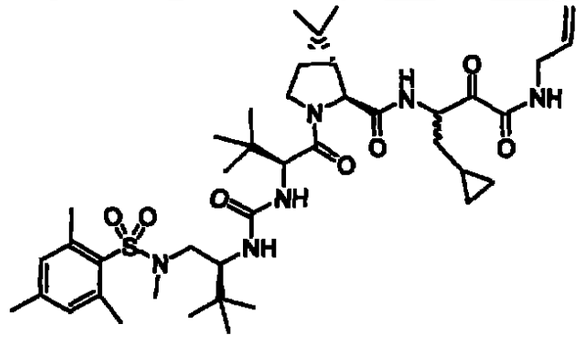
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11312		C

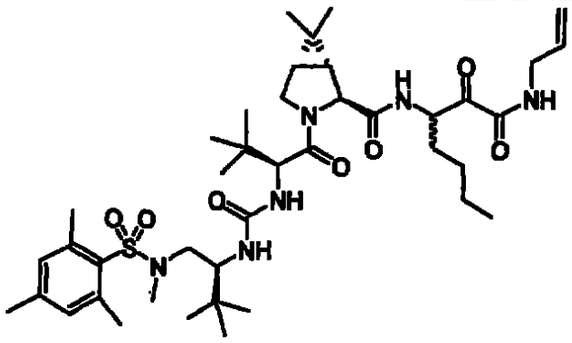
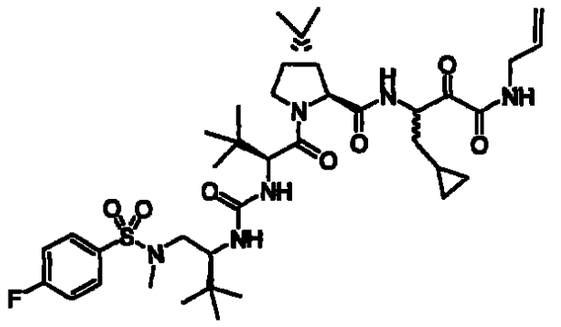
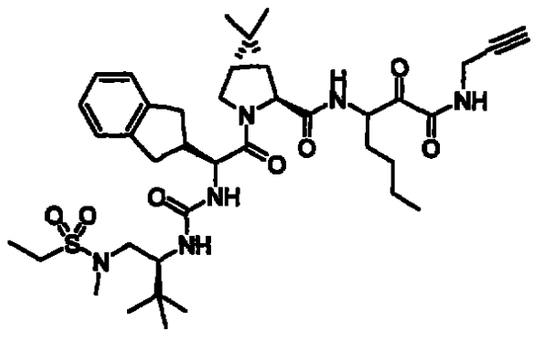
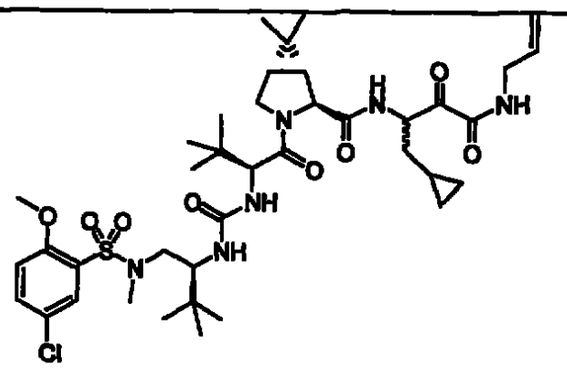
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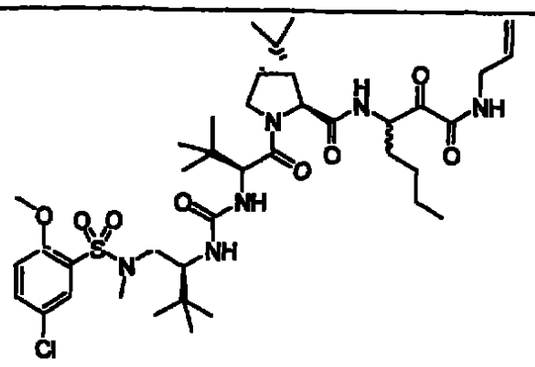
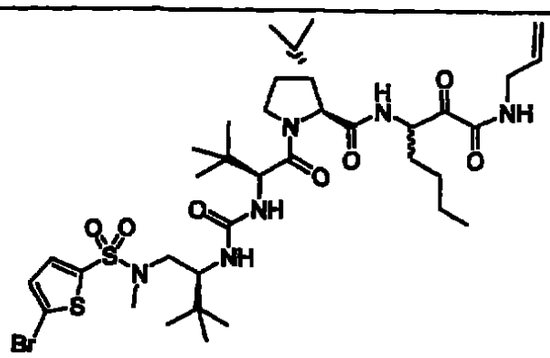
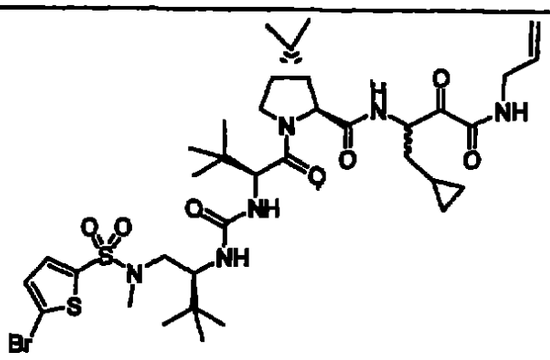
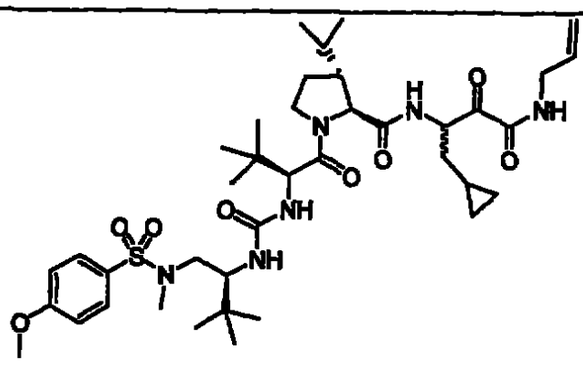
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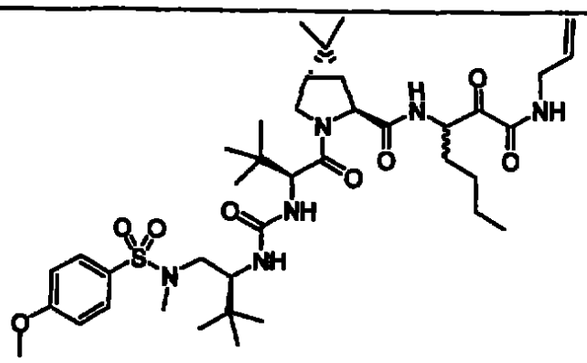
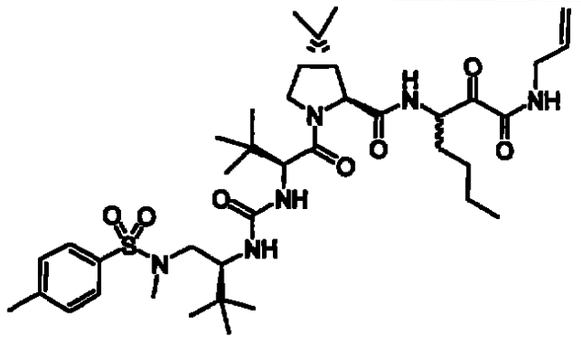
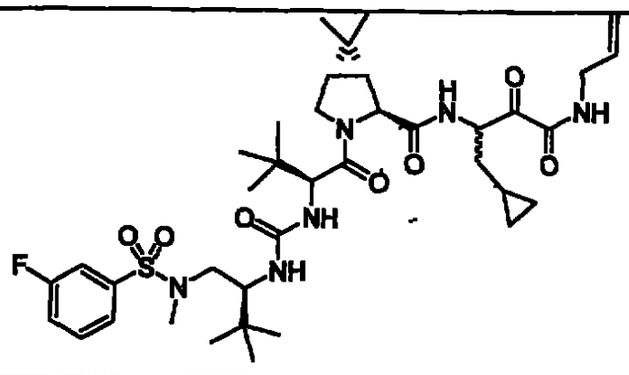
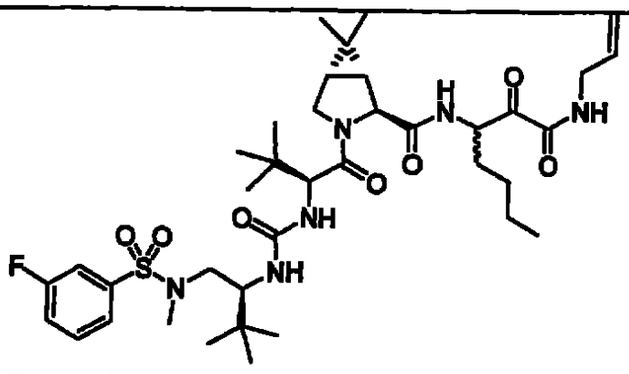
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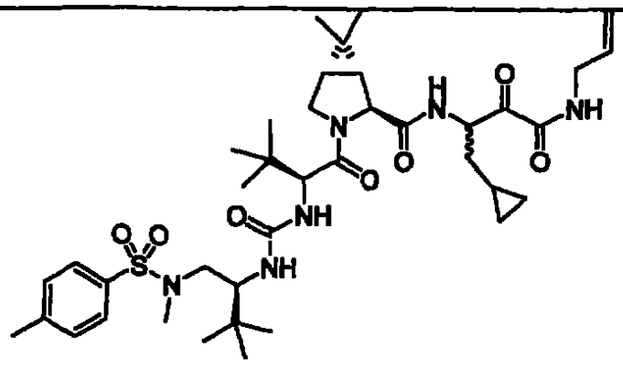
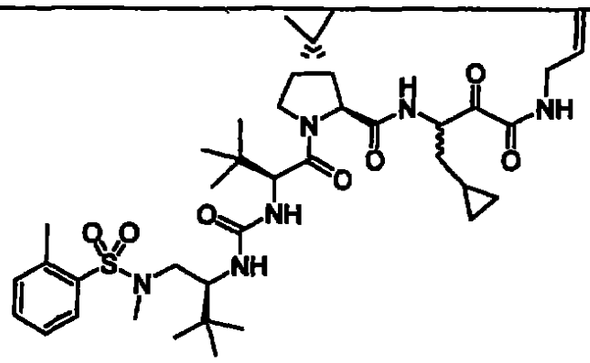
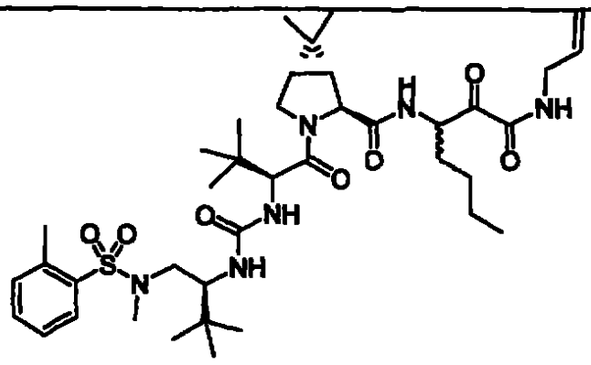
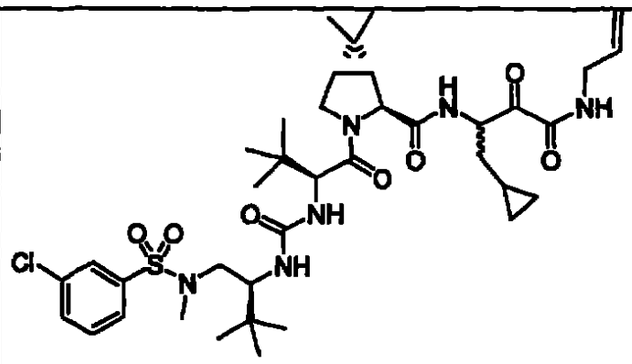
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11328		A

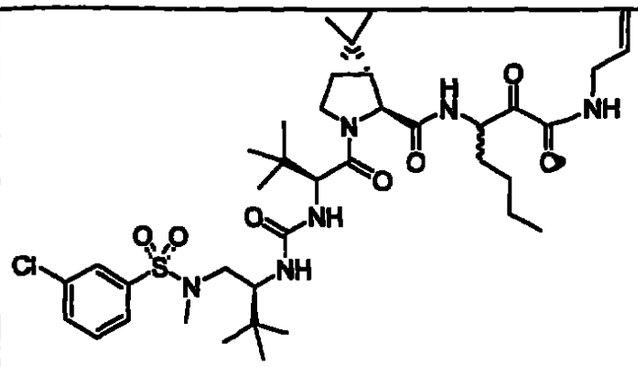
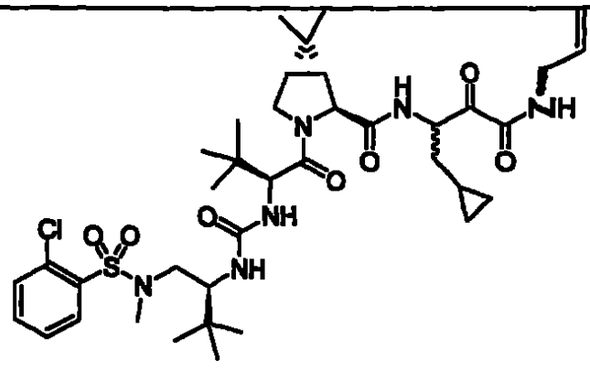
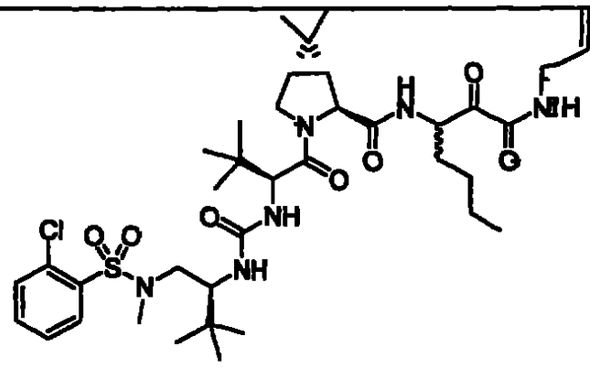
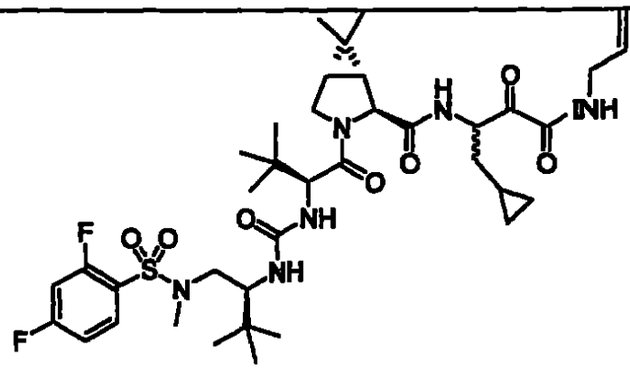
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11332		B

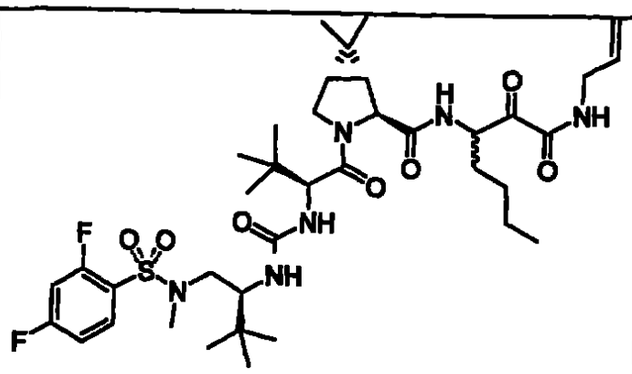
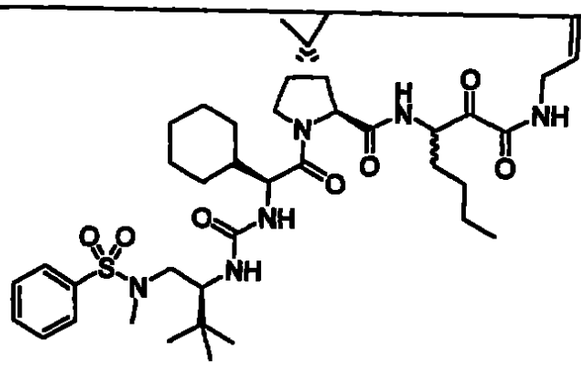
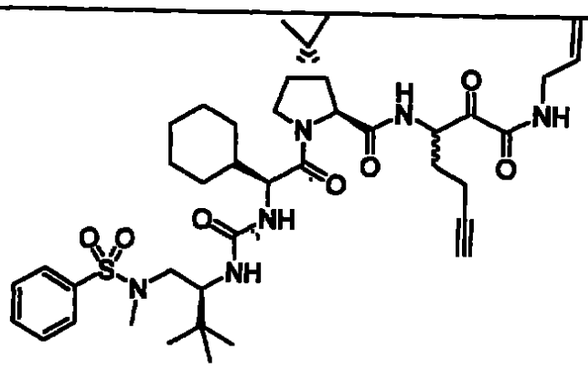
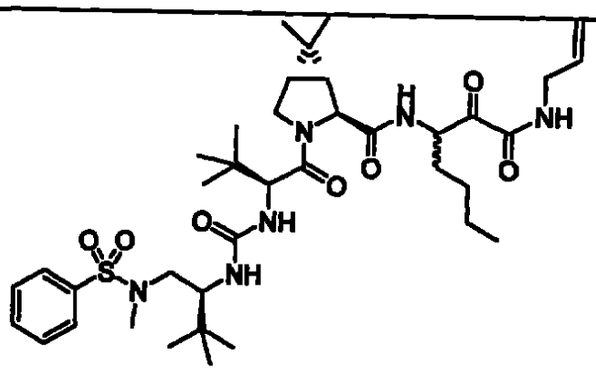
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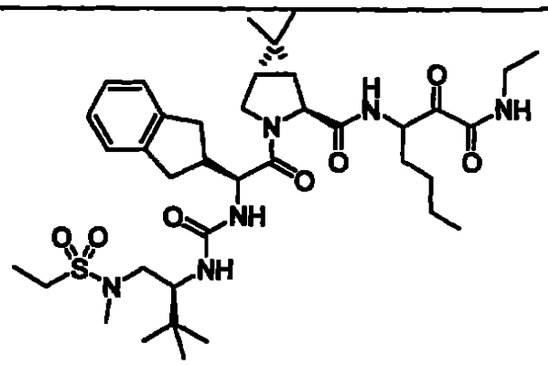
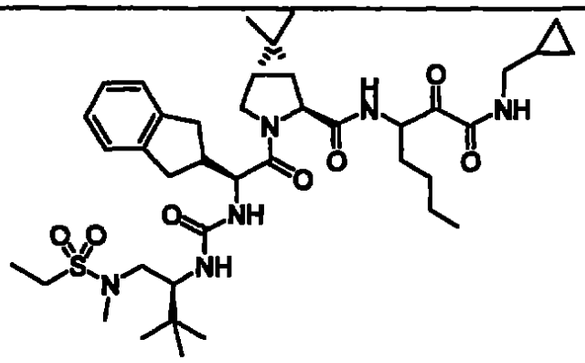
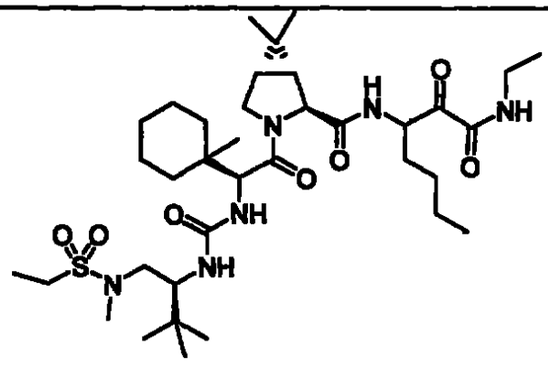
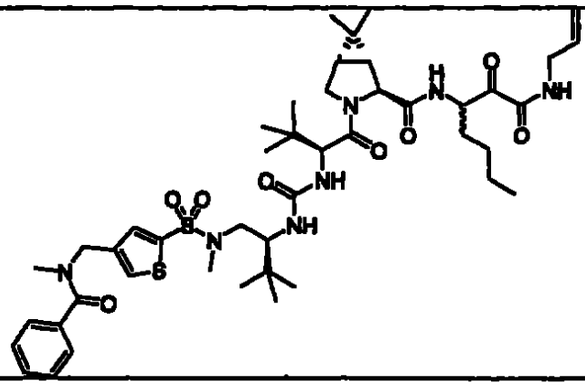
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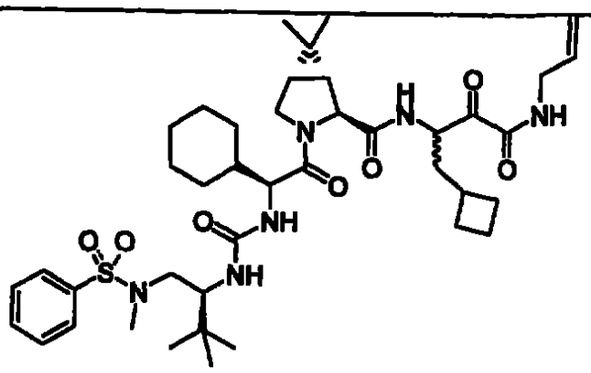
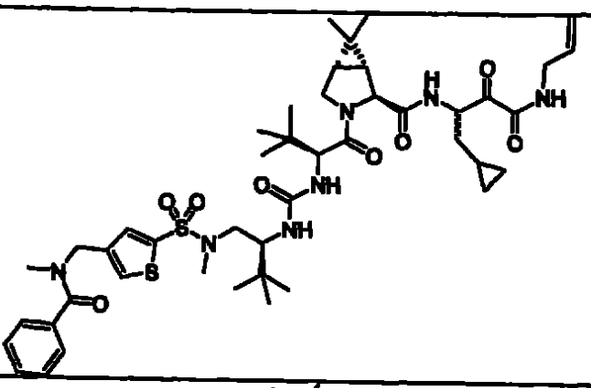
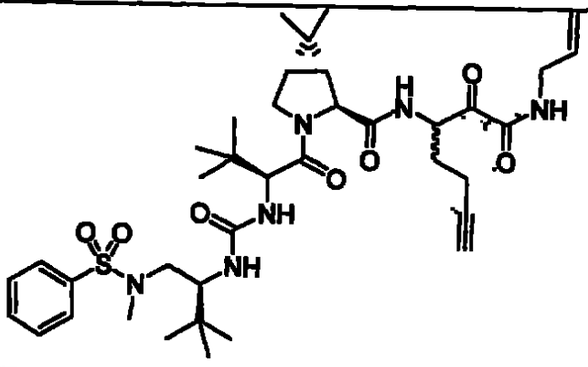
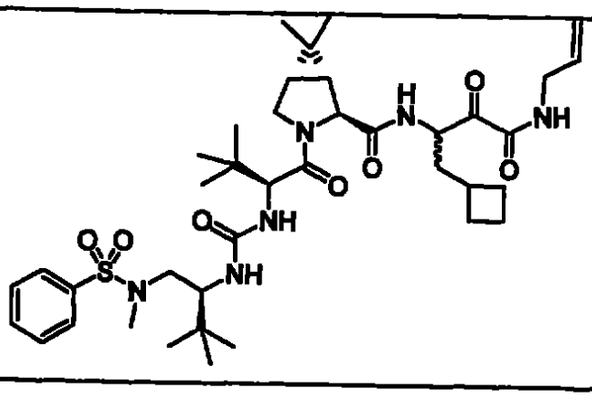
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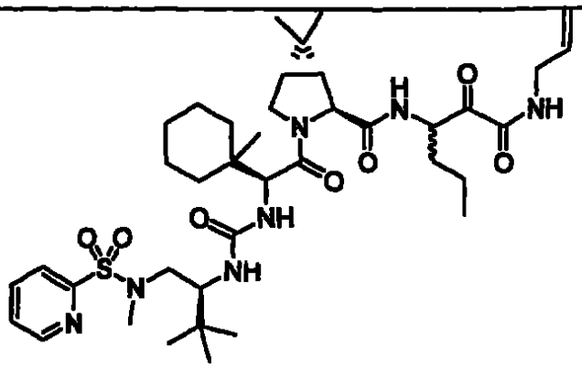
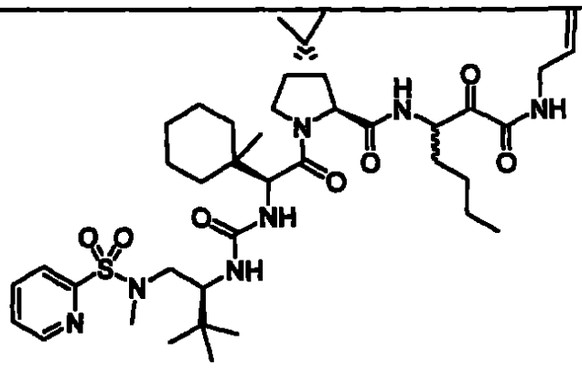
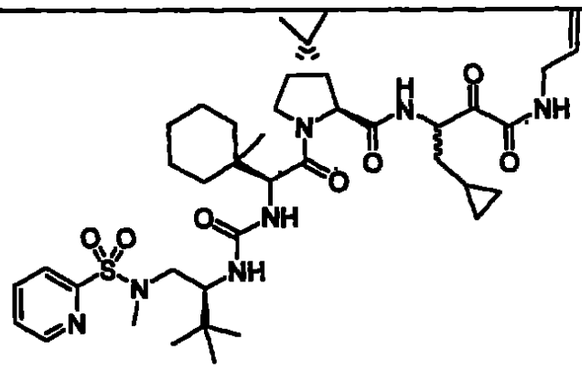
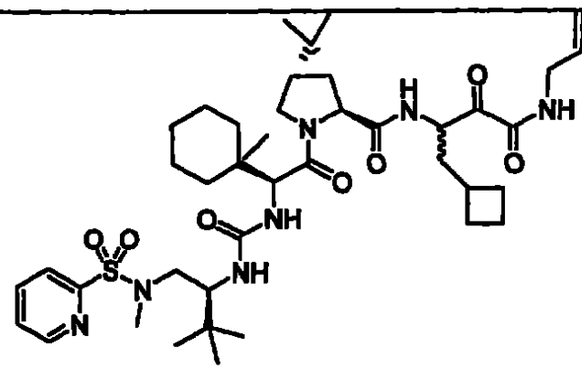
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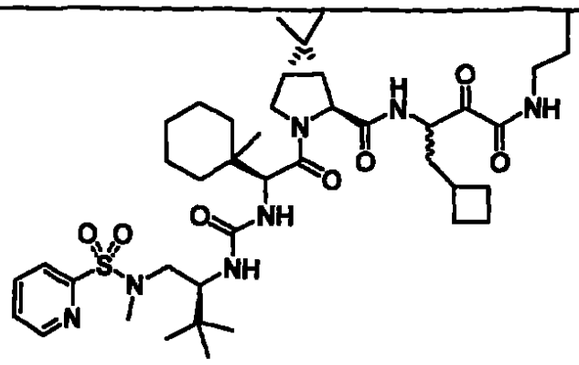
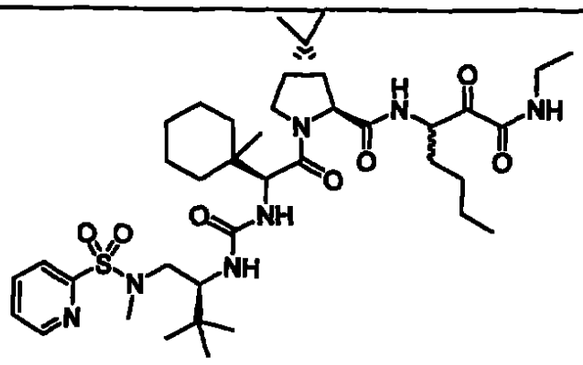
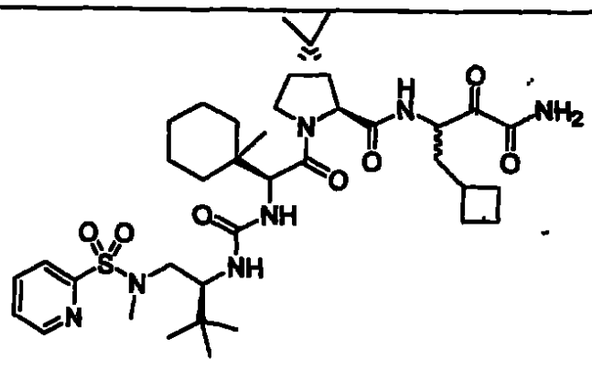
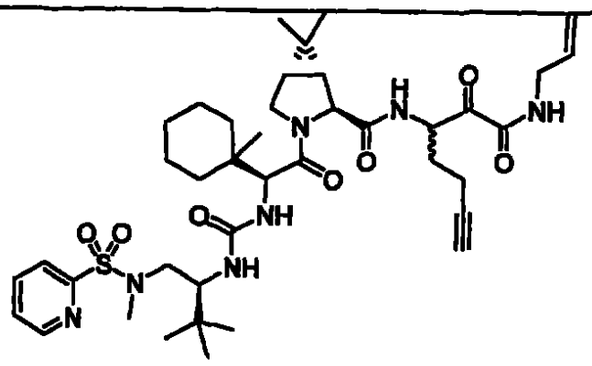
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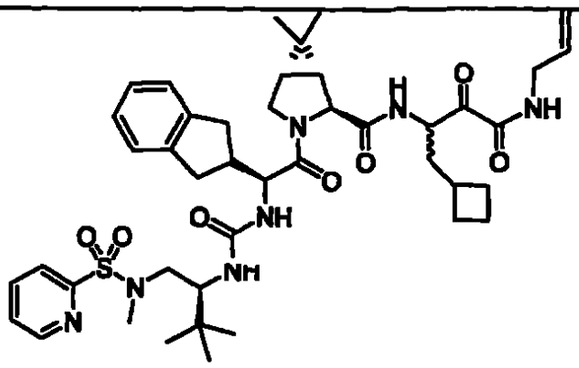
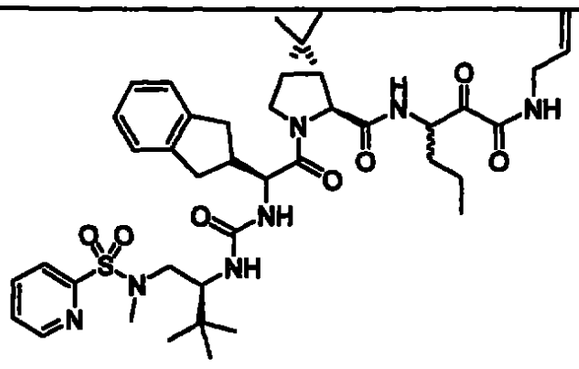
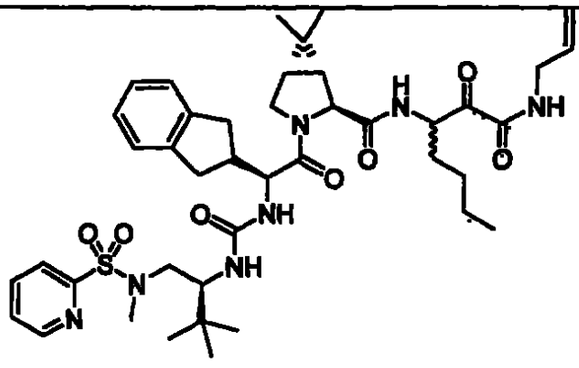
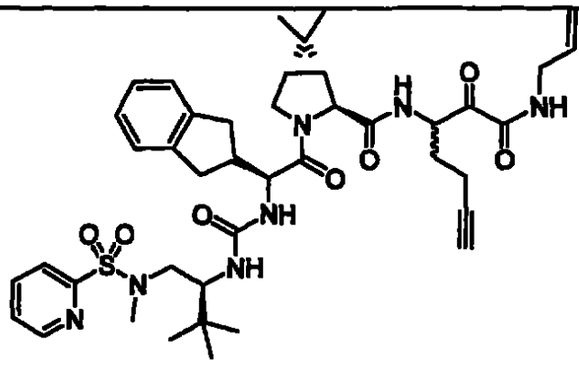
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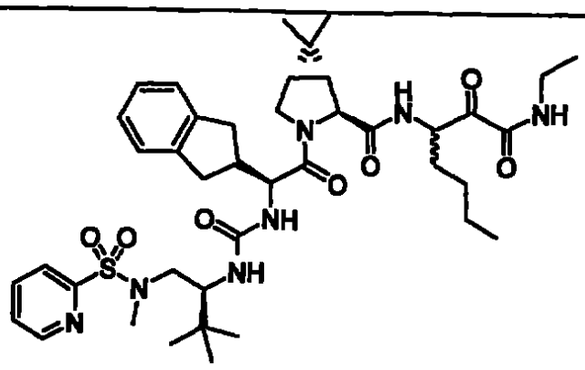
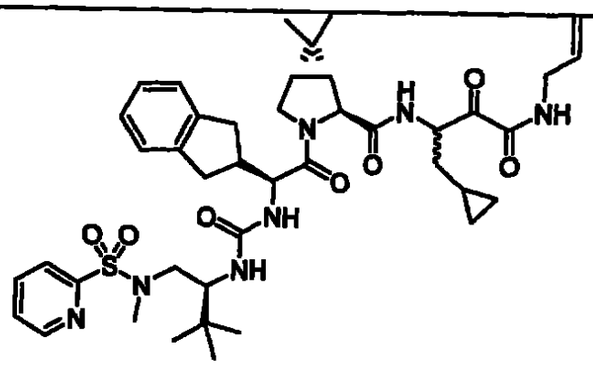
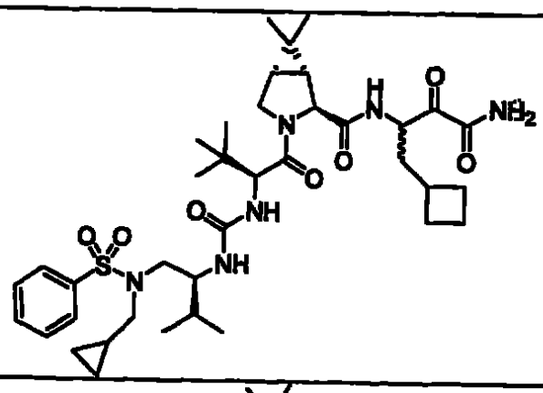
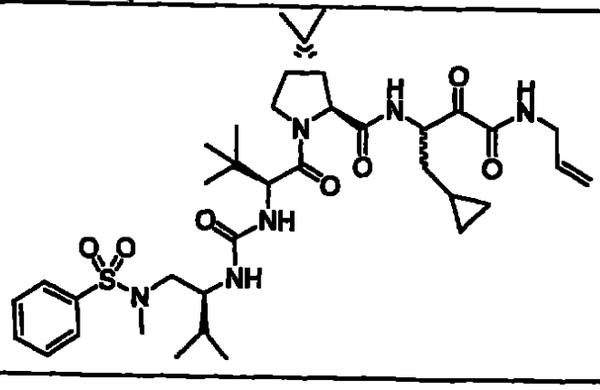
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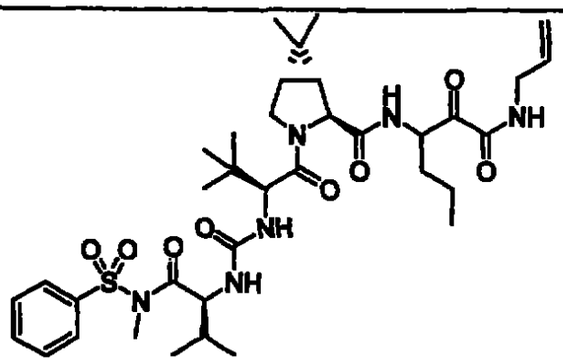
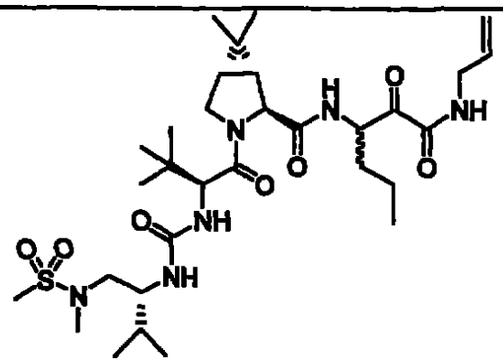
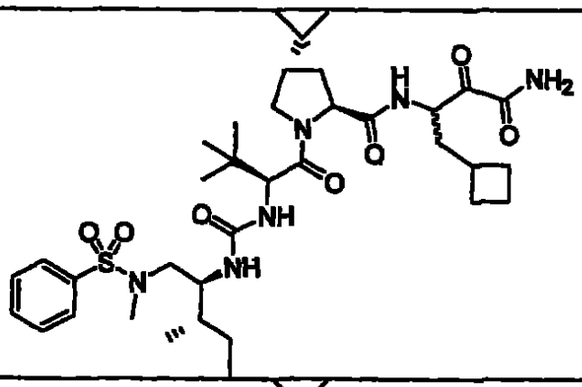
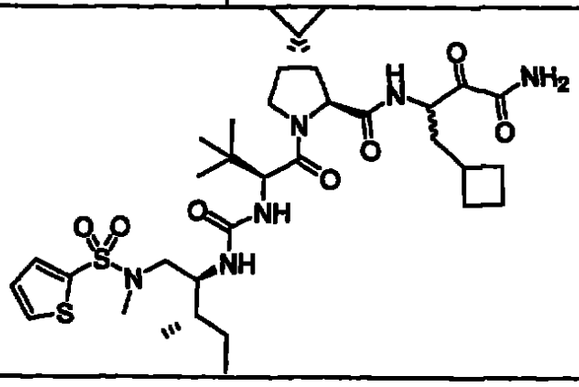
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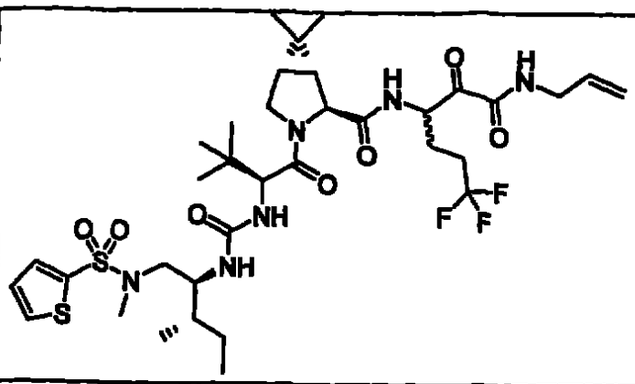
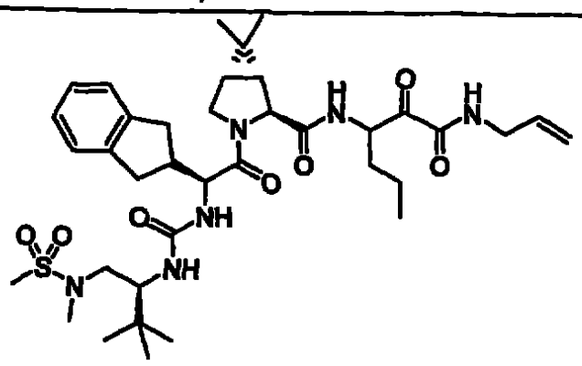
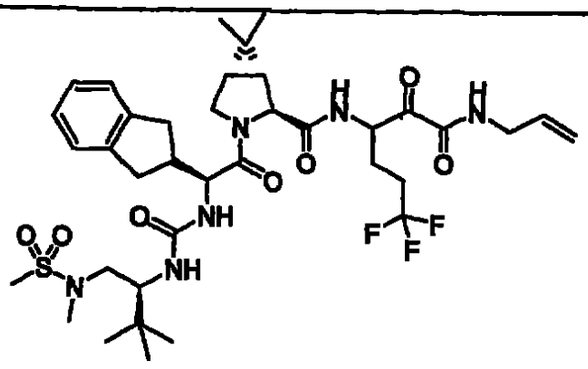
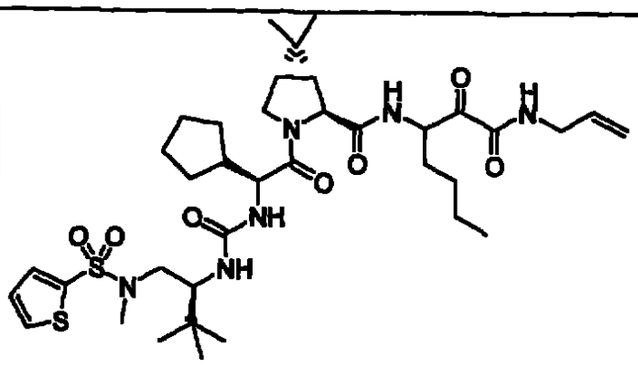
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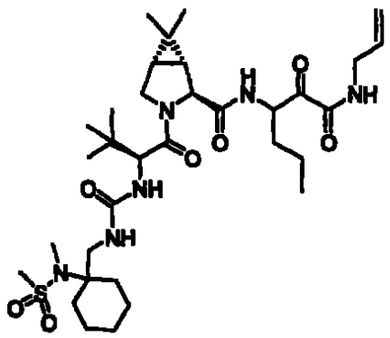
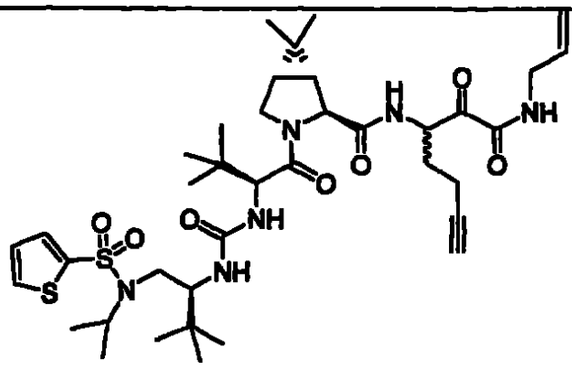
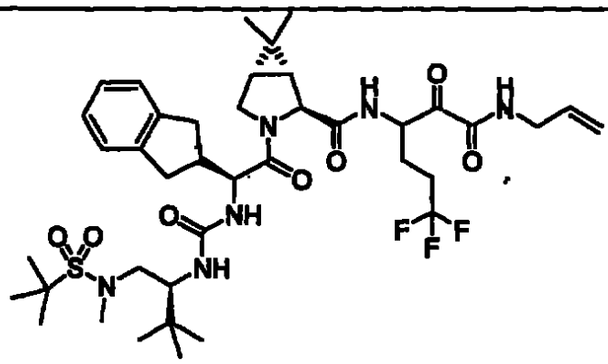
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11372		A

11373		A
11374		A
11375		A
11376		A

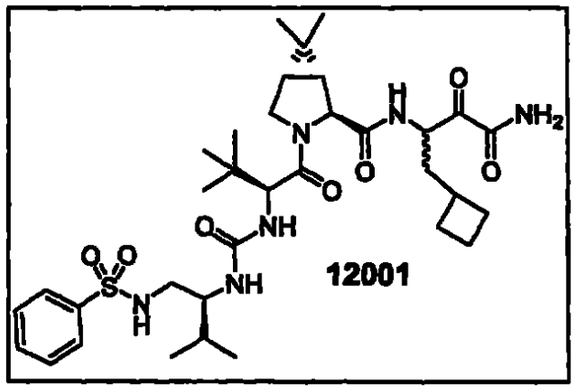
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11380		A

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11382		A
11383		A
11384		A

11385		A
11386		A
11387		A
11388		A

11389		C
11390		A
11391		B

Example-10 Synthesis of Compound of Formula 12001



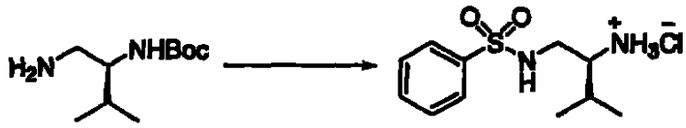
Step A.



12001a 12001b

A solution of **12001a** (2 0 g, 9 2 mmol, Indofine chemicals) in toluene (150 mL) was treated with BH_3•DMS (~ 10 M, 3 mL) and heated at 90 °C for 2 h The reaction mixture was cooled to 0° C and diluted with 2 M aq NaOH The organic layer was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) filtered concentrated in *vacuo* to yield 1 1 g of **12001b.**

Step B

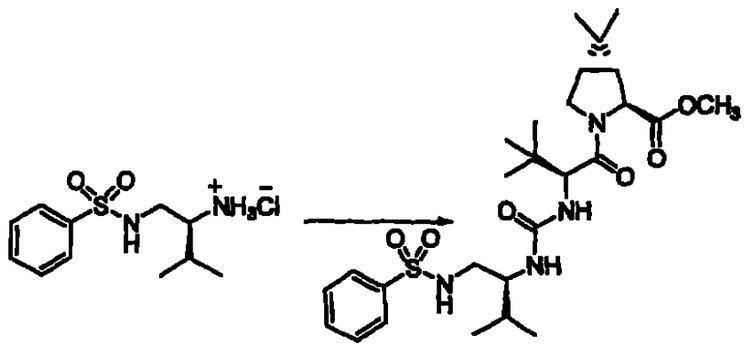


12001b 12001c

A solution of amine **12001b** (500 mg, 2 5 mmol) in CH_2Cl_2 (10 mL) was treated with benzene sulfonyl chloride (669 mg, 3 8 mmol) and Et_3N (384 mg, 3 8 mmol) and stirred overnight at 0 °C The reaction mixture was diluted with aq 1 M HCl and extracted with CH_2Cl_2 The combined organic layer was dried, filtered and concentrated in *vacuo* The residue was purified by chromatography (SiO_2, EtOAc/Hexanes 1 3) to yield 552 mg of boc protected phenyl sulfonamide compound

A solution of Boc-compound (552 mg, 1 6 mmol) in 4M HCl in dioxane at rt. was stirred for 1 h and concentrated in *vacuo* The residue was triturated with ether and the solid separating out was isolated by decanting the ether layer and dried in vacuum to yield **12001c**

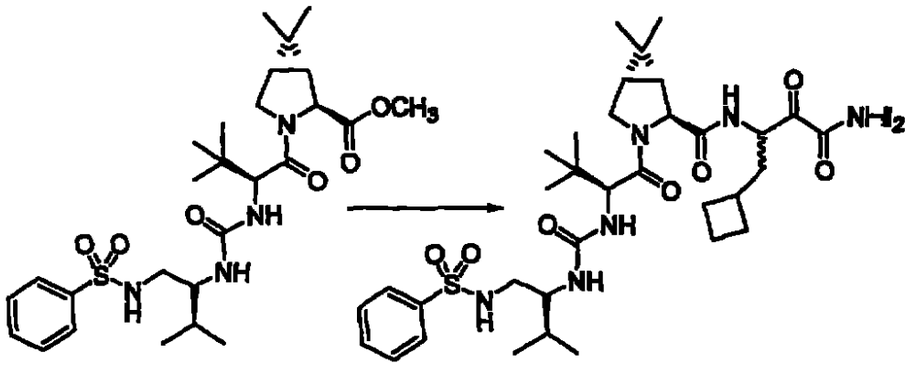
Step C



12001c 12001d

A solution of deprotected amine 12001c (139 mg, 0 5 mmol) in CH_2Cl_2/DMF (1 1, 20 mL) was treated with 4-nitrophenylcarbamate 1 1 6 (1 879 g, 4 20 mmol), NMM (1 062 g, 10 5 mmol) and stirred at rt. overnight. The reaction mixture was concentrated in *vacuo* diluted with CH_2Cl_2 (200 mL) and washed with aq HCl (1M, 2x125 mL), aq saturated $NaHCO_3$ (2x1 25 mL), brine (100 mL), dried ($MgSO_4$), filtered, and purified by chromatography (SiO_2, Hexanes/EtOAc 1 2) to yield ***12001d***

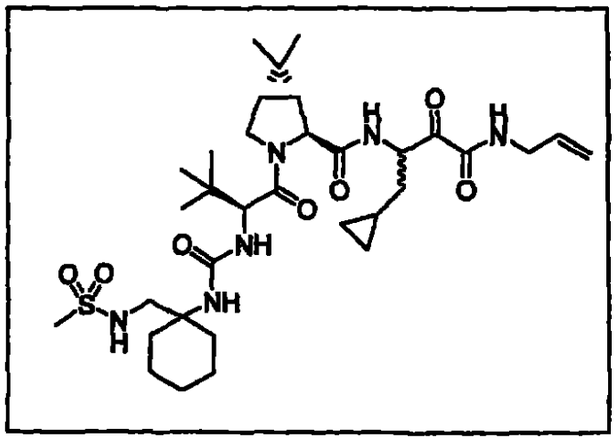
Step D



12001d 12001

Intermediate 12001d was converted to 12001 by coupling to intermediate 10 11 followed by Moffett oxidation identical to the procedu res described in preparatve example-6 of synthesis of 11001, Step D and S-tep E

Example 11 Synthesis of Compound of Formula 12002



12002

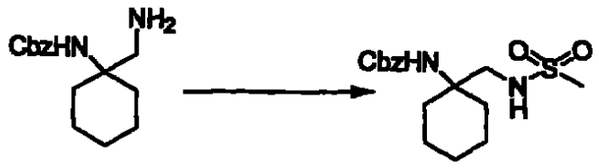
Step A



12002a 12002b

A solution 12002a (Gregory, H *et al*, *J Chem Soc* 1968, 531) (11 62 g, 42 08 mmol) in dry toluene was treated with BH_3•DMS (~10 M soln, 6 3 mL) and heated at 70°C overnight. The reaction mixture was cooled to rt and quenched with aq NaOH and extracted with CH_2Cl_2 The combined organic layers were extracted with brine and concentrated in *vacuo* to yield 12002b 8 77 g (80%)

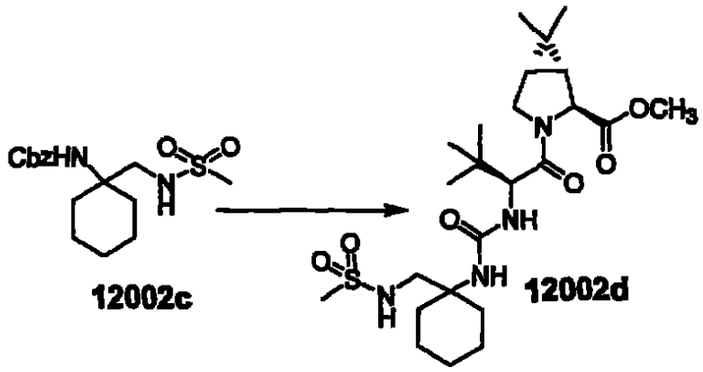
Step B



12002b 12002c

A solution of 12002b (2 g, 7 24 mmol) in methylene chloride was treated with pyridine (7 9 g, 100 mmol), and methanesulfonyl chloride (1 24 g, 10 86 mmol) and stirred at rt. for 24 h The reaction mixture was washed with aq HCl, saturated $NaHCO_3$ and brine The organic layer was dried ($MgSO_4$) filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/Hexanes 1 2) to yield 12002c

Step C



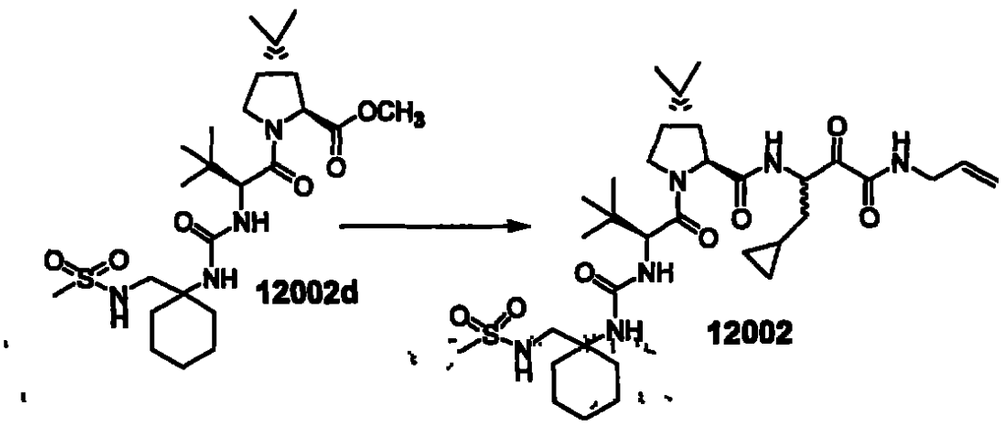
12002c 12002d

A solution of 12002c (465 mg, 1 37 mmol) in methanol was treated with palladium on carbon and hydrogenated for 2 h at 50 *psi* The reaction mixture was filtered through a plug of celite® and concentrated in *vacuo* to

isolate the deprotected amine which was used in the next reaction without further purification

A solution of deprotected amine in CH_2Cl_2/DMF (1 1) was treated with 4-nitrophenylcarbamate 1 16 (612 mg, 1 37 mmol), NMM (548 mg, 5 48 mmol) and stirred at rt for 12 h The reaction mixture was concentrated in *vacuo* diluted with CH_2Cl_2 (200 mL) and washed with aq HCl (1M, 2x125 mL), aq saturated $NaHCO_3$ (2x125 mL), brine (100 mL), dried ($MgSO_4$), filtered, and purified by chromatography (SiO_2, Hexanes/acetone 1 4) to yield 12002d (560 mg)

Step D

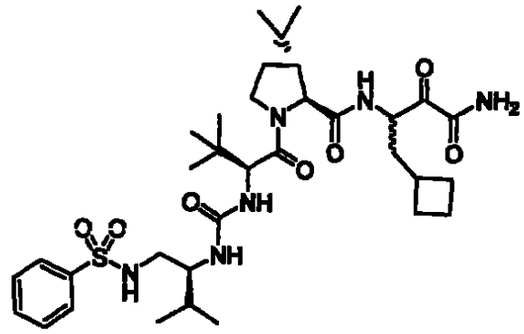
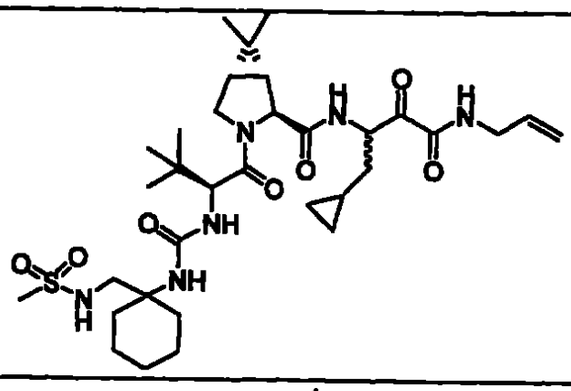
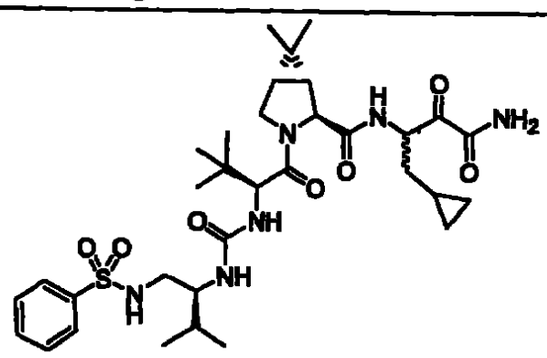
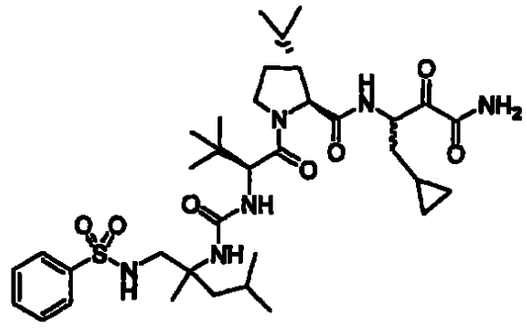


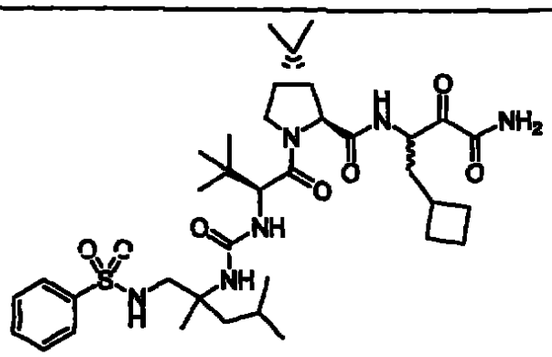
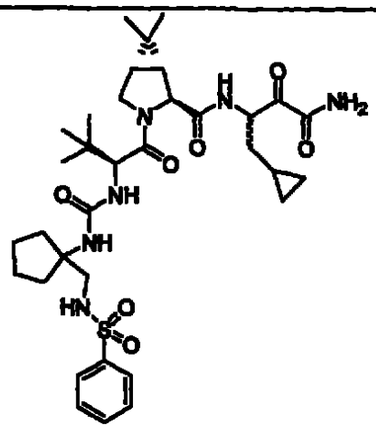
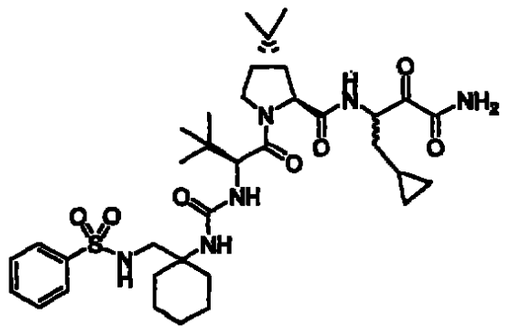
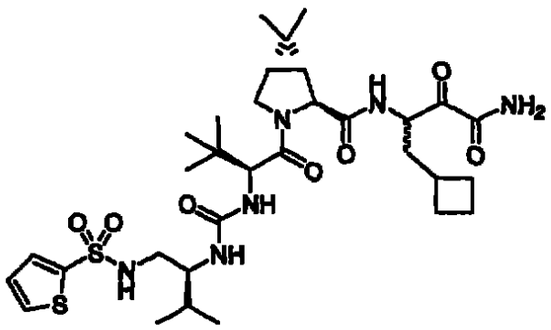
Intermediate 12002d was converted to 12002 by coupling to intermediate 12 04 followed by Dess-Martin oxidation identical to the procedures described in preparative example of synthesis of 11003, Step C and Step D

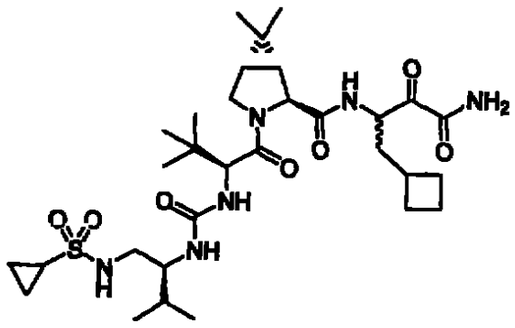
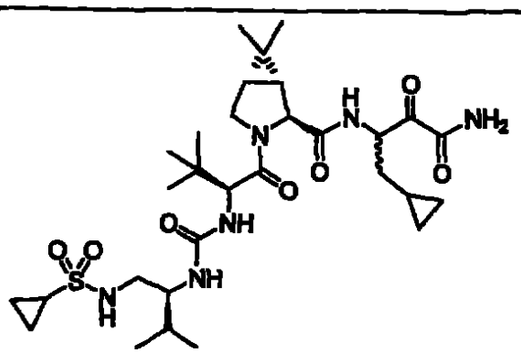
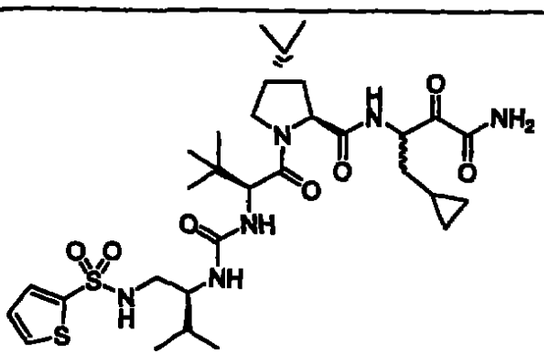
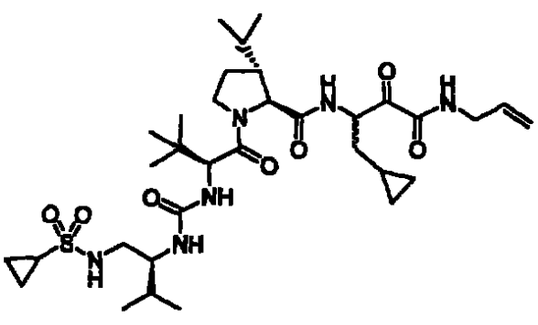
Compounds shown in the following Table 3 were synthesized using similar reactions as shown in Examples above Range of KI* indicated A≤75 nM, 75<B≤250 nM, C>250 nM

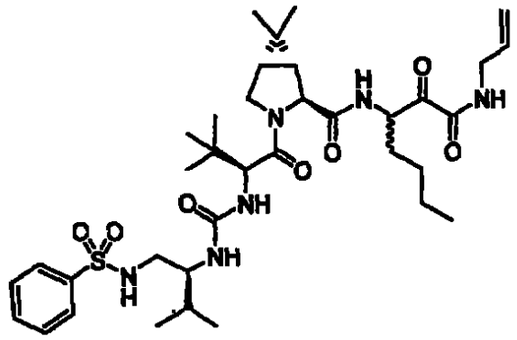
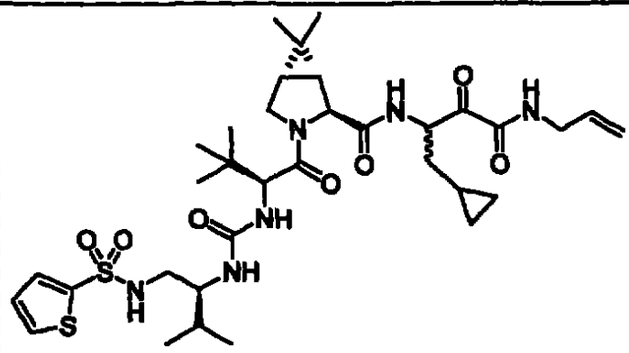
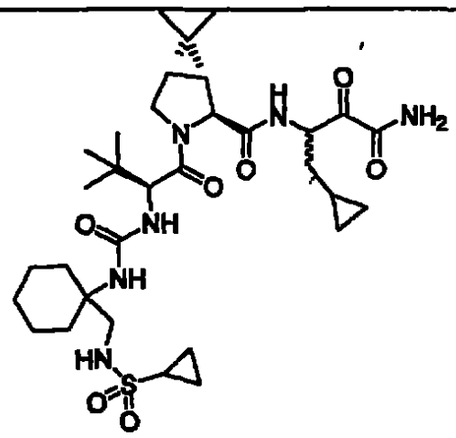
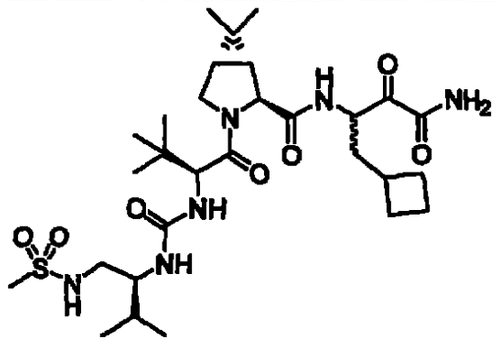
Table 3

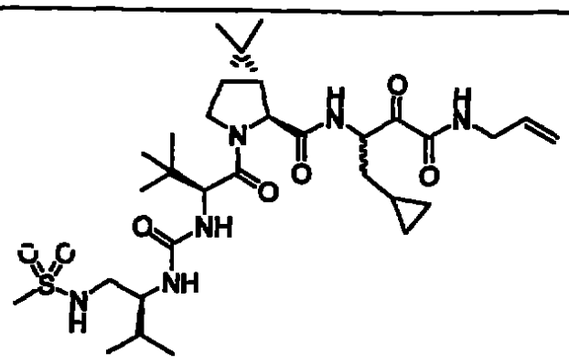
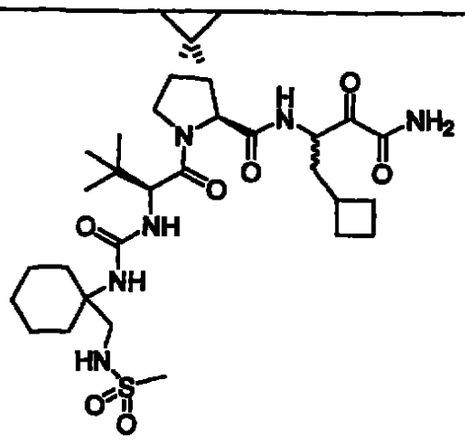
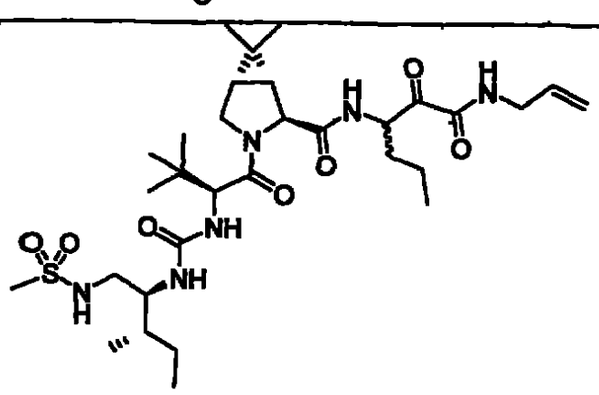
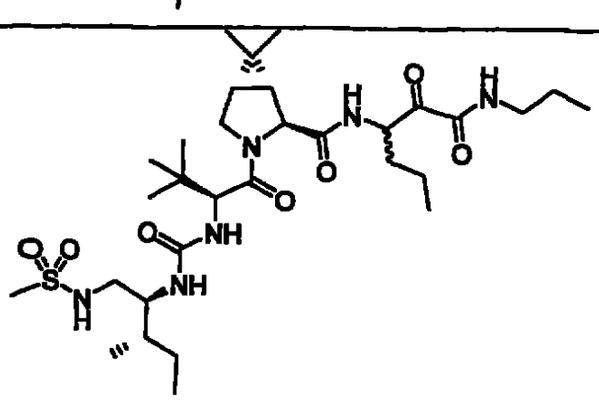
Entry	Structure	KI*

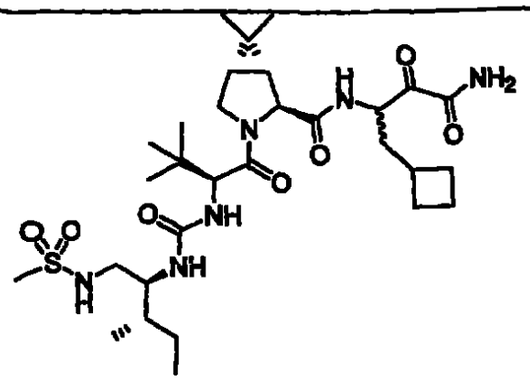
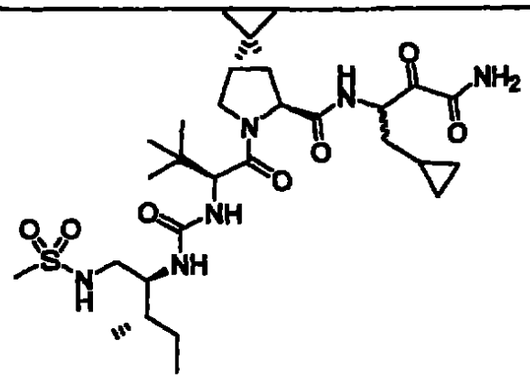
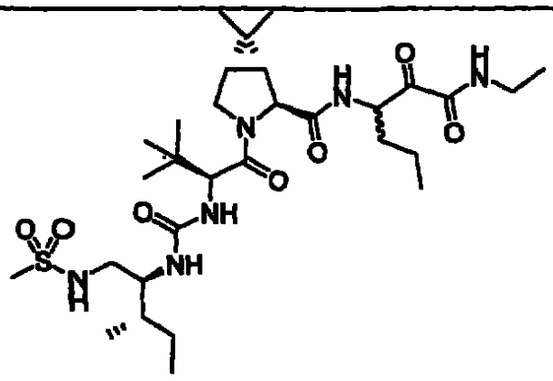
12001		A
12002		A
12003		A
12005		B

12006		B
12007		A
12008		A
12009		A

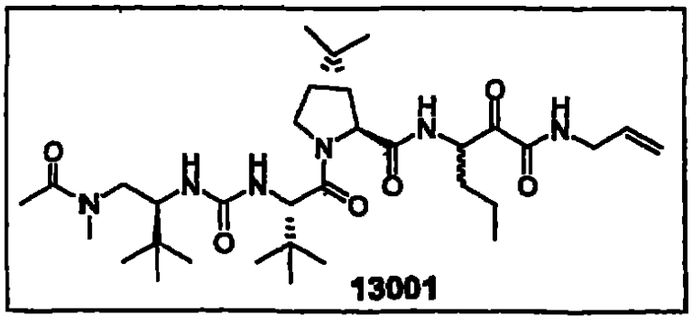
12010		A
12012		A
12013		A
12014		C

12015		C
12016		B
12017		A
12018		A

12019		A
12020		A
12021		A
12022		C

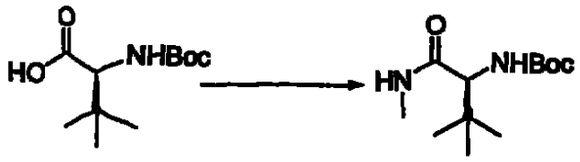
12023		A
12024		B
12025		C

Example-12.Synthesis of compound of molecular formula 13001



13001

Step A.



13001a 13001b

The acid, 13001a, (5 g, 21 6 mmol 1 equiv Fluka) and methyl amine hydrochloride (1 2 equiv , 25 92 mmol) were dissolved in dry N, N-dimethyl formamide (20 ml) and cooled to 0 °C Added HATU (1.2 equiv , 25 92 mmol) followed by DIPEA (Sigma-Aldrich), (172 8 mmol , 8 equiv) under N_2 atmosphere The temperature was slowly raised to room temperature and stirred further for 4 h at room temperature Diluted with EtOAc and washed with 1N HCl, $NaHCO_3$ and finally with brine Dried over anhydrous sodium sulfate, filtered, and evaporated off the solvent Crude product isolated was purified via flash column (1 0-50% EtOAc-Hexane) to afford 5.27 g of 13001b Yield, (99 %)

^{1}H NMR ($CDCl_3$, 300 MHz) δ, 6 0(bs, 1 H), 5 35(d, 1 H,), 3.82 (d, 1 H), 2 8 (s, 3H), 1 4 (s, 9H), 0 98 (s, 9 H)

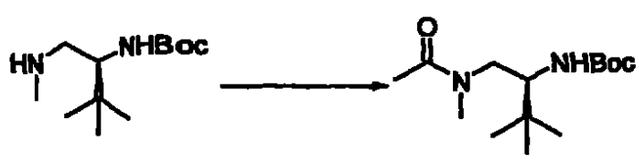
Step B



13001b 13001c

To the amide 13001b (3 37g,13 8 mmol, 1 equiv) in toluene (100 mL) at room temperature, added BH_3•Me_2S (10M, 3 equiv , 41 4 mmol, 4 14 mL) and refluxed at 80 °C for 3 hrs Evaporated off the solvent and the crude product was quenched with 2 M aq sodium hydroxide and extracted with dichloromethane Washed the organic layer with brine and dried over anhydrous sodium sulfate Filtered and evaporated off the solvent to afford 1 8 g of 13001c The crude product was used for next step without purification Yield, (55 %)

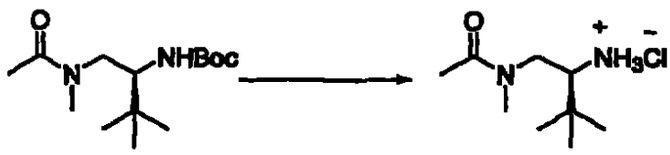
Step C



13001c 13001d

To the Boc-protected amino compound **13001c** (540 mg, 1 equiv) In dichloromethane (25 mL) at ice temp was added triethylamine (3 equiv) and acetyl chloride (3 equiv) Stirred for 1 hr at ice temperature and then at room temperature for overnight Quenched with aq sodium bicarbonate and extracted with EtOAc Washed with 1N HCl and then with brine The organic layer were dried over anhydrous sodium sulfate, filtered and evaporated off the solvent. The crude product was purified via flash column (20-40 % EtOAc-Hexane) Yield = 230 mg (38 %)

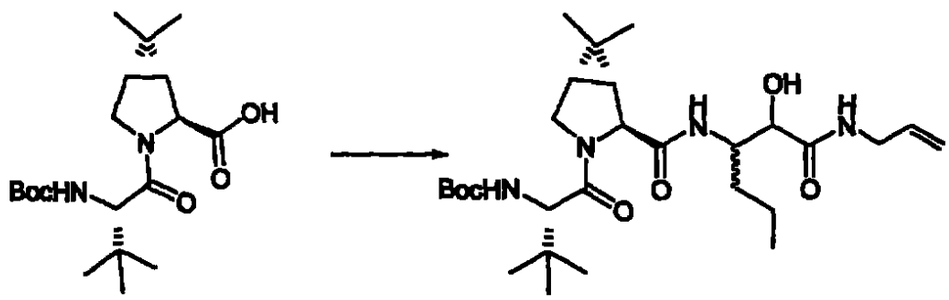
Step D



13001d 13001e

To the amide **13001d** (28 mg, 1 equiv) added 4M HCl/dioxane (2 mL) at room temperature Stirred for 1 hr TLC showed no starting material Evaporated off the solvent and azeotroped with hexane and then with ether Washed out the non polar material with ether and kept under high vac over the week end Used the salt without purification, Product isolated (pale yellow solid) = 22 mg (100 %)

Step E

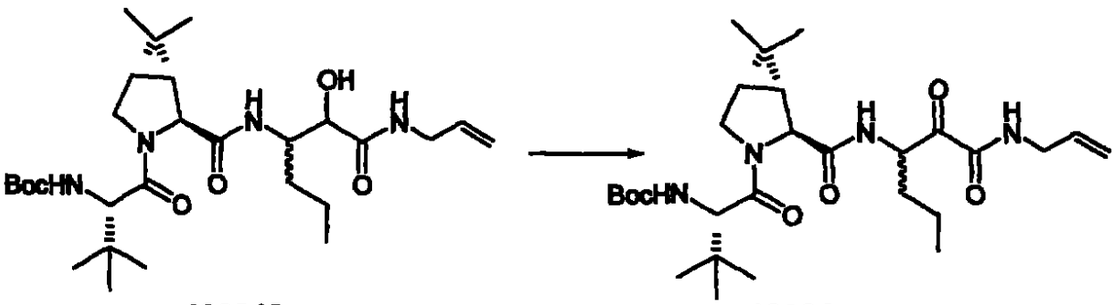


1 17 13001f

To a mixture of acid, **1.17** (860mg, 2 33 mmol, 1 equiv) and amine hydrochloride 13 01 (570 mg, 2 56 mmol, 1 1 equiv) in DMF (15 mL) at ice temperature was added HATU (1 2 equiv , 1 066 g, 2 796 mmol) and DIPEA (8 equiv , 18 69mmol, 3 26 mL) under N_2 and stirred at 0° C overnight The temperature was slowly allowed to rise to room temperature Quenched with 1N HCl and extracted with EtOAc Th combined organic layer were washed

with aq $NaHCO_3$ (sat) and then with brine Washed with ice cold water (5 x 20 ml) and again with brine Dried over anhydrous Na_2SO_4, filtered, and evaporated off the solvent to afford 1.25 g of **13001f** Yield, 100 %

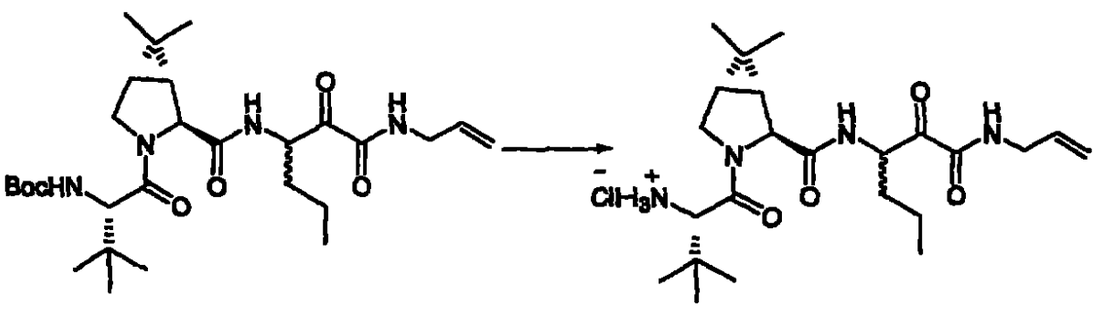
Step F



13001f **13001g**

To the crude hydroxy amide, **13001f** (2 71mmol, 1 45mg, 1 equiv) in DCM (50 mL)at room temperature, was added Dess-Martin periodinane (2 30mg, 5.42 mmol, 2 equiv) and stirred at rt for 5 hrs TLC showed complete consumption of starting material and the appearance of product. Quenched with sat. $NaHCO_3$ aq thiosulfate solution and extracted with EtOAc The organic layer was washed with brine and dried over anhydrous sodium sulfate Filtered and evaporated off the solvent Crude product was purified by silica gel flash column (10-40 % acetone-hexane) to afford 860 mg of **13001g**; Yield, 62 %

Step G

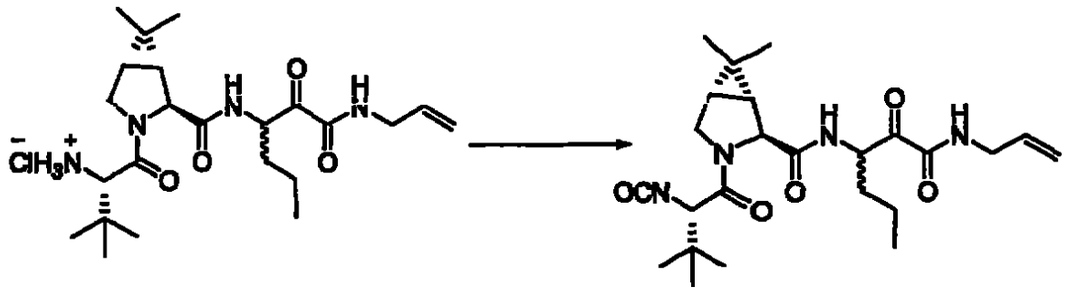


13001g **13001h**

To the Boc amino compound **13001g** (860 mg, 1 equiv) added 4M HCl in dioxane (25 mL) at room temperature Stirred for 1 hr TLC showed no starting material Evaporated off the solvent and azeotroped with hexane and then with ether Washed out the non polar material with ether and kept under

high vacuum over the week end Used the salt without further purification, Product isolated (pale yellow solid) = 750mg (99%)

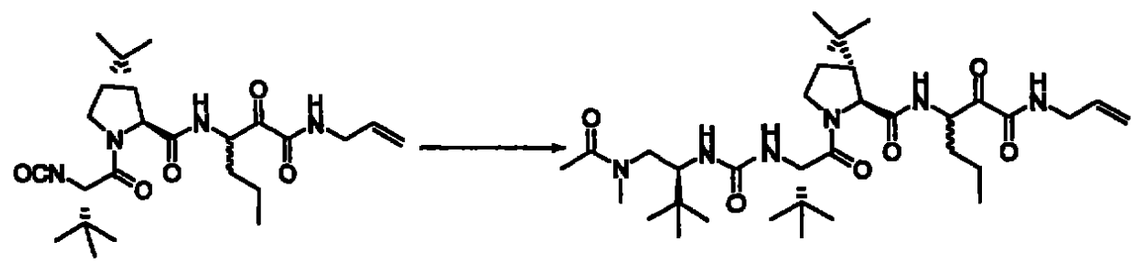
Step H



13001h 13001i

To the ammonium salt, 13001h, (150 mg, 0 318 mmol, 1 equiv) in DCM (5 ml) was added 5 ml of aq sat $NaHCO_3$ Stirred vigorously at ice temperature for 5 min Stopped stirring and phosgene (2 equiv 20 % in toluene, 0 318 mL) was syringed out to the lower layer and restored the vigorous stirring immediately Checked the TLC at times and after 2 hrs it showed complete consumption of starting material and then separated the layers Washed the water layer one more time with DCM (3 ml) and the combined organic layers were dried over sodium sulfate The organic layer was filtered and concentrated in *vacuo* to half the volume Used 13001i as a stock solution of 0 01M by diluting to 30 mL of dichloromethane

Step F



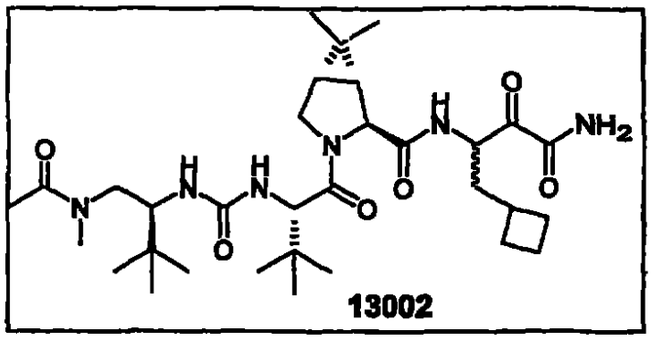
13001i 13001

To the ammonium salt 13001e (22 mg, 0 102 mmol, 1 1 equiv) in DCM (10 ml) was added DIPEA (6 equiv , 135 µL) at ice temperature Added isocyanate 13001i (1 equiv, 9 ml of 0 01M soln) under N_2 atm and stirred for 30 min at ice temperature and 90 min at room temperature Quenched with citric acid and extracted with EtOAc and washed with brine Dried over anhydrous sodium sulfate, filtered and evaporated off the solvent The crude

product was purified via flash column (SiO_2, 10-50% acetone-hexane) to afford 50 mg of 13001 as a colorless solid Yield, (78 %)

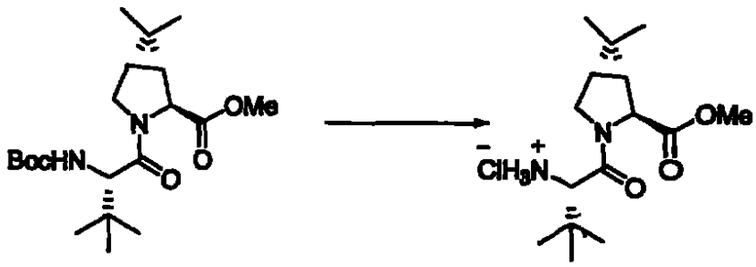
MS (ESI), m/z, 633 (M+1), 312

Example 13 Synthesis of compound of molecular formula 13002



13002

Step A.

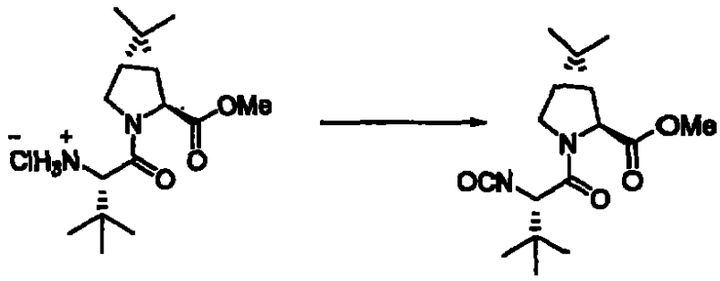


1 03 1.04

To the Boc protected dipeptide 1 03 (3 6 g, 9 42 mmol, 1 equiv) added 4M HCl/dioxane (60 mL) at room temp Stirred for 2 h TLC showed no starting material Evaporated off the solvent and azeotroped with hexane and then with ether Washed out the non polar material with ether and kept under high vac over night. Used the salt, 1 04, without purification

Product isolated = 3g (100 %)

Step B



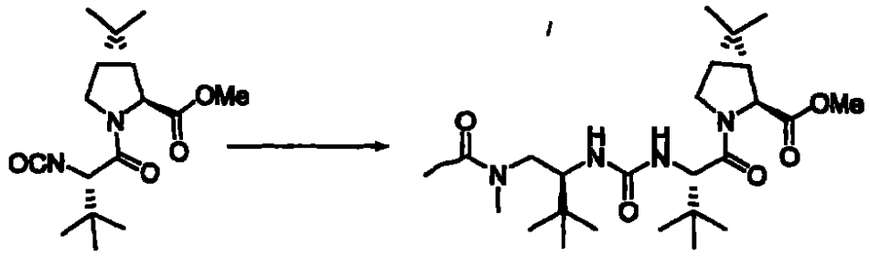
1 04 13002a

To the amine hydrochloride 1.04 (3g, 9 4 mmol) in dichloromethane (50 ml) was added 50 ml of sat. $NaHCO_3$ Stirred vigorously at ice temperature for

126

5 min Stopped stirring and phosgene (2 equiv 20 % in toluene, 10 mL) was syringed out to the lower layer and restored the vigorous stirring immediately Checked the TLC at times and after 2 hrs it showed complete consumption of starting material and then separated the layers Washed the water layer one more time with dichloromethane (3 ml) and dried over anhydrous sodium sulfate Filtered and evaporated off the solvent using rotary evaporator under reduced pressure to half the volume and then flushed N_2 for 15 minutes Diluted to 33 5 mL with dichloromethane and used as 0 28 M solution for further couplings

Step C

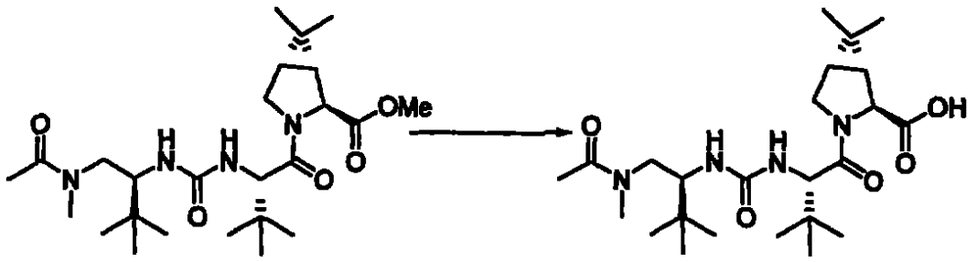


13002a 13002b

To the amine salt, 13001e, prepared as described before (151 mg, 0 73mmol, 1 equiv) in DCM (10 ml) was added DIPEA (8 equiv., 1 01 mL, 5 84 mmol) at ice temperature Added isocyanate 13002a (1 equiv, 13ml of 0 02M soln) under N_2 atm and stirred for 30 min at ice temperature and 90 min at room temperature Quenched with 10 % citric acid and extracted with EtOAc and washed with brine Dried over anhydrous sodium sulfate and filtered and evaporated off the solvent. The crude product was purified via flash column (20-80 % EtOAC-hexane) to afford 270 mg of 13002b as a white solid Yield, (76 %)

^{1}H NMR ($CDCl_3$, 300 MHz) δ, 5 8(bs, N H), 5 4(bs, NH), 5 2 (d, 1H), 4 4(d, 1H), 4-4 2(m, 2H), 3 8-4(m, 3H), 3 01(s, 3H), 2 01(bs, 6H), 1 6 (m,1H), 1 4(m, 1H), 1 02-0 98 (m, 24 H)

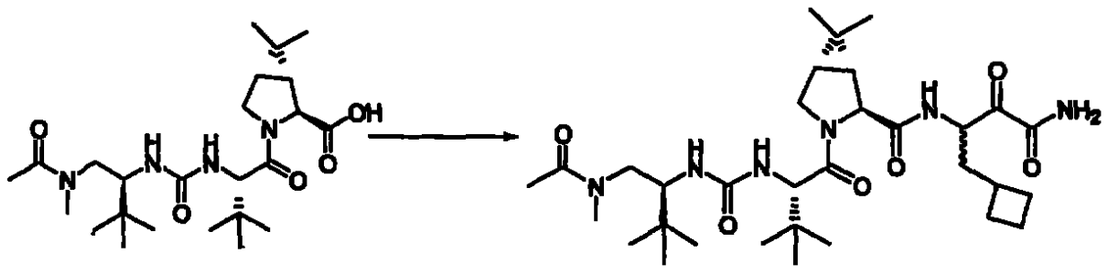
Step D



13002b 13002c

To the methyl ester, 13002b (270 mg, 0 562 mmol, 1 equiv) in dioxane (10 ml) was added a solution of LiOH (10 equiv , 6 mL of 1N soln in water) and stirred overnight. Quenched with 1N HCl and extracted with EtOAC Washed with brine and dried over anhydrous sodium sulfate Filtered and evaporated off the solvent. crude yield 260 mg (99 %)

Step E



13002c 13002

To the ammonium salt, 10 11 (16 06 mg, 0 077mmol, 1.2 equiv) in DCM (10 ml) was added 13002 c (30 mg, 0 064 mmol, 1 equiv) and cooled to – 20 C and added HATU (1 2 equiv , 0 077 mmol, 29 37 mg) followed by DIPEA (8 equiv , 89 94 µL, 0 515 mmol) The reaction mixture was stirred overnight at that temperature Quenched with 1N HCl and extracted with EtOAC Washed the organic layer with aq saturated sodium bicarbonate and then with brine Dried over anhydrous sodium sulfate, filtered, and evaporated off the solvent Purified via flash column (SiO_2, 10-90 % EtOAc-Hexane) to afford 40 mg of hydroxyamide Yield, (100 %)

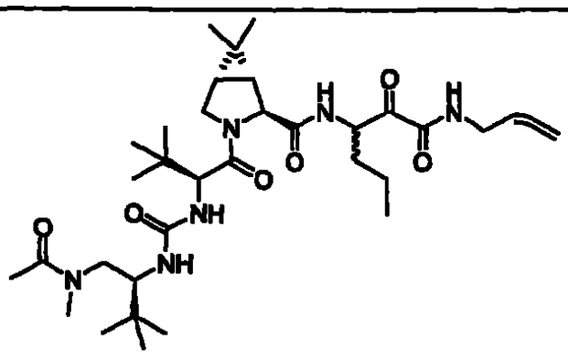
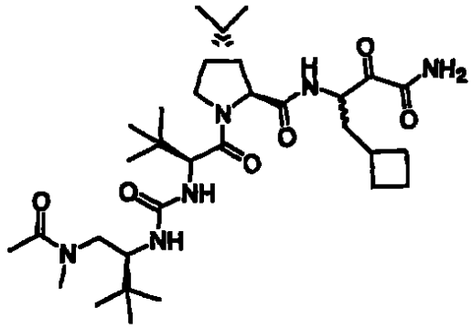
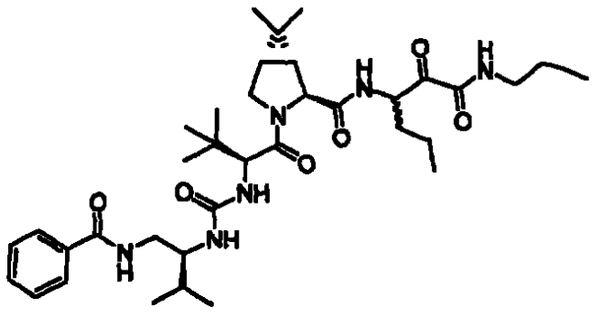
To the hydroxyl amide (40 mg, 0 0645mmol, 1 equiv) in 1 1 mixture of DMF/toluene (6 mL) at Ice temperature was added EDCI•HCl (123 mg, 10 equiv , 0 645 mmol) and dichloroacetic acid (27 µL, 5 equiv , 0 322 mmol) and stirred for 5 min and room temperature for 3 h Quenched with brine and washed with 1N HCl followed by aq sat $NaHCO_3$ and again with brine Dried

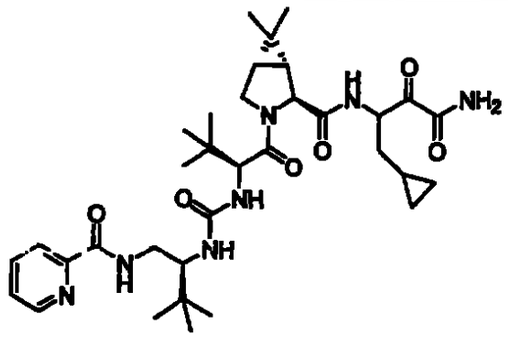
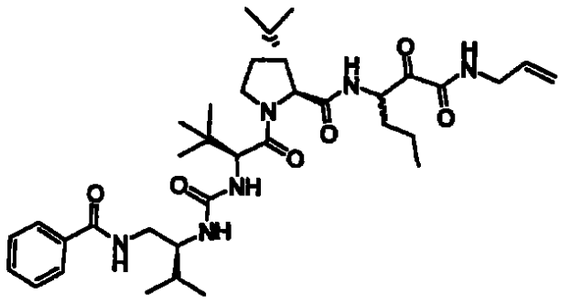
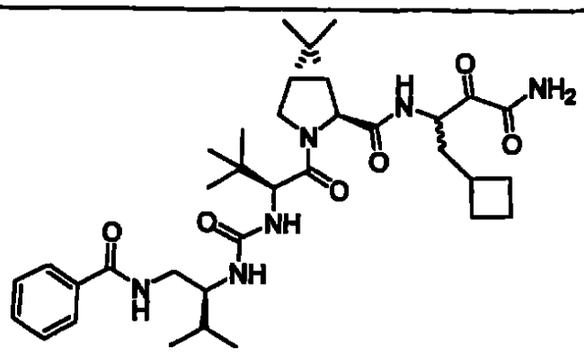
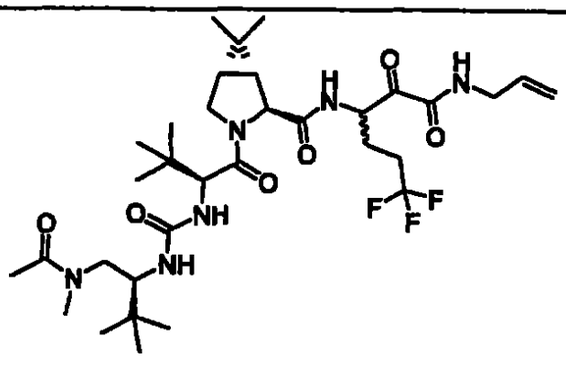
over anhydrous sodium sulfate, filtered and evaporated off the solvent. Purified via silica gel preparative TLC (50 % acetone-hexane) to afford 30 mg of **13002** Yield (75 %)

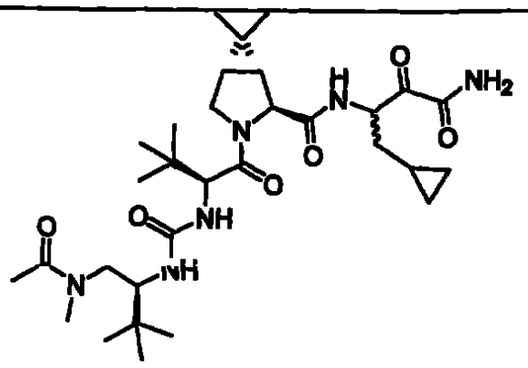
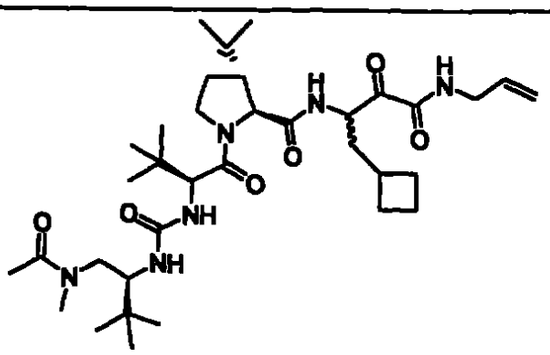
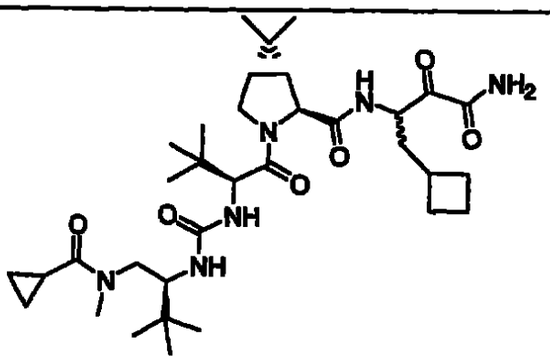
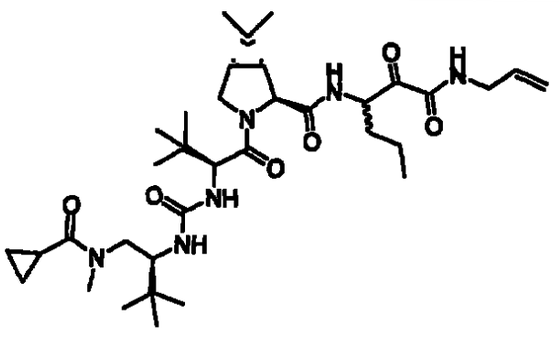
MS (ESI), m/z, 619(M+1), 312

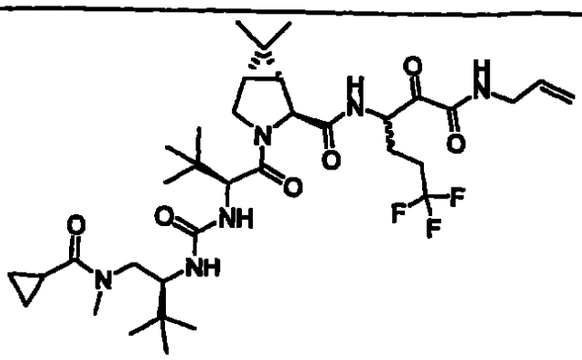
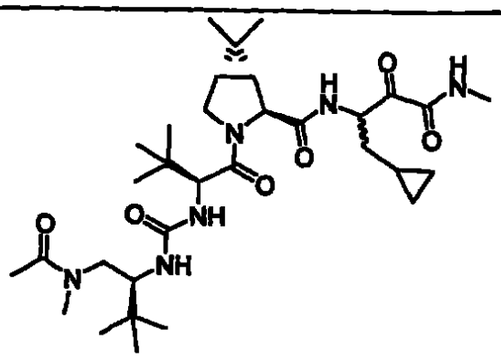
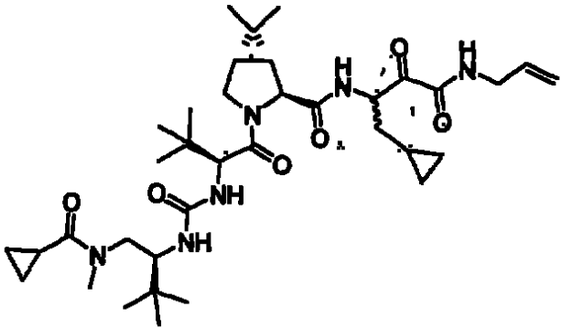
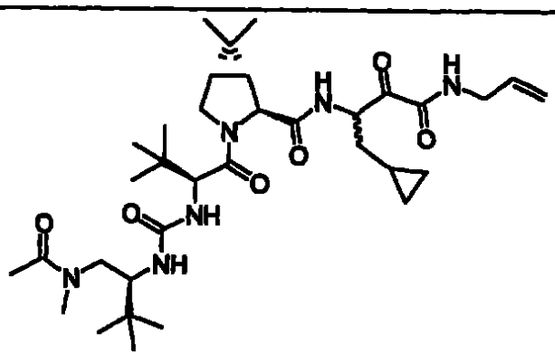
Compounds shown in the following **Table 4** were synthesized using similar reactions as shown in Examples above Range of KI* indicated A ≤75 nM, 75< B ≤250 nM, C>250 nM

Table 4

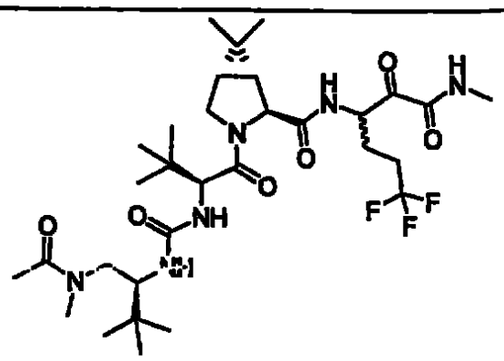
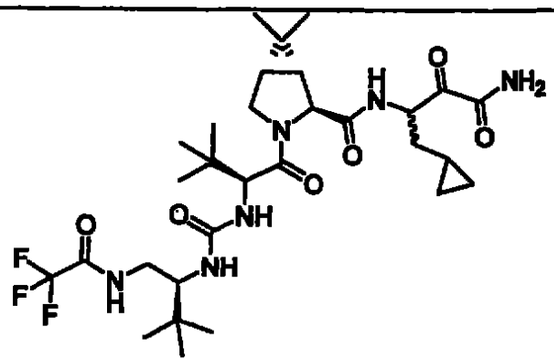
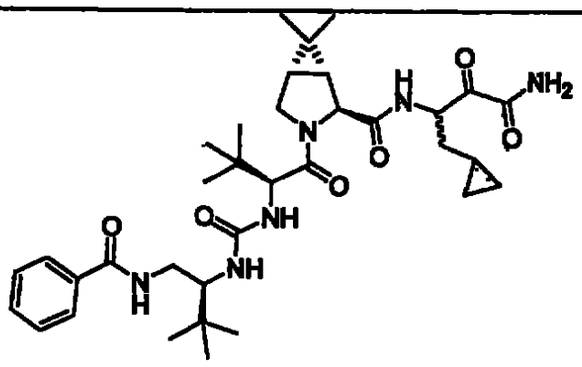
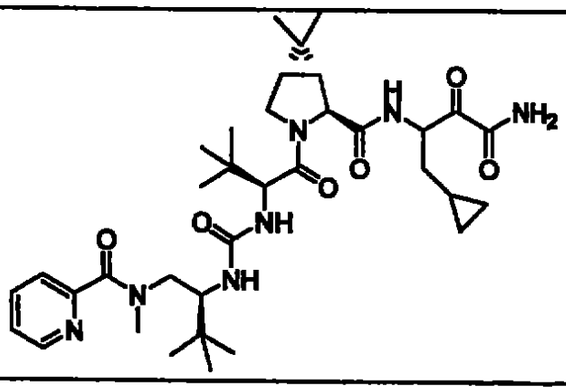
Entry	Structure	KI*
13001		A
13002		A
13003		B

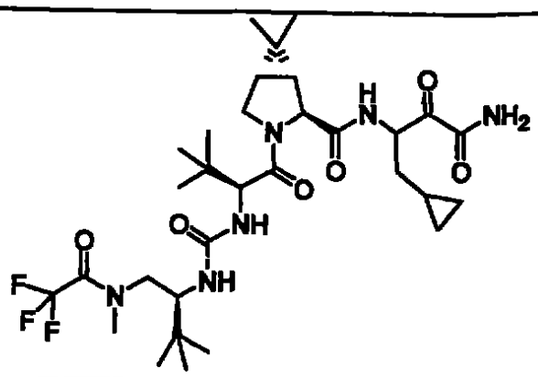
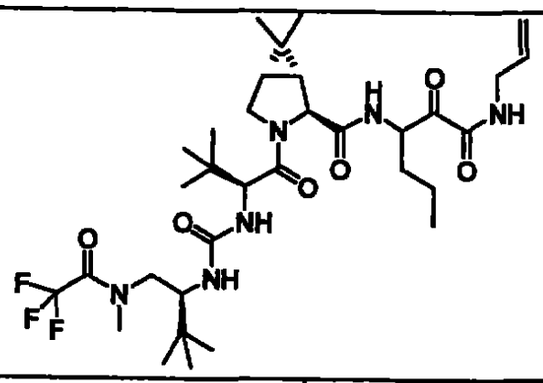
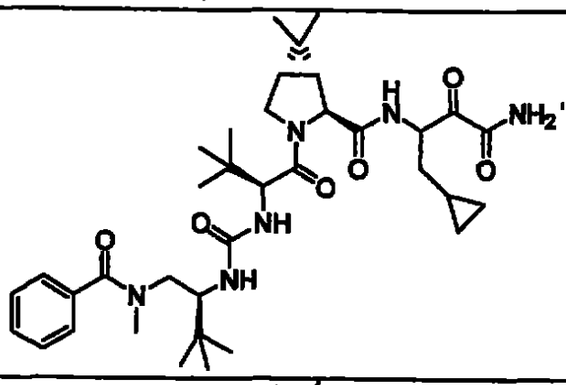
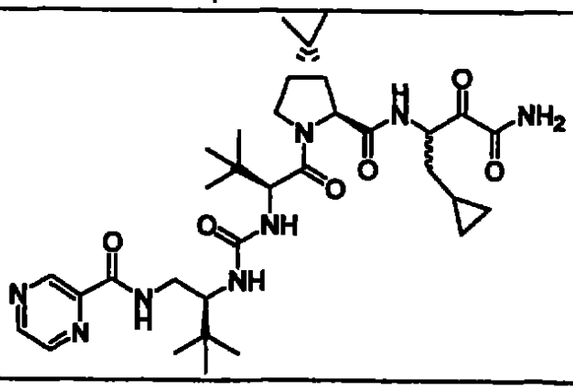
13004		A
13008		A
13009		A
13010		A

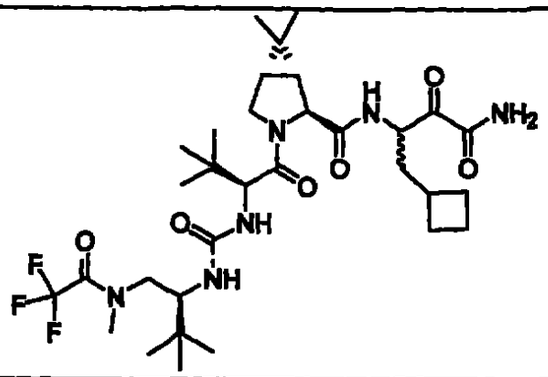
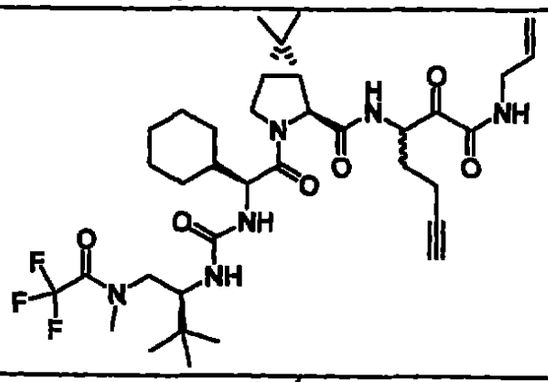
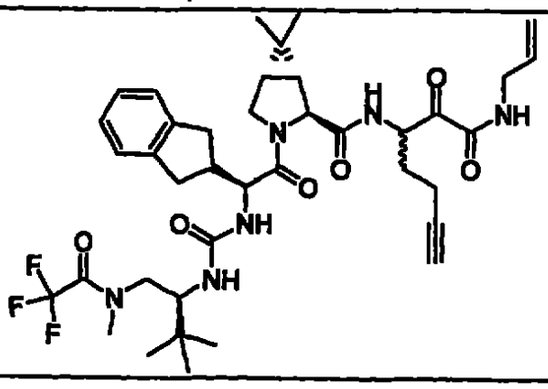
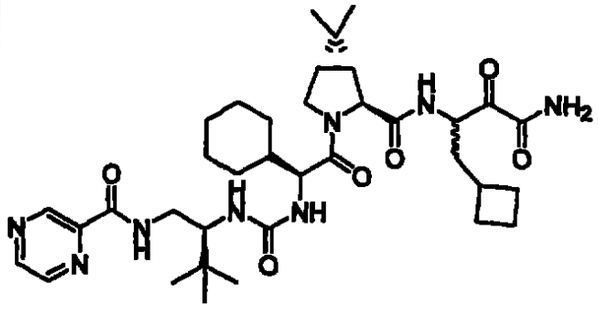
13011		A
13012		B
13013		A
13014		B

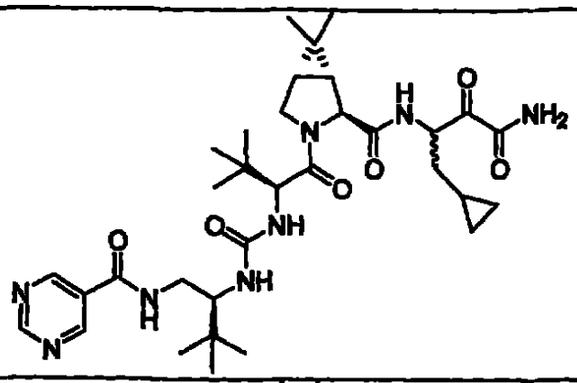
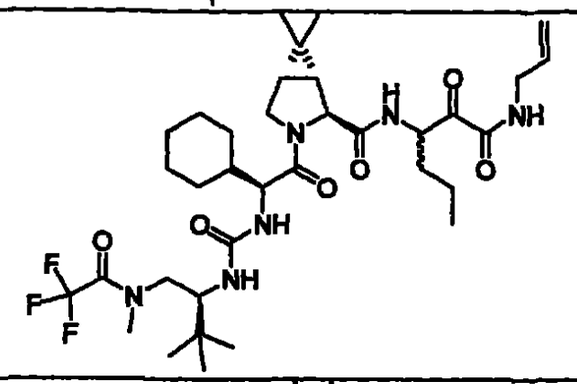
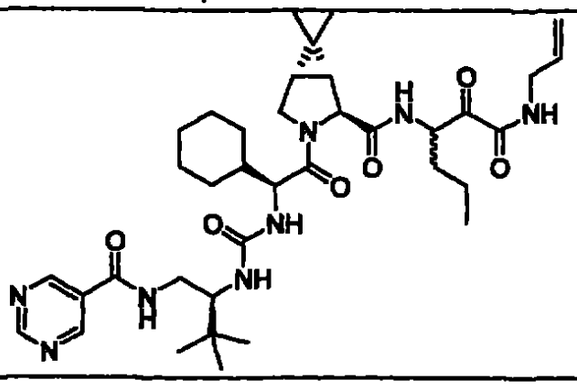
13015		B
13016		A
13017		C
13018		A

129
129

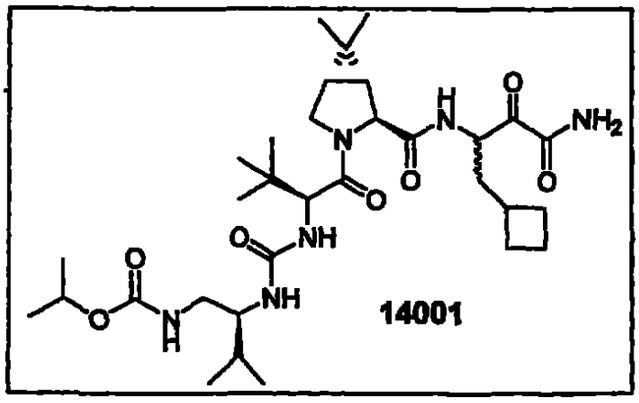
13019		A
13020		A
13021		A
13022		A

13023		A
13024		A
13025		A
13026		A

13027		A
13028		A
13029		A
13030		A

13031		A
13032		A
13033		A

Example-14: Synthesis of compound of Formula 14001



Step A.



14001a 14001b

A solution of **14001a** (10 0 g, 40 0 mmol Indofine chemicals) in toluene (150 mL) was treated with BH_3•DMS (~ 2 M, 40 mL) and heated at 90 °C overnight. The reaction mixture was cooled to 0° C and diluted with 2 M aq NaOH The reaction mixture was heated at 90 °C for 15 min The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) filtered concentrated in *vacuo* to yield 11 g of **14001b**

Step B

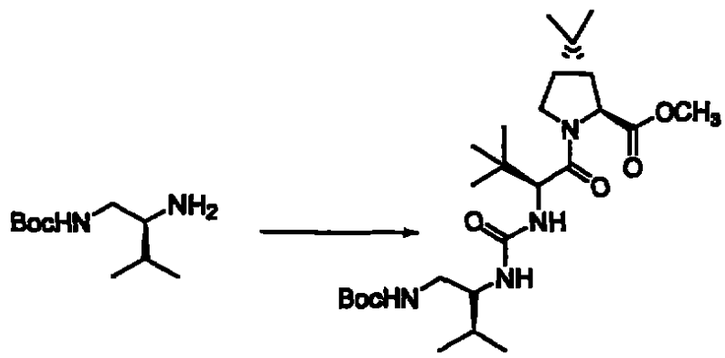


14001b 14001c

A solution of amine **14001b** (10 g, 42 0 mmol) in CH_2Cl_2/DMF (1 5) was cooled to -78 °C and treated with di-*tert*-butyldicarbonate (13 8 g, 63 mmol) The reaction mixture was stirred at rt for 48 h and diluted with aq 1 M HCl and extracted with EtOAc The combined organic layer was washed with aq $NaHCO_3$, brine, dried, filtered and concentrated in *vacuo* The residue was purified by chromatography (SiO_2, EtOAc/Hexanes 1 3) to yield 4 g of Boc protected compound

A solution of Boc-compound (6 g, 17 8 mmol) in methanol was treated with $Pd(OH)_2/C$ (1 89 g, 20% on C) and hydrogenated for 1h The reaction mixture was filtered through a plug of celite and concentrated in *vacuo* The residue **14001c** was used further reaction without purification

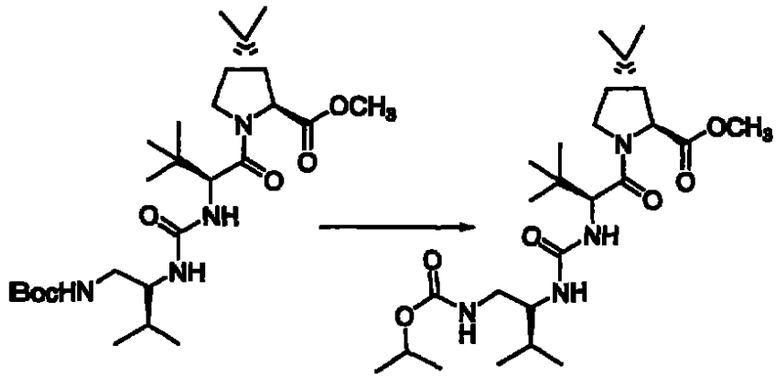
Step C



14001c 14001d

A solution of deprotected amine **14001c** (3 6 g, 17 8 mmol) in CH_2Cl_2/DMF (1 1, 20 mL) was treated with 4-nitrophenylcarbamate 1 16 (7 97 g, 17 8 mmol), NMM (4 g, 14 0 mmol) and stirred at rt overnight The reaction mixture was concentrated in *vacuo* diluted with EtOAc and washed with aq HCl, aq saturated $NaHCO_3$, brine, dried ($MgSO_4$), filtered, and purified by chromatography (SiO_2, Hexanes/EtOAc 3 7) to yield **14001d**

Step D

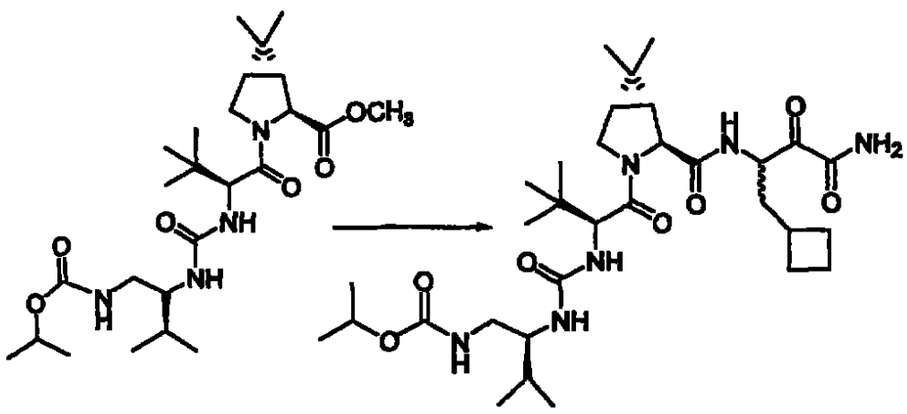


14001d **14001e**

A solution of **14001d** was dissolved in 4 M HCl in dioxane and stirred at rt for 2 h. The reaction mixture was concentrated in *vacuo* and used in further reactions without purification

The ammonium salt (100 mg, 0 224 mmol) dissolved in DMF/CH_2Cl_2 (1 1) was treated with isopropylchloroformate (54 mg, 0 448 mmol) and Et_3N (45 mg, 0 448 mmol) at 0 °C and stirred at rt overnight The reaction mixture was diluted with EtOAc and the organic layer was washed with aq 1M HCl, aq saturated $NaHCO_3$, and brine It was dried ($MgSO_4$) filtered, concentrated in *vacuo* and used as it is in the next reaction

Step E



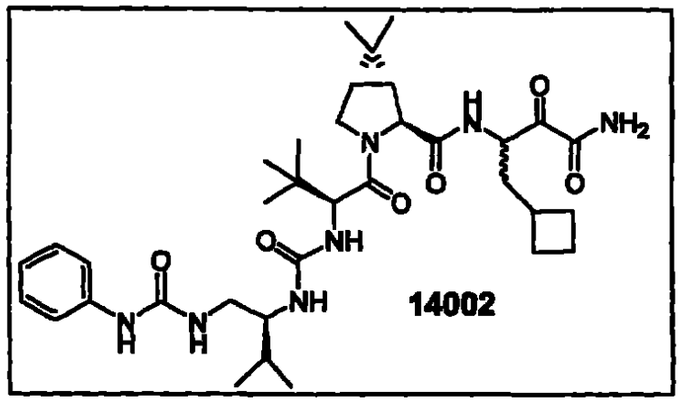
132

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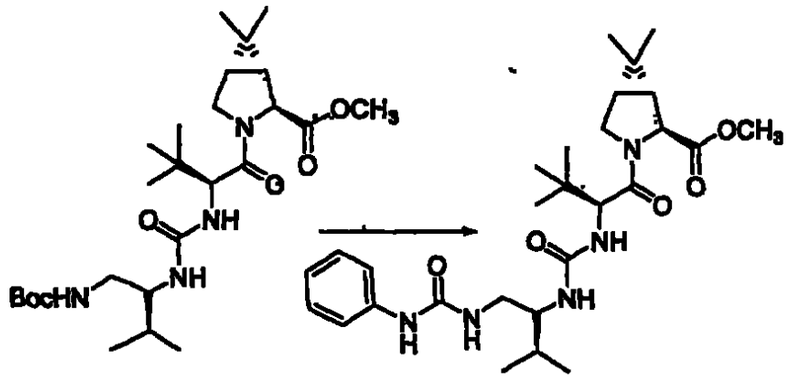
14001e 14001

Intermediate 14001e was converted to 14001 by coupling to intermediate 10 11 followed by Moffett oxidation identical to the procedures described in preparative example 6 of synthesis of 11001, Step D and Step E

Example 15 Synthesis of compound of Formula 14002



Step A.

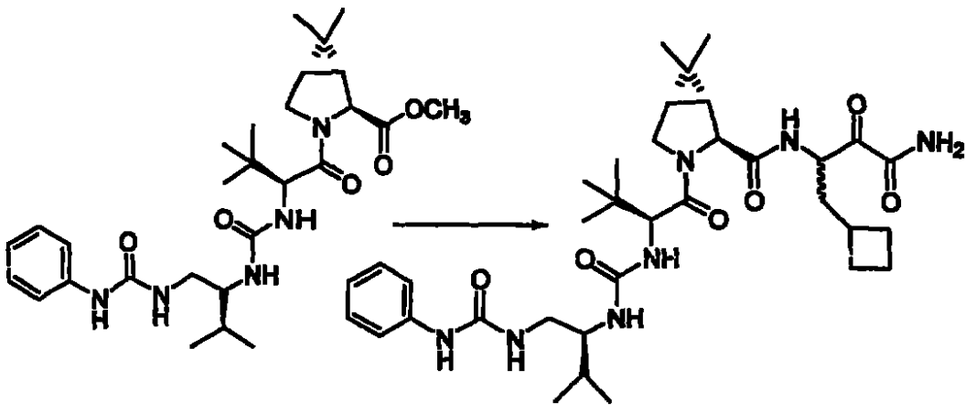


14001d 14002a

A solution of 14001d was dissolved in 4 M HCl in dioxane and stirred at rt for 2 h The reaction mixture was concentrated in *vacuo* and used in further reactions without purification

The ammonium salt (100 mg, 0 224 mmol) dissolved in DMF/CH_2Cl_2 (1 1) was treated with phenylisocyanate (53 mg, 0 448 mmol) and Et_3N (45 mg, 0 448 mmol) at 0 °C and stirred at rt overnight. The reaction mixture was diluted with EtOAc and the organic layer was washed with aq 1M HCl, aq saturated $NaHCO_3$, and brine It was dried ($MgSO_4$) filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hex 2 3) to yield 14002a.

Step B

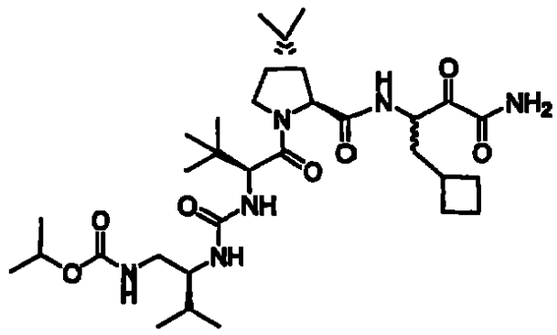
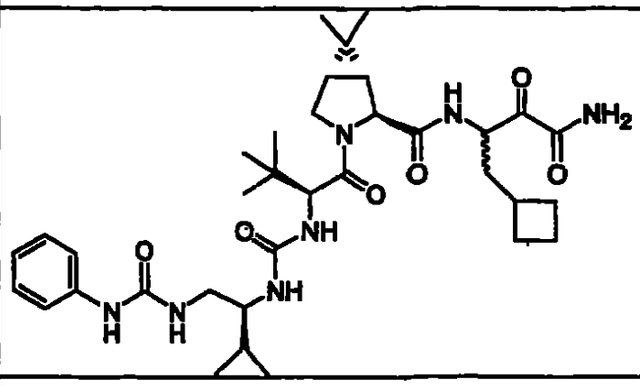
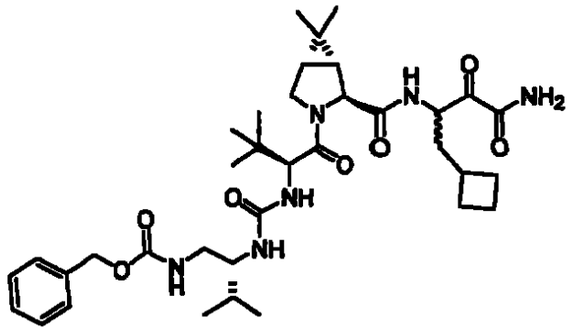
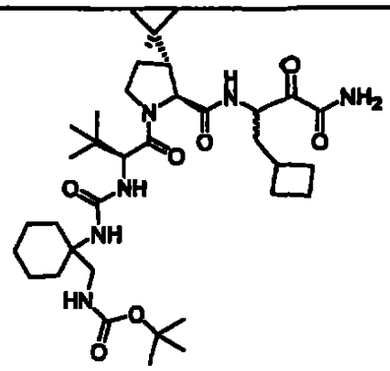


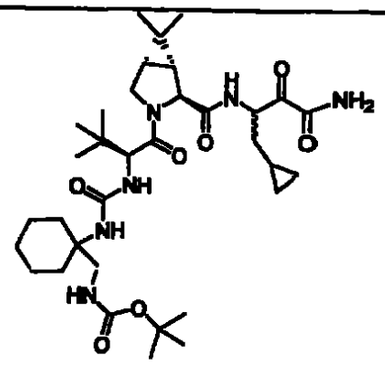
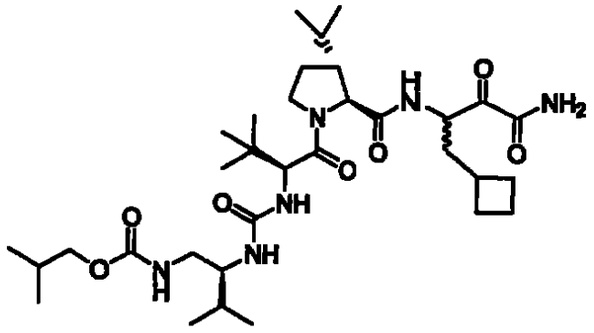
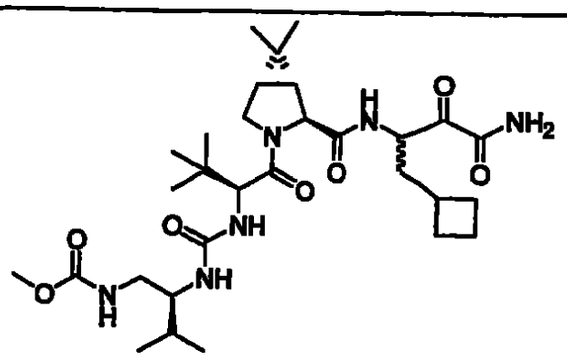
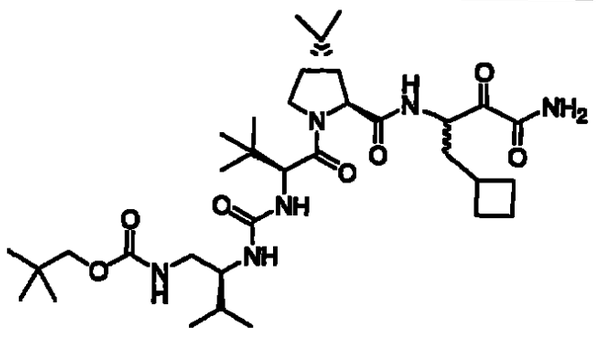
14002a 14002

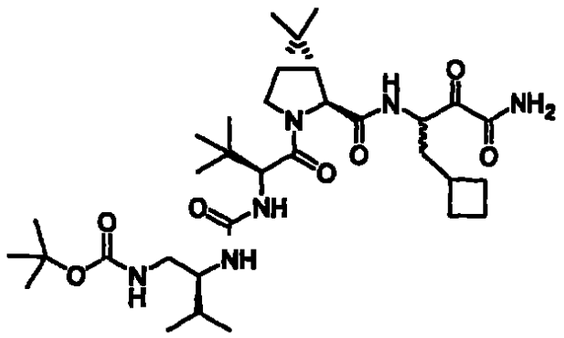
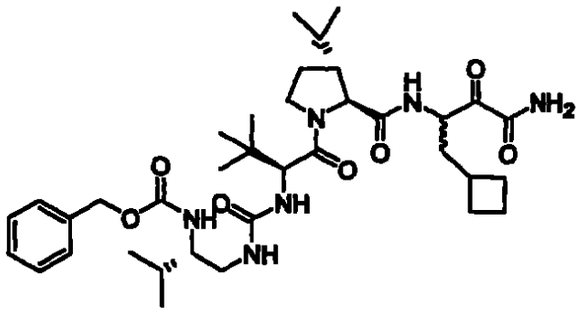
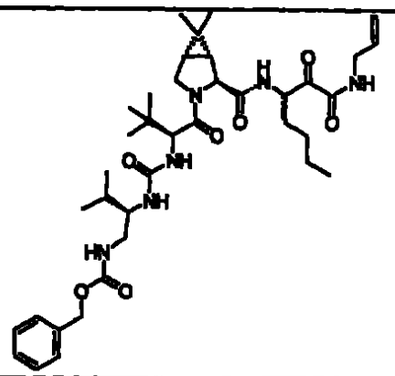
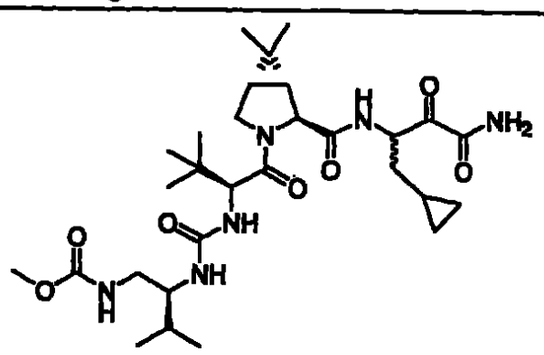
Intermediate **14002a** was converted to **14002** by coupling to intermediate **10 11** followed by Moffett oxidation identical to the procedures described in preparative example 6 of synthesis of **11001**, Step D and Step E Compounds shown in the following **Table 5** were synthesized using similar reactions as shown in Examples above Ki* Range Indicated A ≤75 nM, 75<B ≤250 nM, C>250 nM

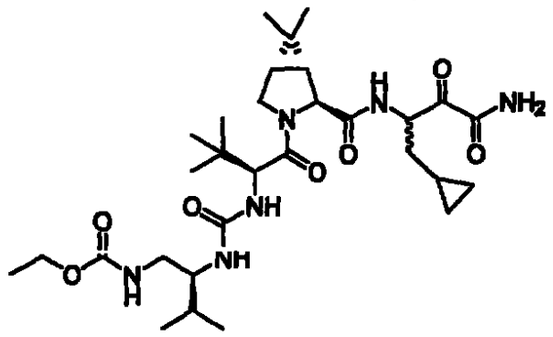
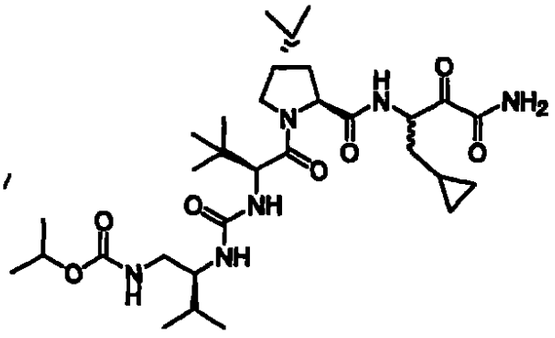
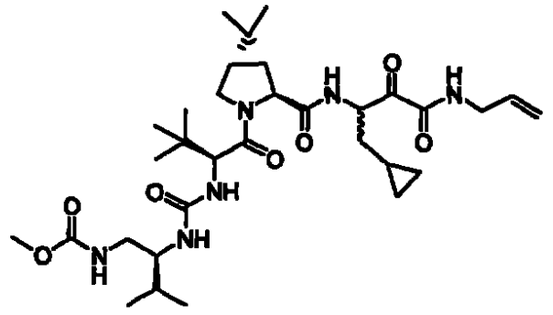
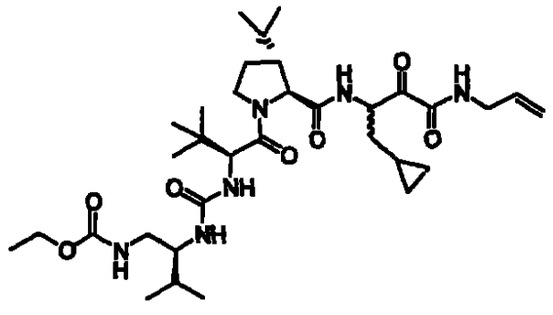
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Table 5

Entry	Structure	K_i*
14001		A
14002		A
14003		B
14004		A

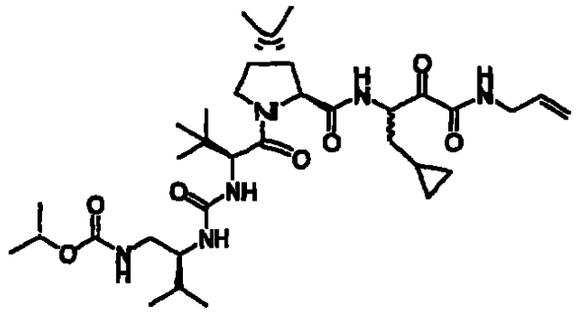
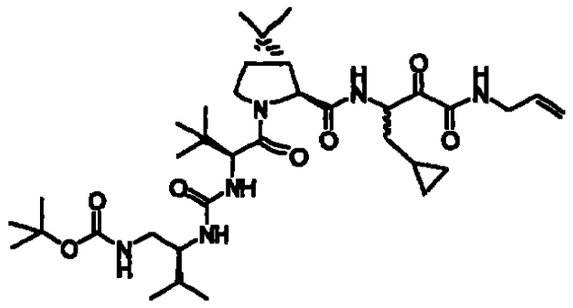
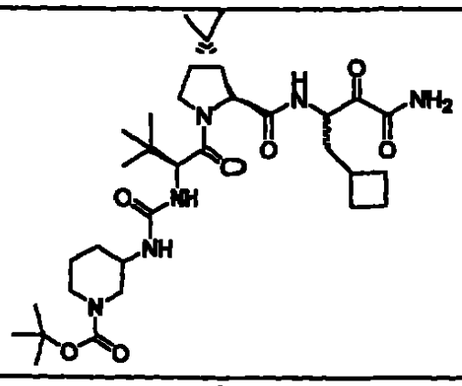
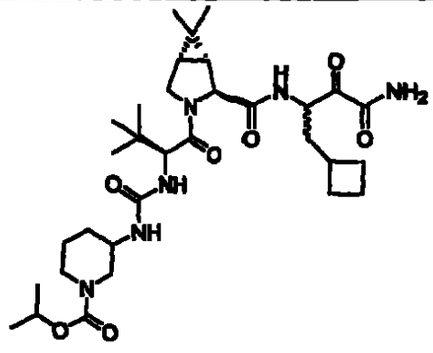
14005		A
14009		A
14010		A
14011		A

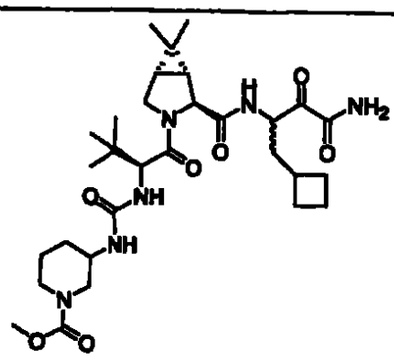
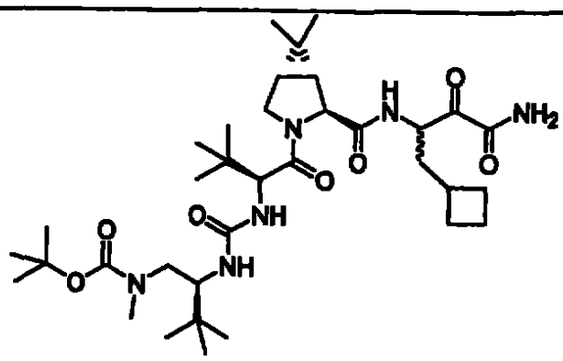
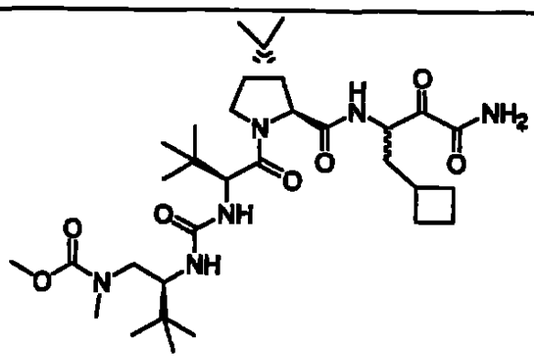
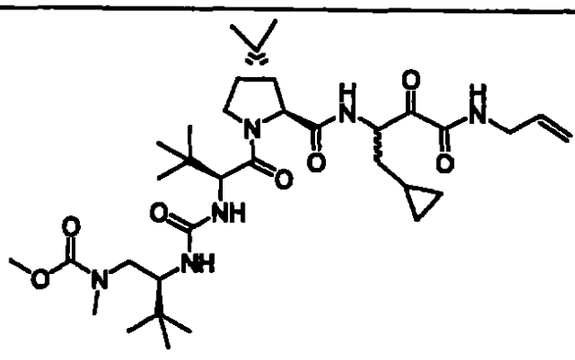
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14016		B
14017		B
14019		A

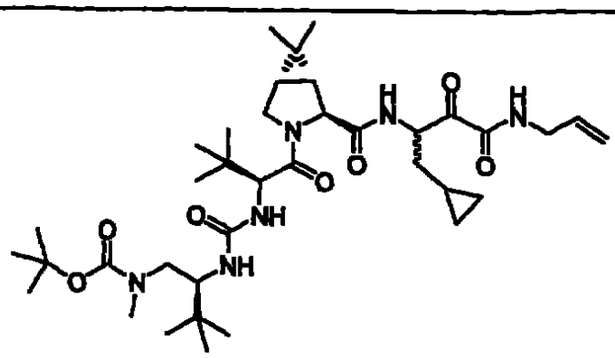
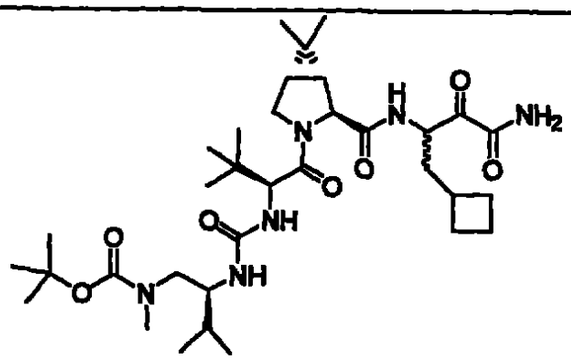
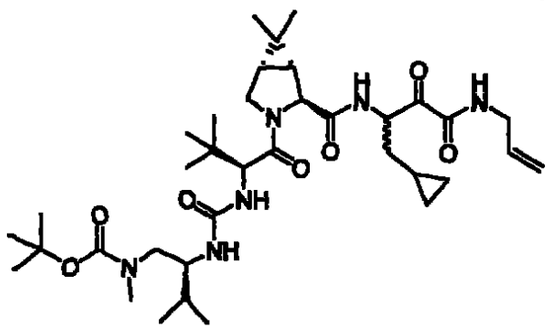
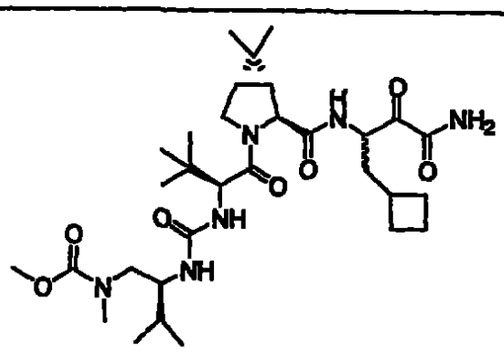
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14021		A
14022		A
14023		B

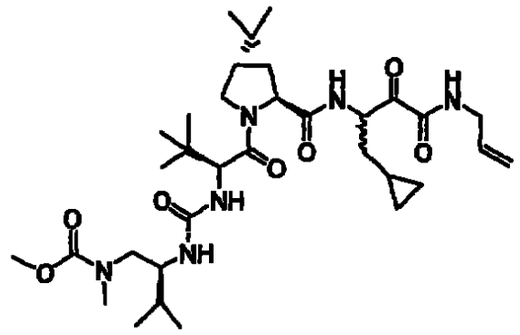
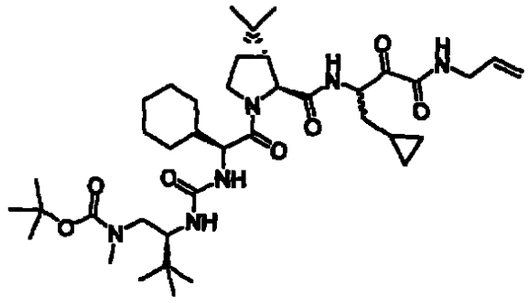
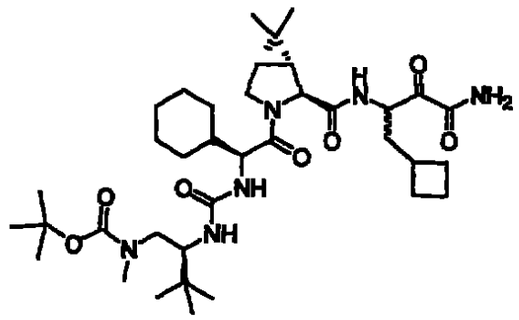
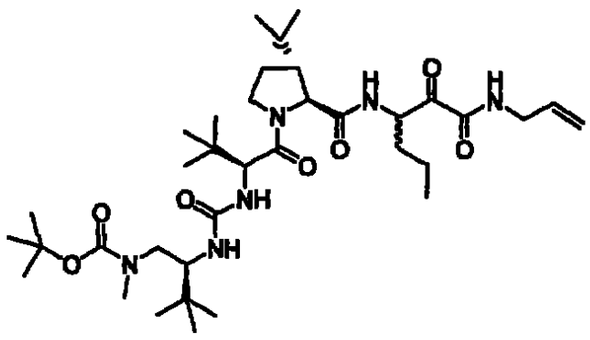
135

135

14024		B
14025		C
14026		C
14027		B

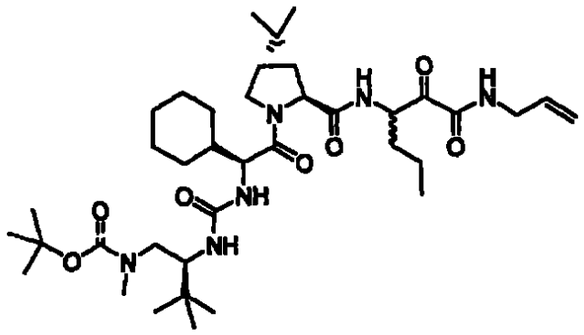
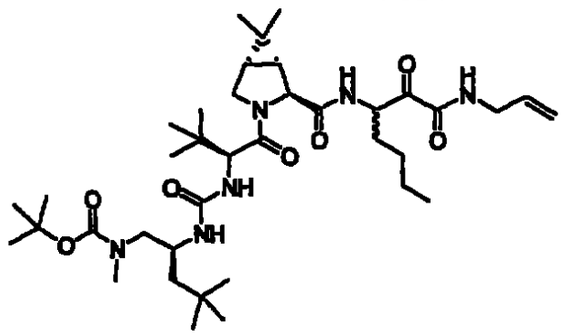
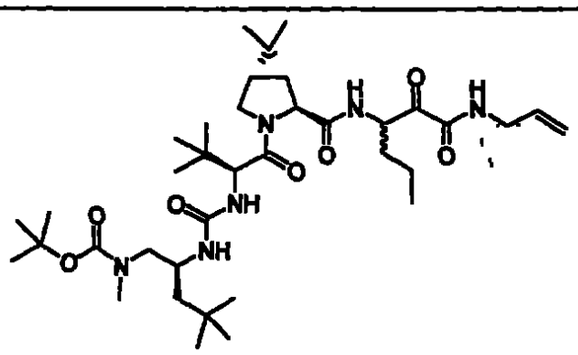
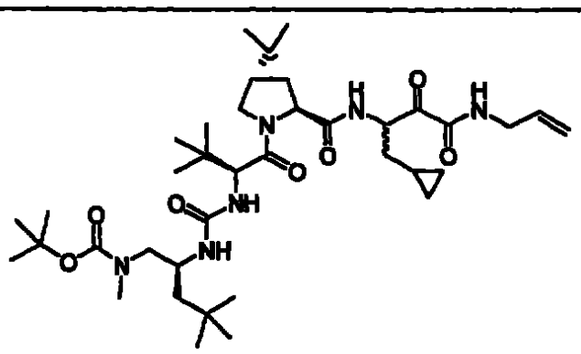
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14029		C
14030		A
14031		B

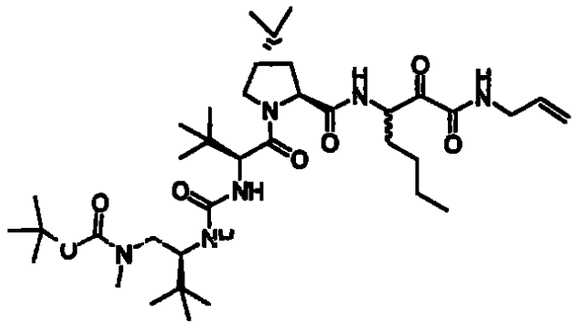
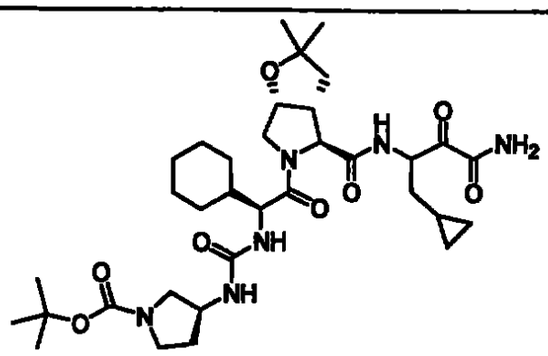
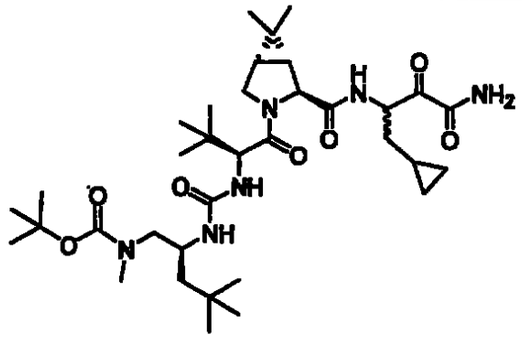
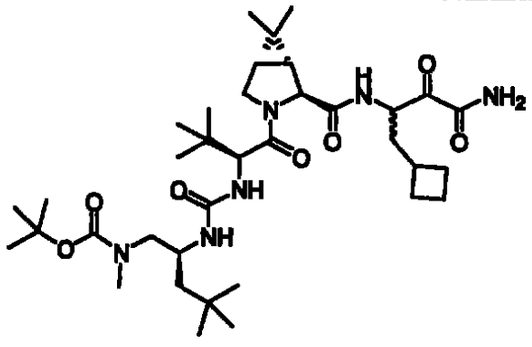
14032		C
14033		B
14034		C
14035		A

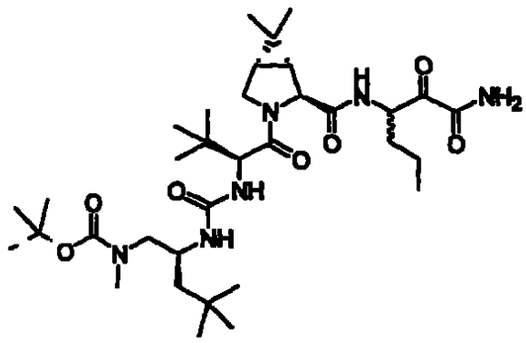
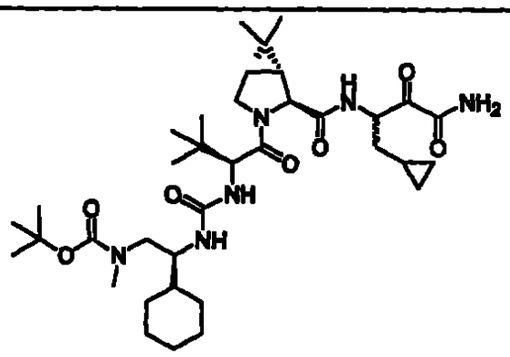
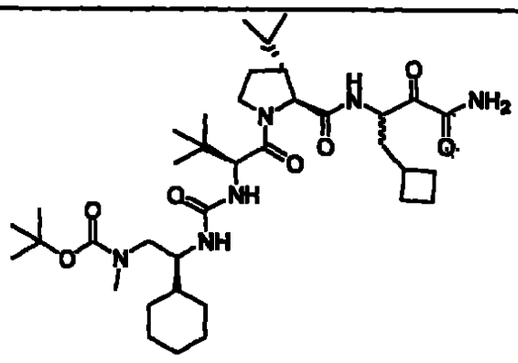
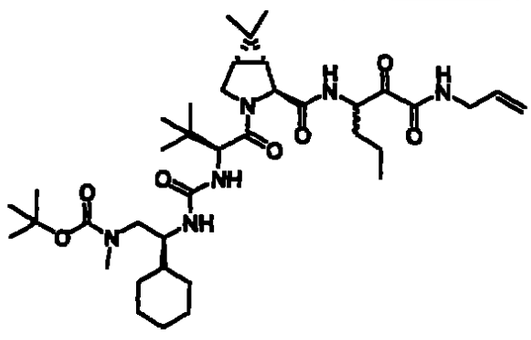
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14037		C
14038		B
14039		C

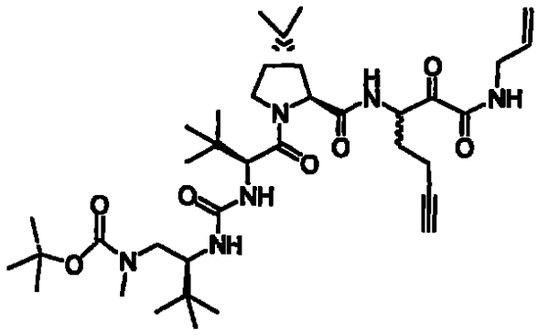
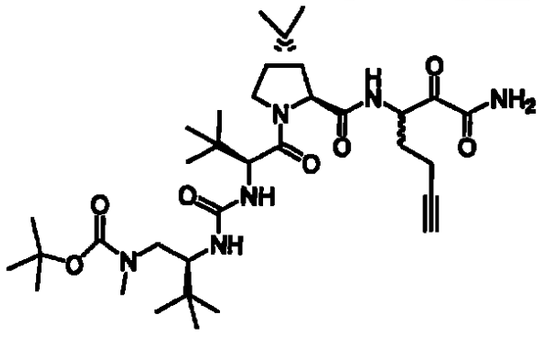
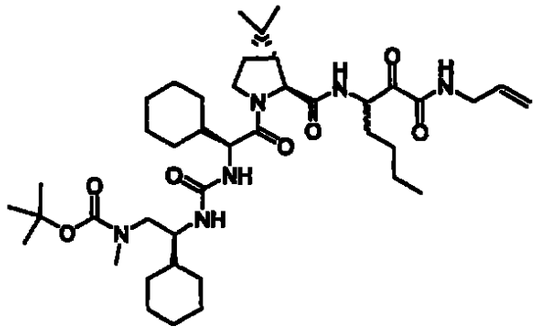
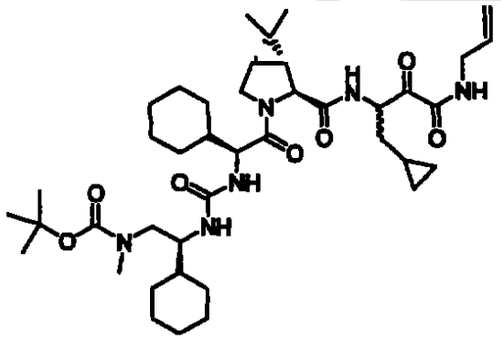
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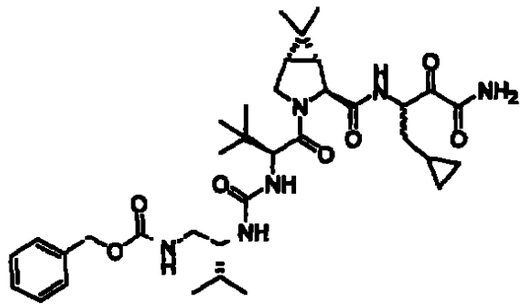
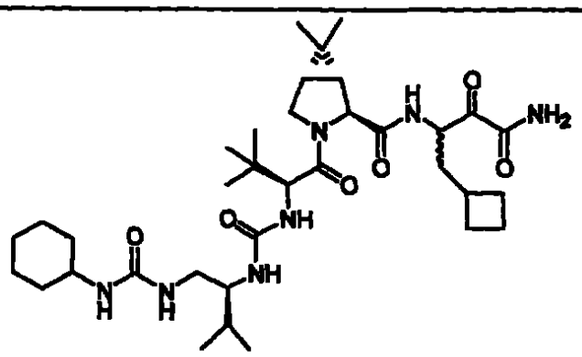
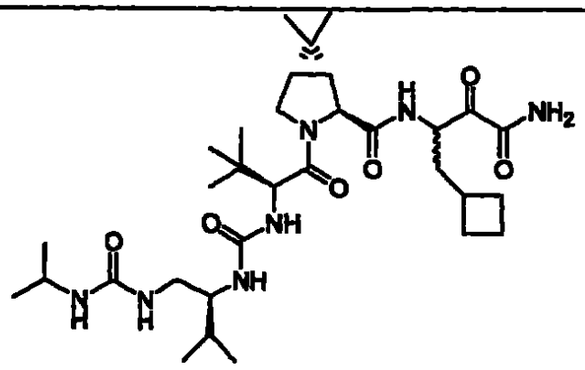
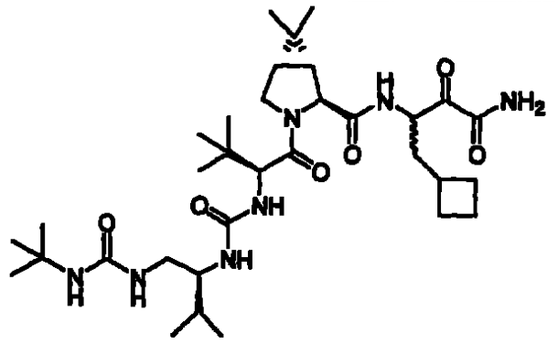
137

14040		C
14041		C
14042		C
14043		C

14044		C
14045		C
14046		C
14047		C

14048		C
14049		C
14050		C
14051		C

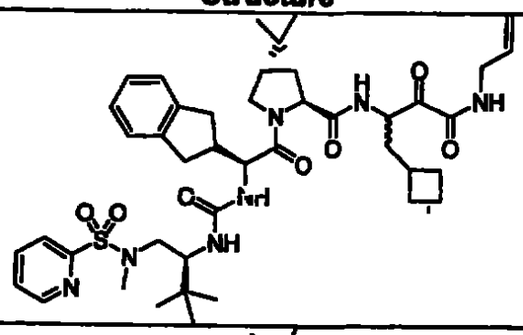
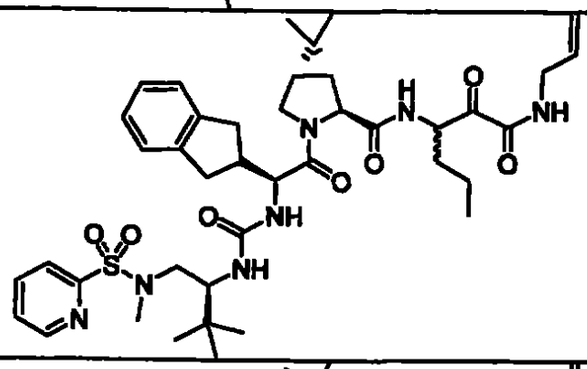
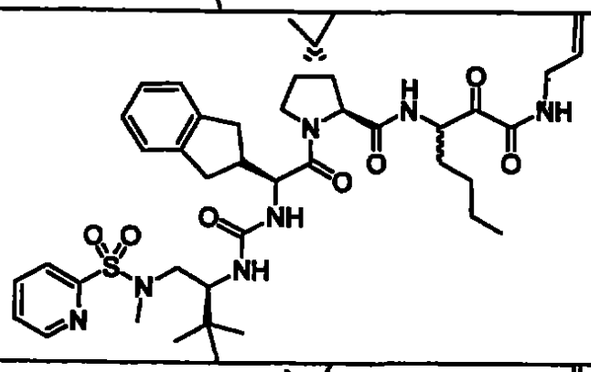
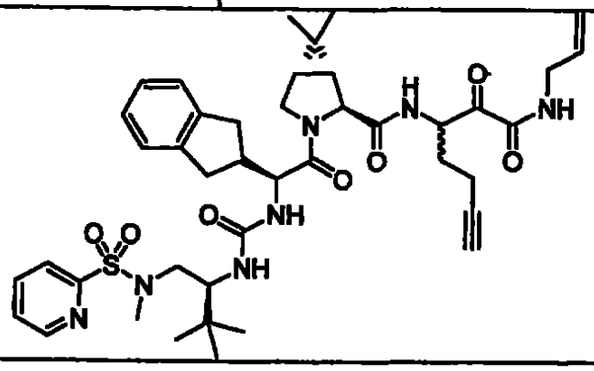
14052		C
14053		C
14054		C
14055		C

14056		A
14057		A
14058		A
14059		A

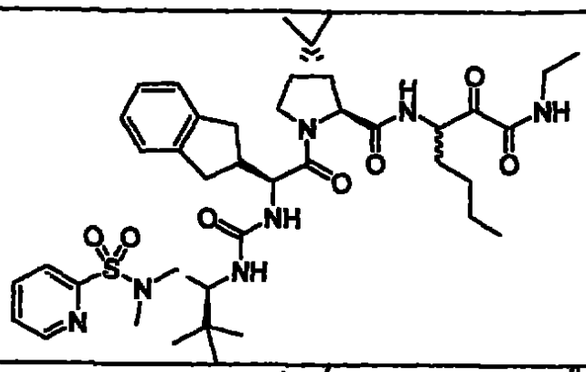
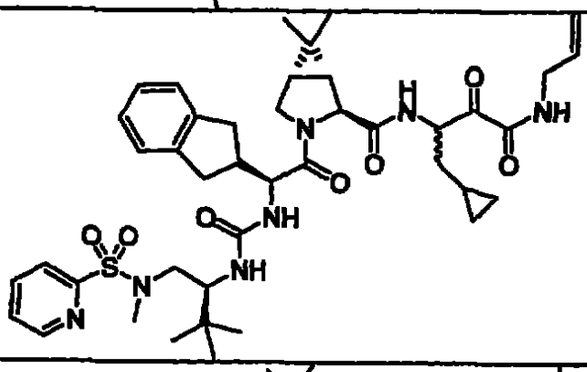
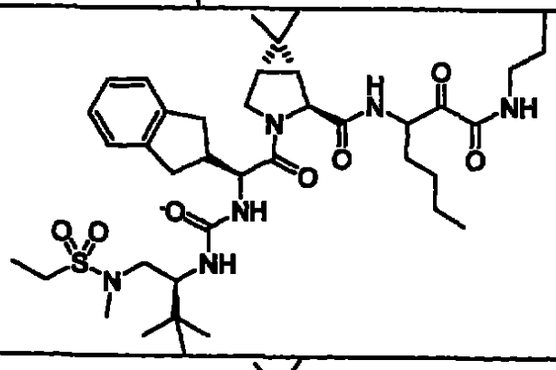
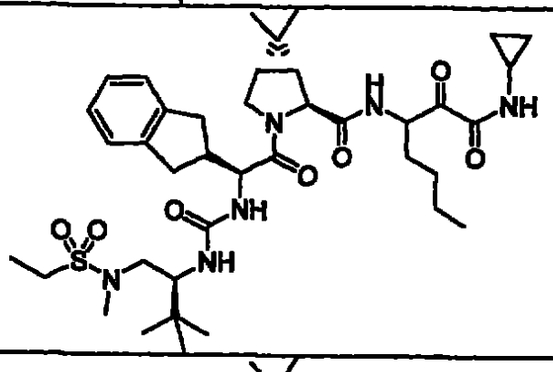
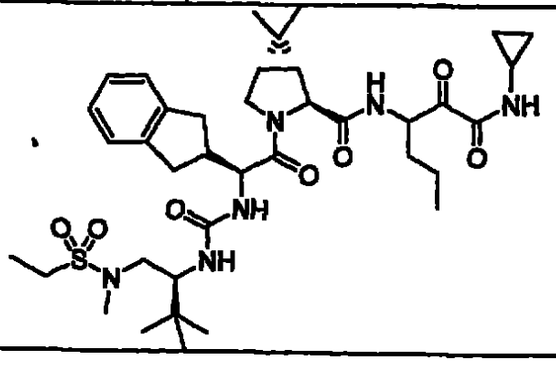
Additional compounds of the present invention are shown in Table 5A.

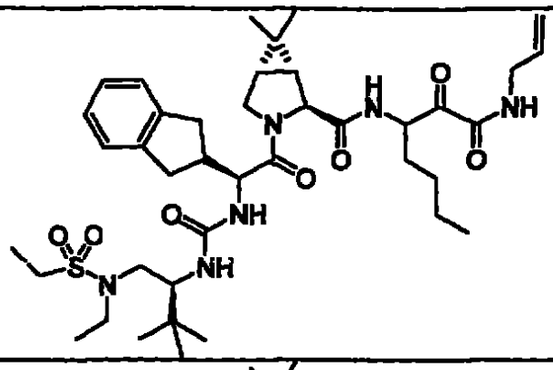
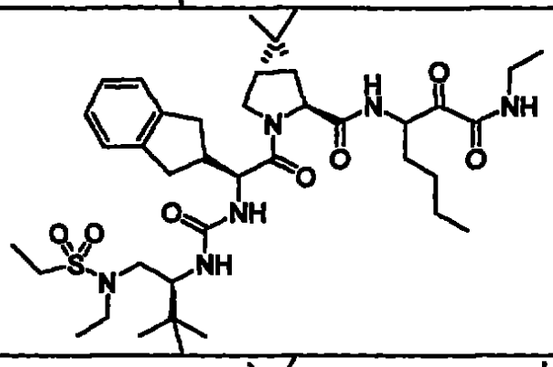
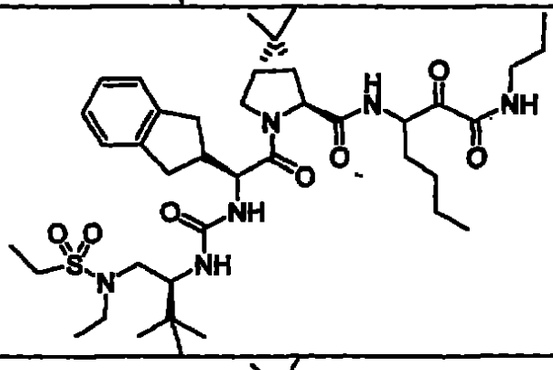
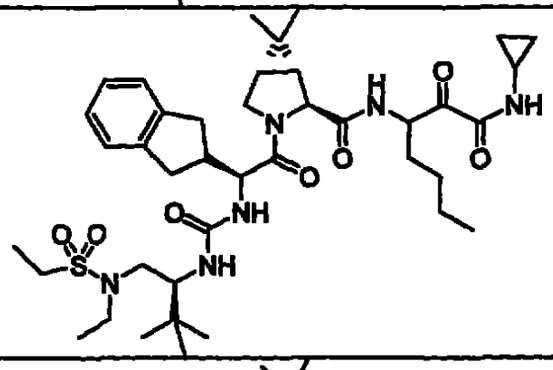
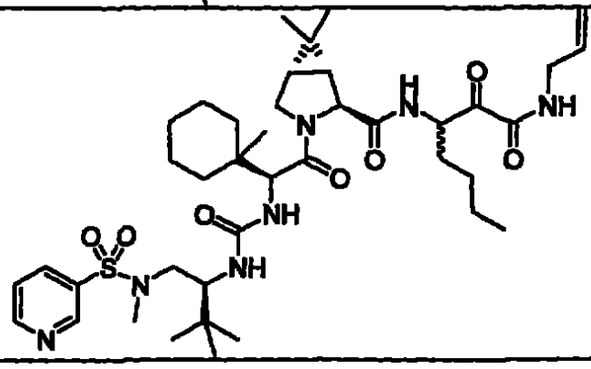
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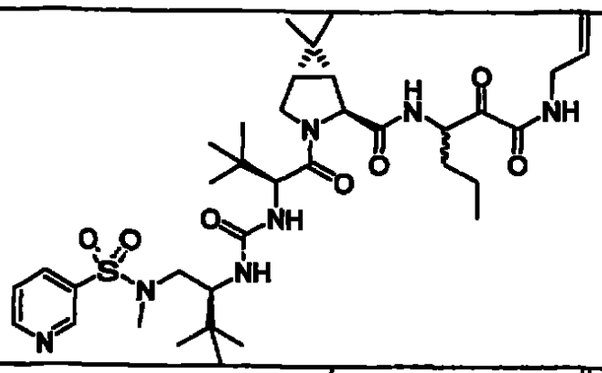
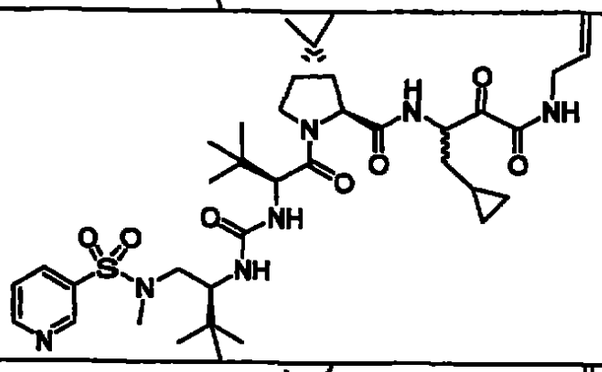
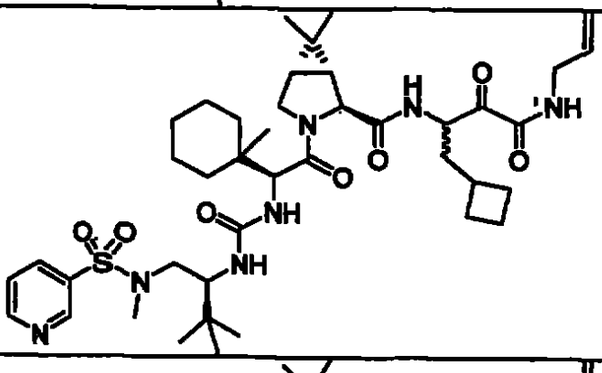
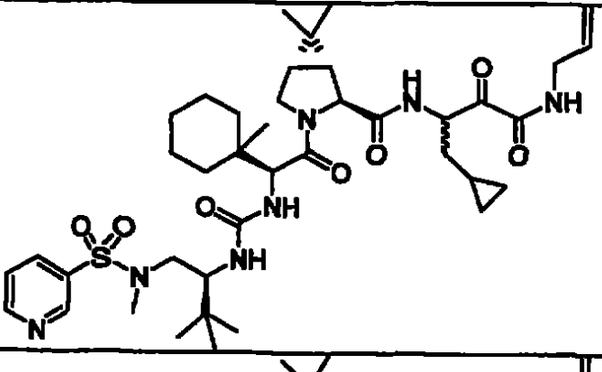
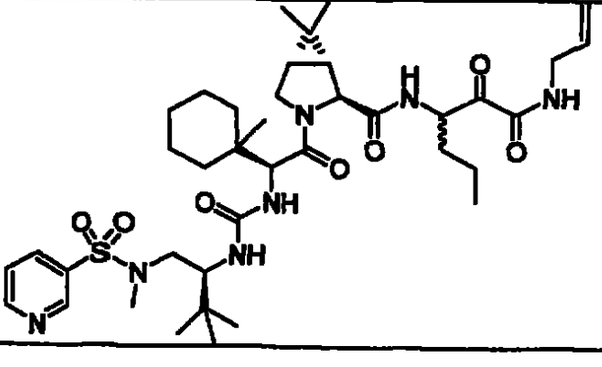
Table 5A

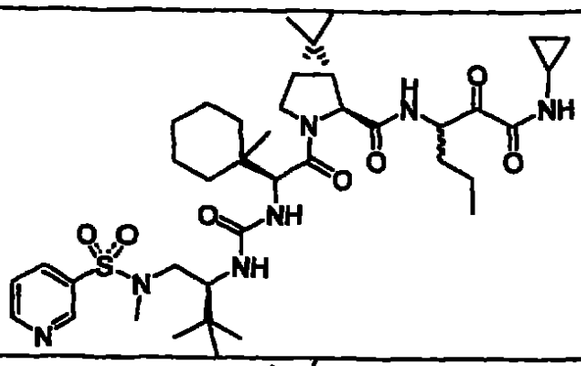
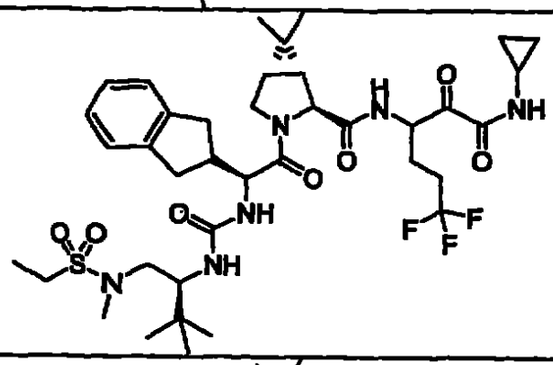
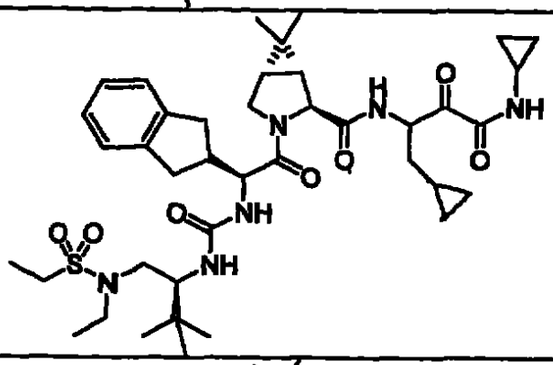
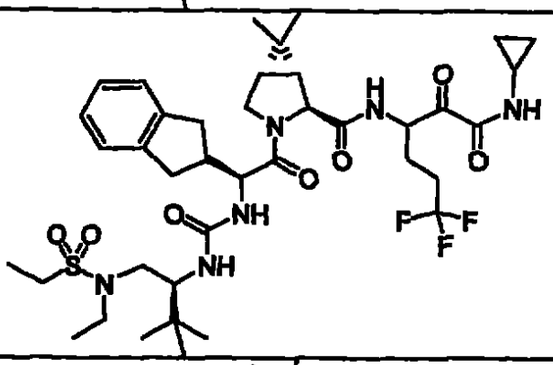
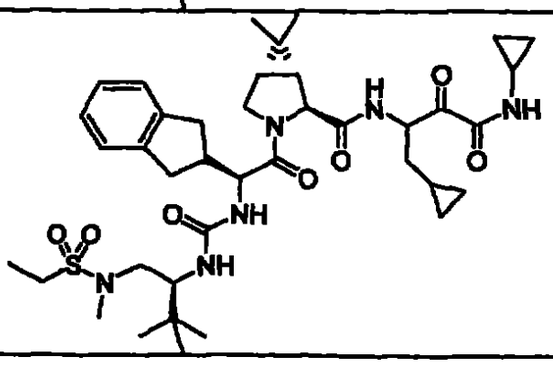
Entry	Structure	K_i*
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11394		A
11395		A

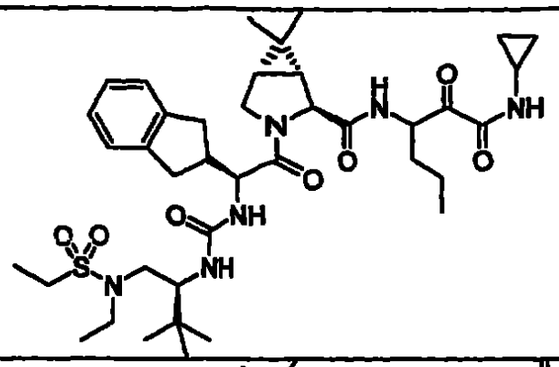
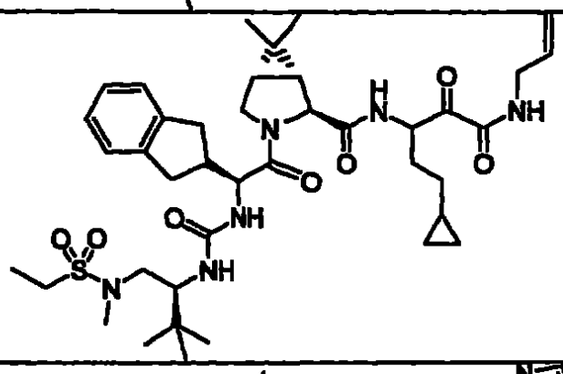
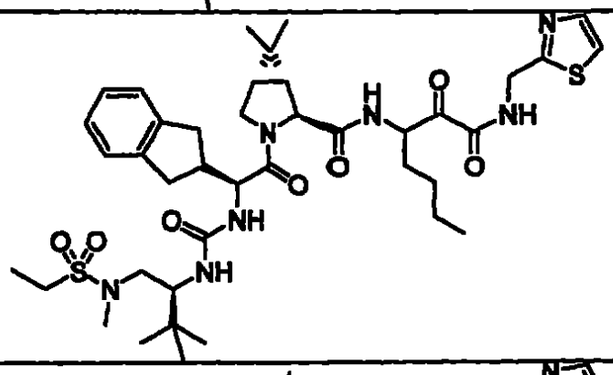
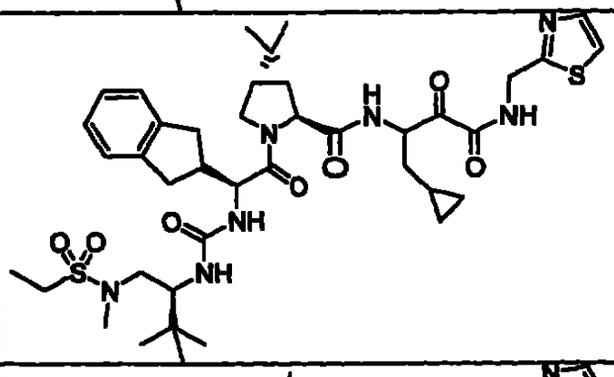
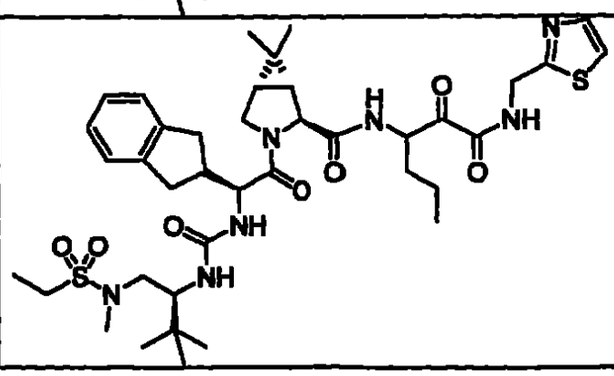
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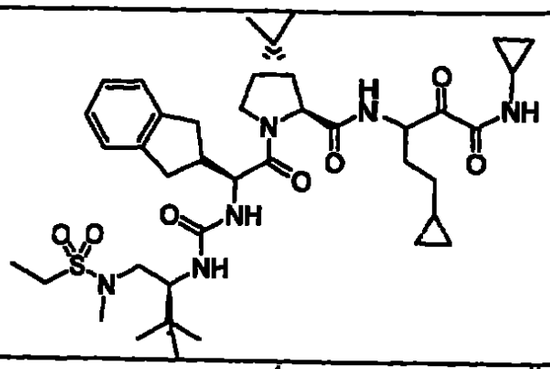
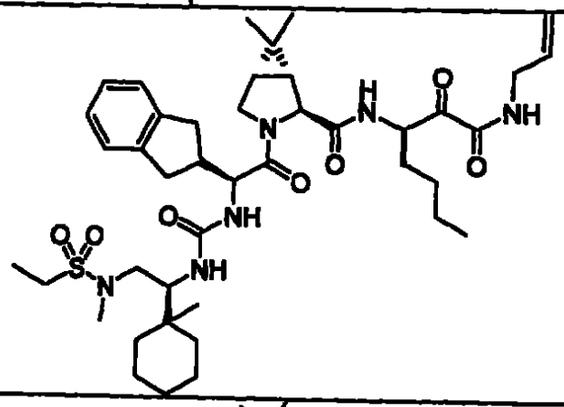
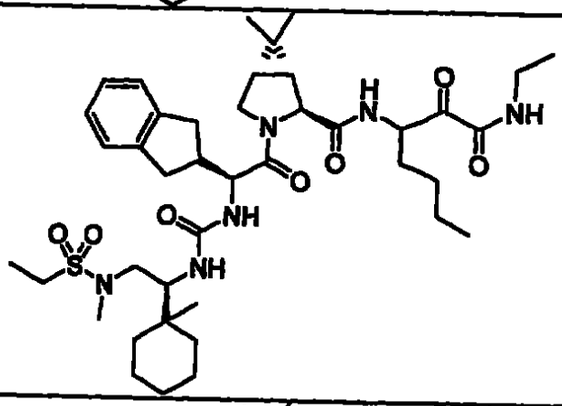
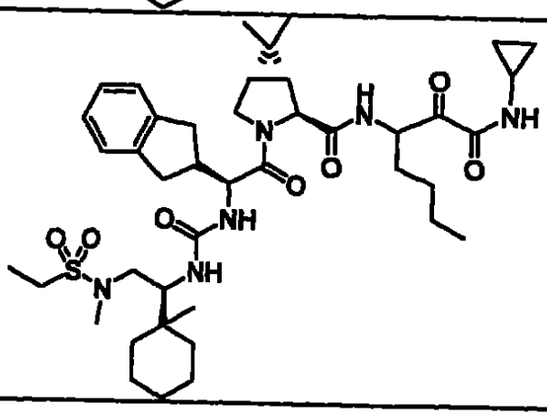
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11397		B
11398		A
11399		A
11400		A

11401		A
11402		A
11403		A
11404		A
11405		A

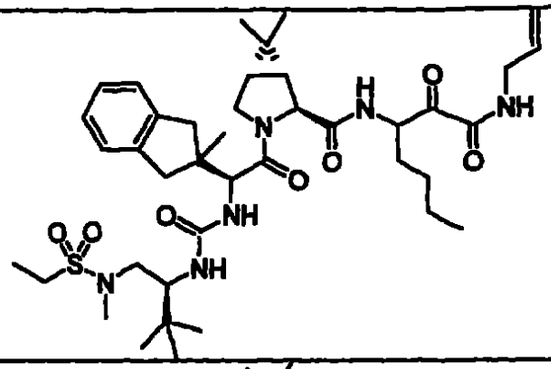
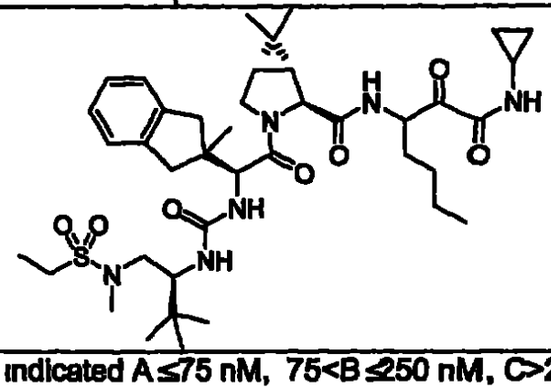
11406		A
11407		A
11408		A
11409		A
11410		A

11411		A
11412		A
11413		A
11414		A
11415		A

11416		A
11417		A
11418		A
11419		A
11420		A

11421		A
11422		A
11423		A
11424		A

143

11425		A
11426		A

Range of Ki* indicated A≤75 nM, 75<B≤250 nM, C>250 nM

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

Assay for HCV Protease Inhibitory Activity

Spectrophotometric Assay: Spectrophotometric assay for the HCV serine protease can be performed on the inventive compounds by following the procedure described by R Zhang *et al*, *Analytical Biochemistry*, 270 (1999) 268-275, the disclosure of which is incorporated herein by reference The assay based on the proteolysis of chromogenic ester substrates is suitable for the continuous monitoring of HCV NS3 protease activity The substrates are derived from the P side of the NS5A-NS5B junction sequence (Ac-DTEDVVX(Nva), where X = A or P) whose C-terminal carboxyl groups are esterified with one of four different chromophoric alcohols (3- or 4-nitrophenol, 7-hydroxy-4-methyl-coumarin, or 4-phenylazophenol) Illustrated below are the synthesis, characterization and application of these novel spectrophotometric ester substrates to high throughput screening and detailed kinetic evaluation of HCV NS3 protease inhibitors

Materials and Methods

Materials Chemical reagents for assay related buffers are obtained from Sigma Chemical Company (St Louis, Missouri) Reagents for peptide synthesis were from Aldrich Chemicals, Novabiochem (San Diego, California), Applied Biosystems (Foster City, California) and Perseptive Biosystems (Framingham, Massachusetts) Peptides are synthesized manually or on an 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 that wavelength yielding the maximum fractional difference in absorbance between substrate and product (product OD - substrate OD)/substrate OD)

Protease Assay HCV protease assays are performed at 30°C using a 200 µl reaction mix in a 96-well microtiter plate Assay buffer conditions (25 mM MOPS pH 6 5, 300 mM NaCl, 10% glycerol, 0 05% lauryl maltoside, 5 µM EDTA and 5 µM DTT) are optimized for the NS3/NS4A heterodimer (D L Sali *et al, Ibid*)) Typically, 150 µl mixtures of buffer, substrate and inhibitor are placed in wells (final concentration of DMSO ≤4 % v/v) and allowed to preincubate at 30 °C for approximately 3 minutes Fifty µls of prewarmed

protease (12 nM, 30°C) in assay buffer, is then used to initiate the reaction (final volume 200 µl) The plates are monitored over the length of the assay (60 minutes) for change in absorbance at the appropriate wavelength (340 nm for 3-Np and HMC, 370 nm for PAP, and 400 nm for 4-Np) using a Spectromax Plus microtiter plate reader equipped with a monochrometer (acceptable results can be obtained with plate readers that utilize cutoff filters) Proteolytic cleavage of the ester linkage between the Nva and the chromophore is monitored at the appropriate wavelength against a no enzyme blank as a control for non-enzymatic hydrolysis The evaluation of substrate kinetic parameters is performed over a 30-fold substrate concentration range (~6-200 µM) Initial velocities are determined using linear regression and kinetic constants are obtained by fitting the data to the Michaelis-Menten equation using non-linear regression analysis (Mac Curve Fit 1 1, K Raner) Turnover numbers (k_{cat}) are calculated assuming the enzyme is fully active

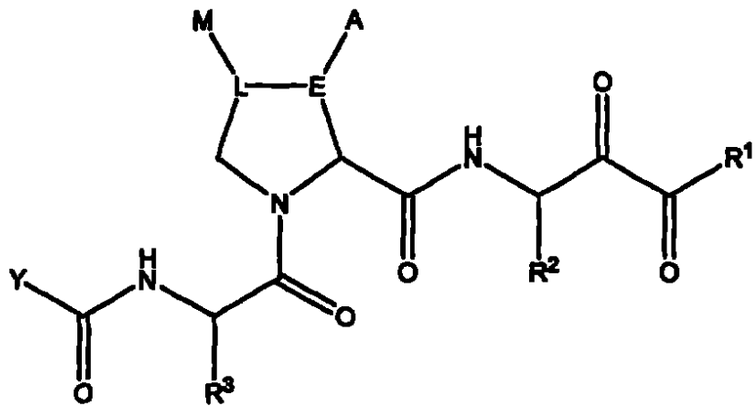
Evaluation of Inhibitors and Inactivators The inhibition constants (K_i) for the competitive inhibitors Ac-D-(D-Gla)-L-I-(Cha)-C-OH (27), Ac-DTEDVVA(Nva)-OH and Ac-DTEDVVP(Nva)-OH are determined experimentally at fixed concentrations of enzyme and substrate by plotting v_o/v_i vs inhibitor concentration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

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

Claims

What is claimed is

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

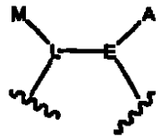


Formula I

wherein.

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

A and M can be the same or different, each being independently selected from R, NR^9R^{10}, SR, SO_2R, and halo, or A and M are connected to each other (in other words, A-E-L-M taken together) such that the moiety



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

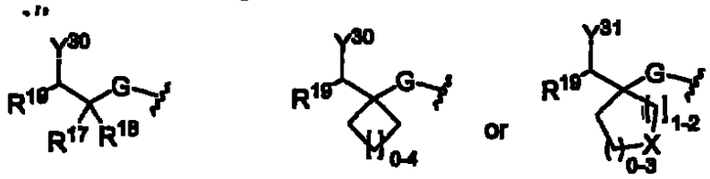
E is C(H) or C(R),

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

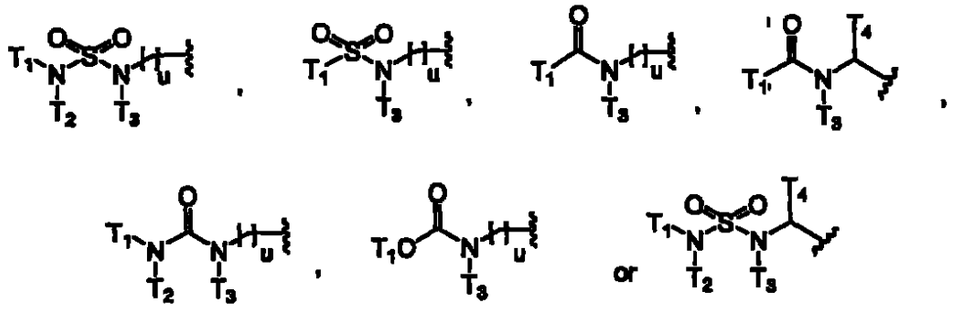
R, R', R^2, and R^3 can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-,

alkynyl-, cycloalkyl-, heteroalkyl-, heterocyclyl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocyclyl)alkyl-, aryl-alkyl-, and heteroaryl-alkyl-, or alternately R and R' in NRR' are connected to each other such that NR^9R^{10} forms a four to eight-membered heterocyclyl,

Y is selected from the following moieties



wherein Y^{30} and Y^{31} are selected from



where u is a number 0-6,

X is selected from O, NR^{15}, $NC(O)R^{16}$, S, S(O) and SO_2,

G is NH or O, and

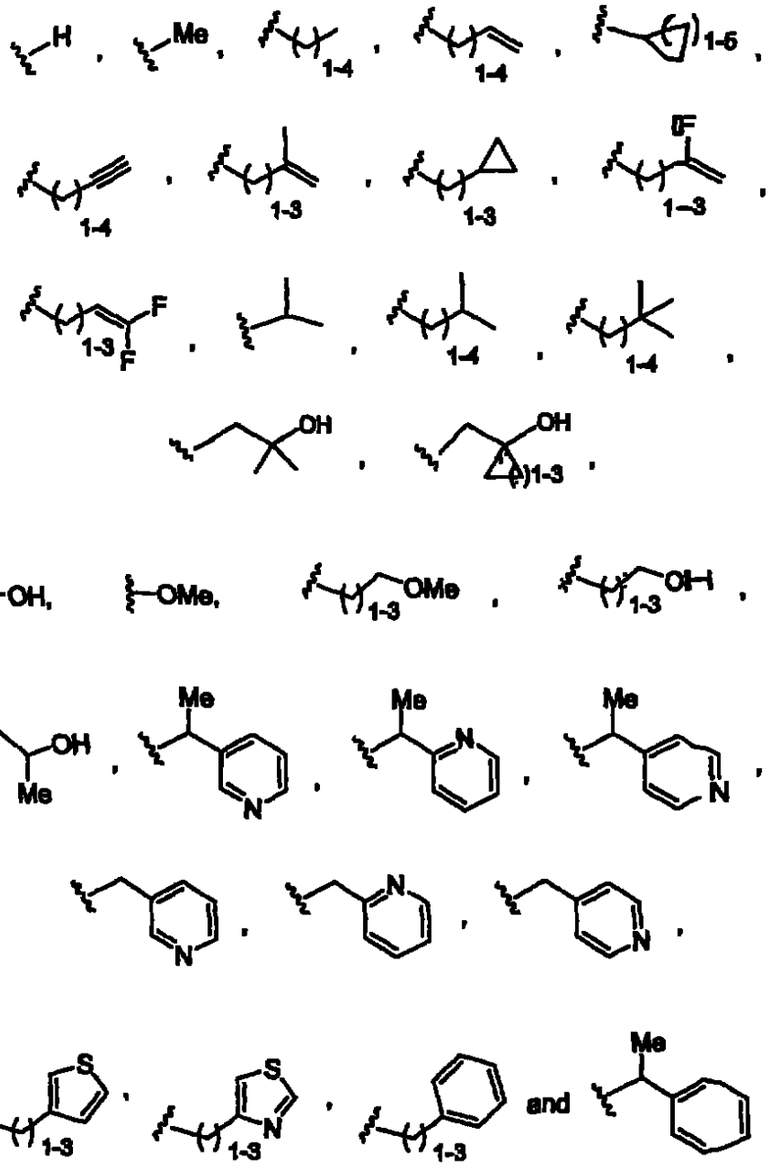
R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, T_1, T_2, T_3 and T_4 can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately, R^{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, alkyl, aryl, heteroaryl, alkylsulfonamido, arylsulfonamido, keto, carboxy, carbalkoxy, carboxamido,

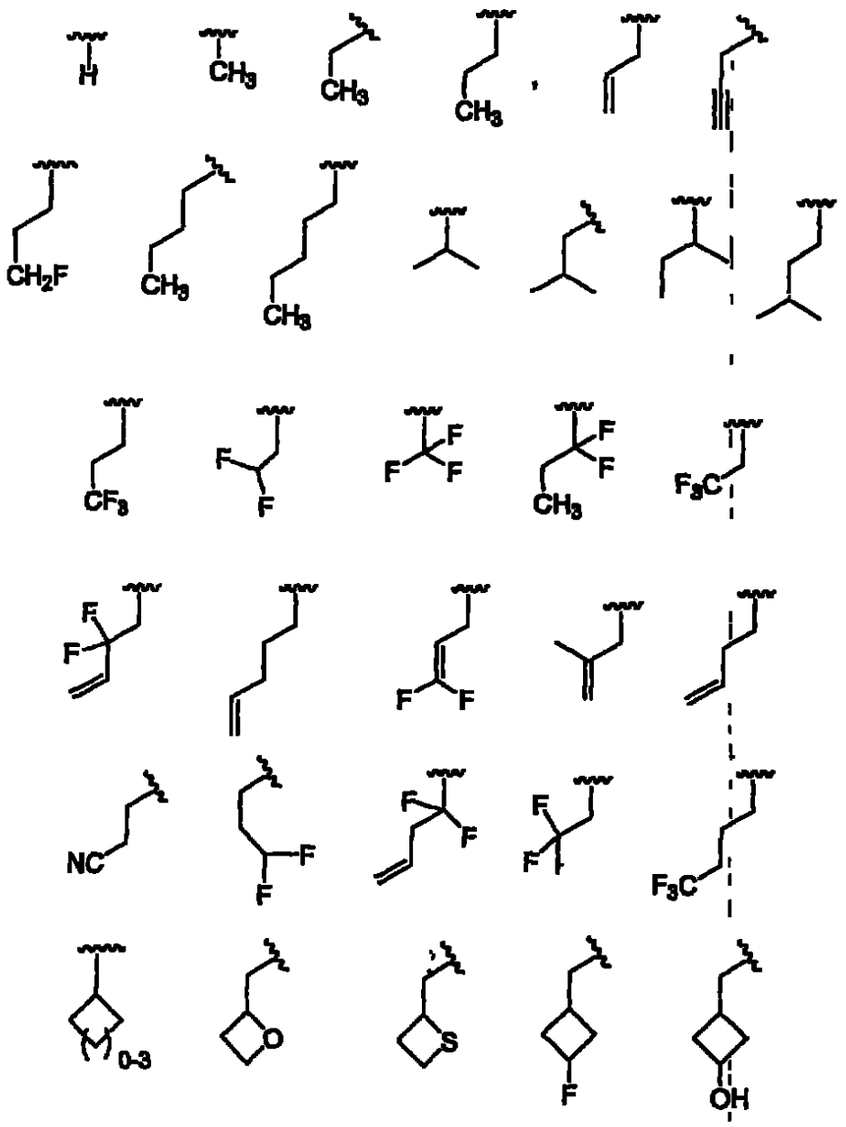
alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halo, cyano, and nitro

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

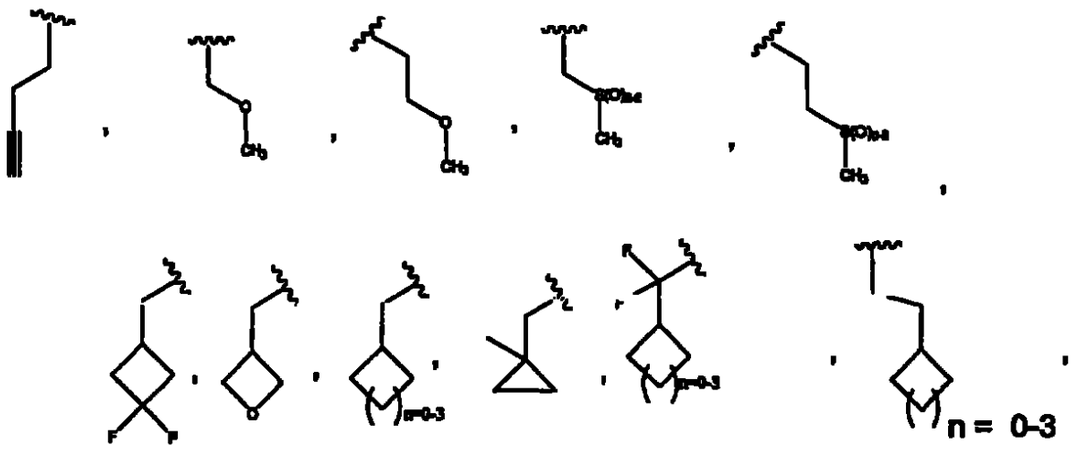
3 The compound of claim 2 wherein R^{14} is selected from the group consisting of



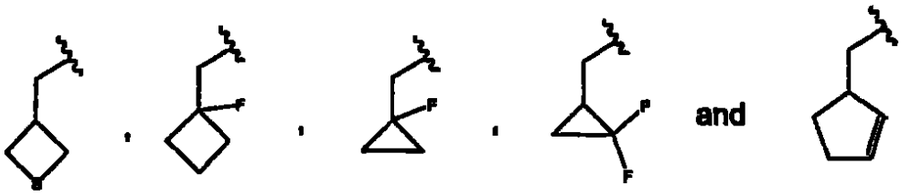
4 The compound of claim 1, wherein R^2 is selected from the group consisting of the following moieties


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

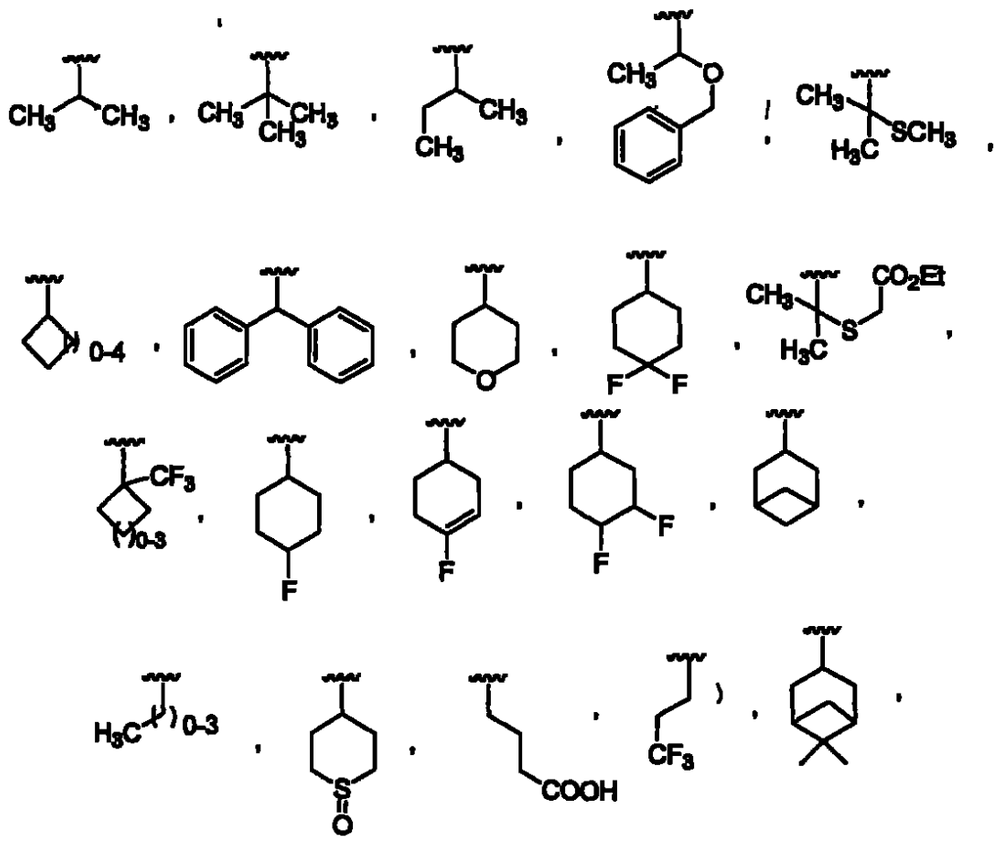
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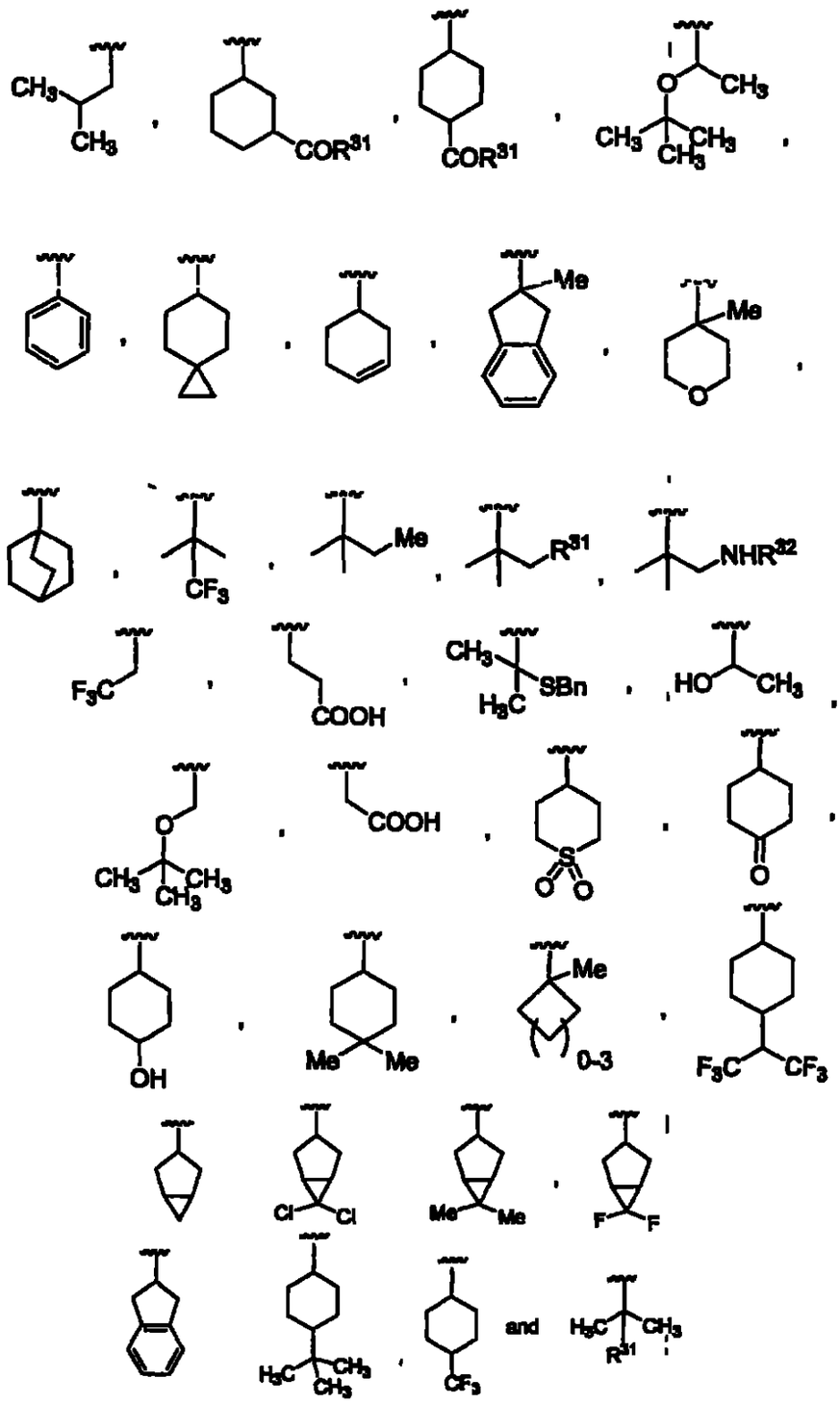


and



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

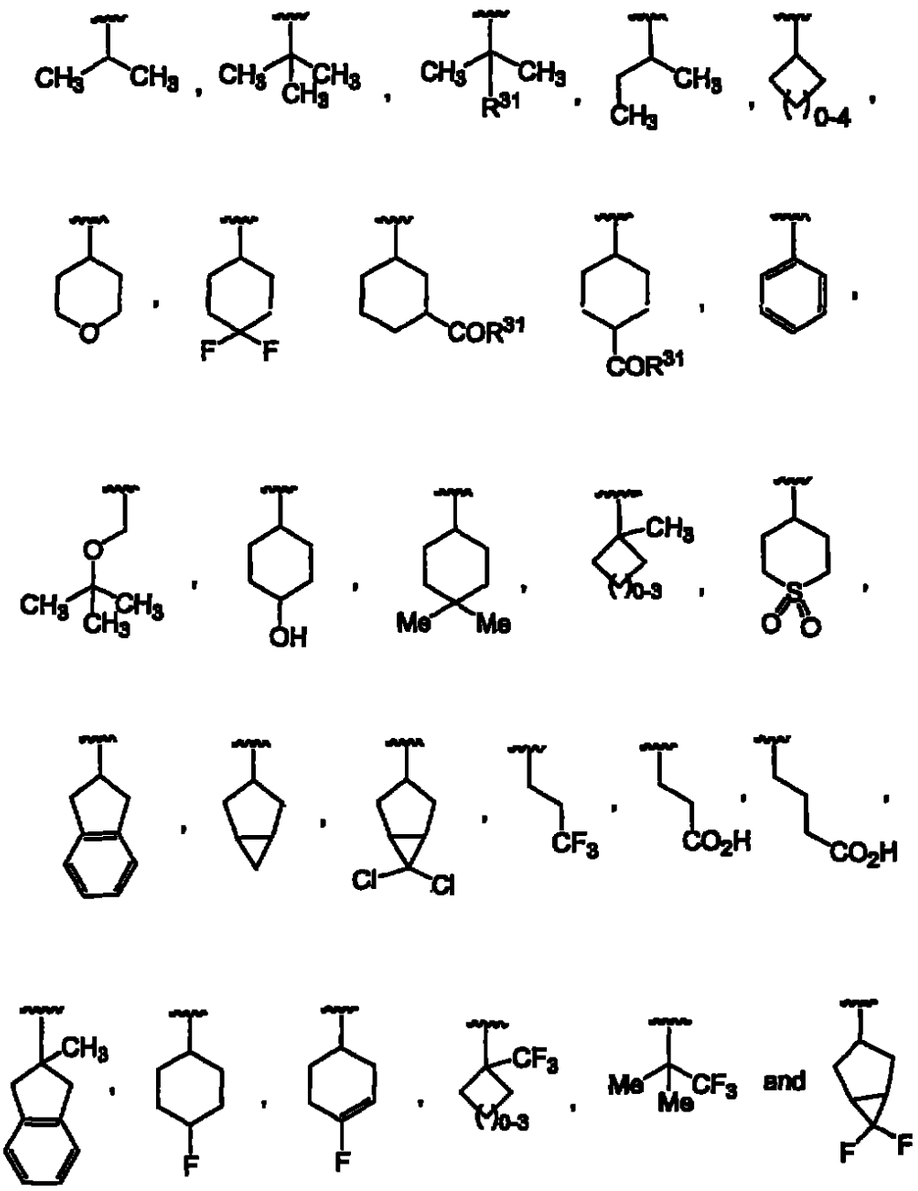




wherein R^{31} is OH or O-alkyl, and

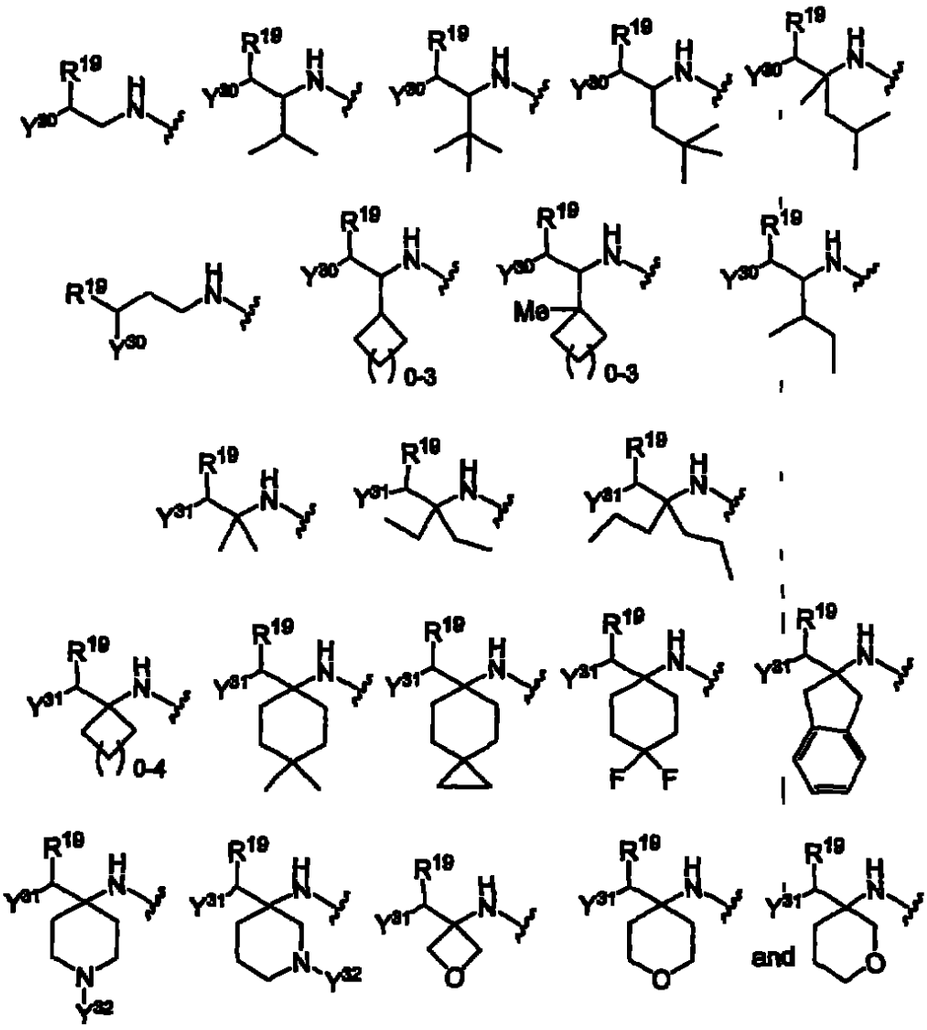
R^{32} is H, $C(O)CH_3$, C(O)OtBu or C(O)N(H)tBu

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

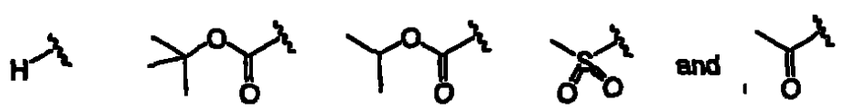


7 The compound of claim 1, wherein G is NH

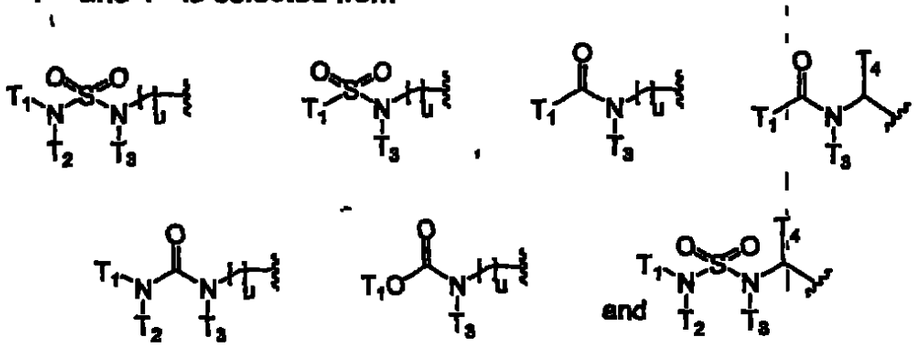
8 The compound of claim 7, wherein Y is selected from the following moieties



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



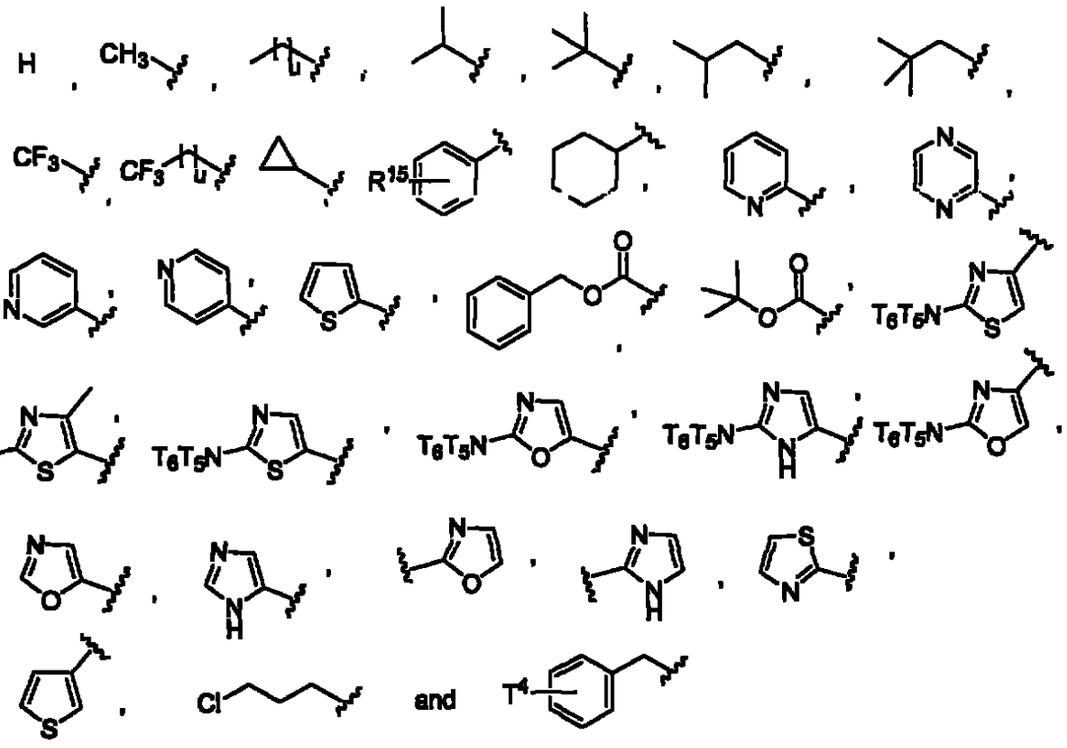
Y^{30} and Y^{31} is selected from



wherein u is a number 0-6 and

R^{19} is selected from H, alkyl, phenyl or benzyl

9 The compound of claim 8, wherein T_1 and T_2 can be the same or different, each being independently selected from the group consisting of

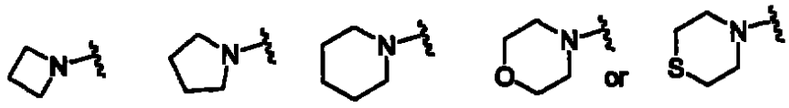


wherein T_5 and T_6 can be the same or different, each being independently selected from the group consisting of alkyl, aryl, cycloalkyl, heteroaryl and heterocyclyl,

or the moiety

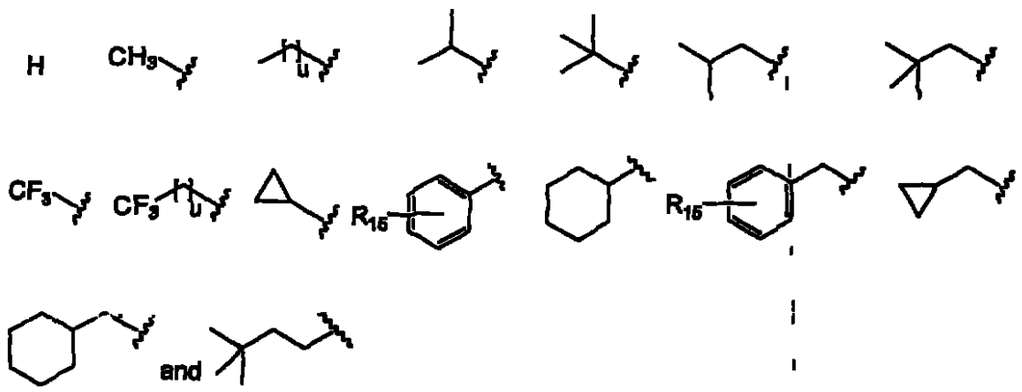


taken together represents



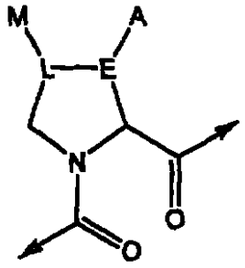
and

T_3 and T_4 can be the same or different, each being independently selected from

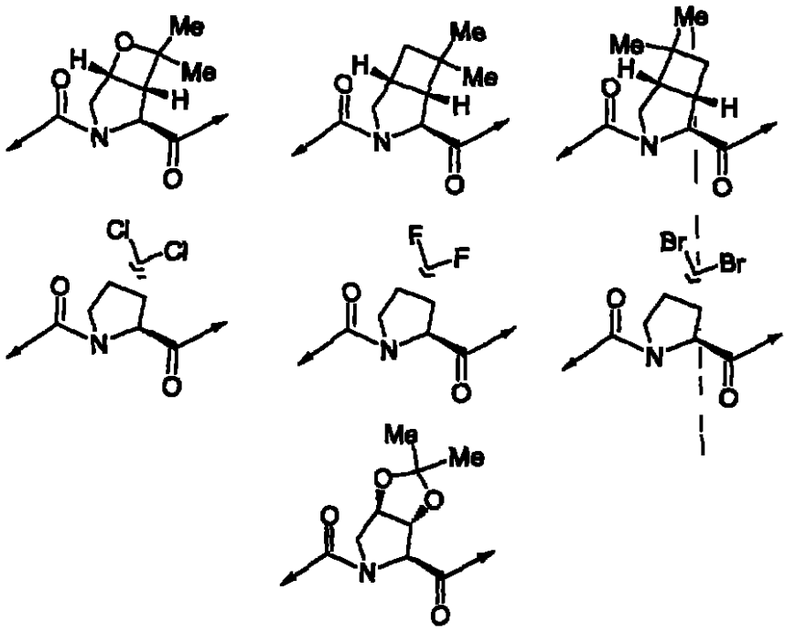


or T_3 and T_4 taken together may form part of a four to seven membered heterocyclic ring

The compound of claim 1 wherein the moiety

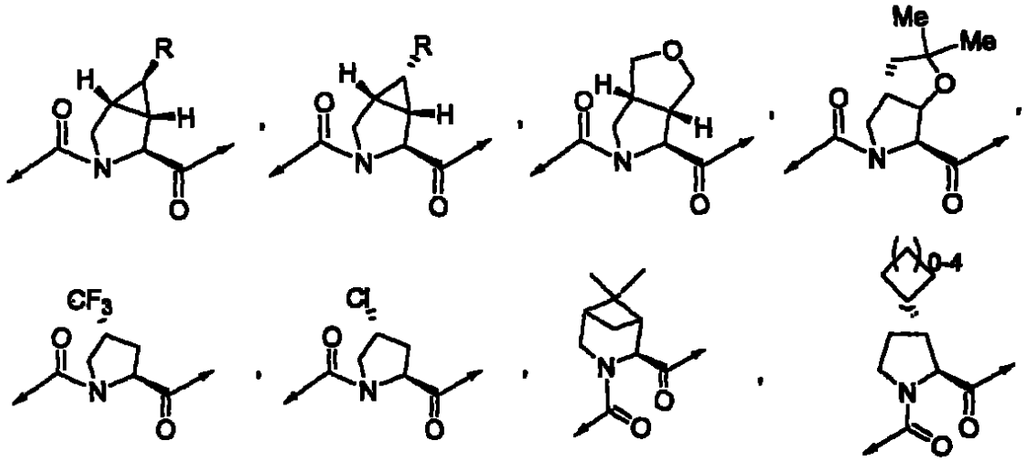


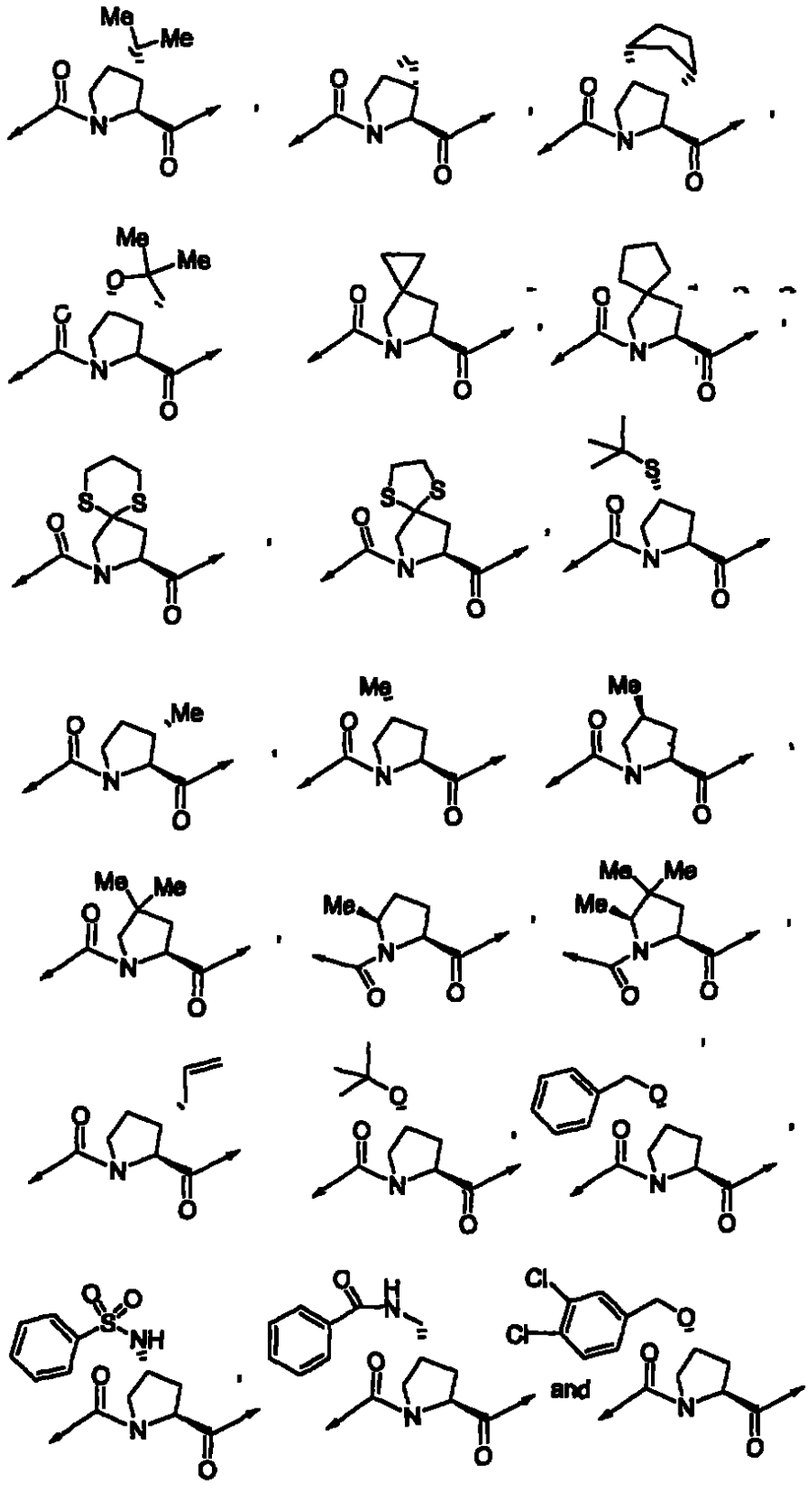
is selected from the following structures



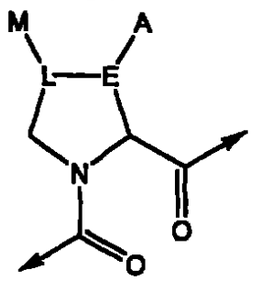
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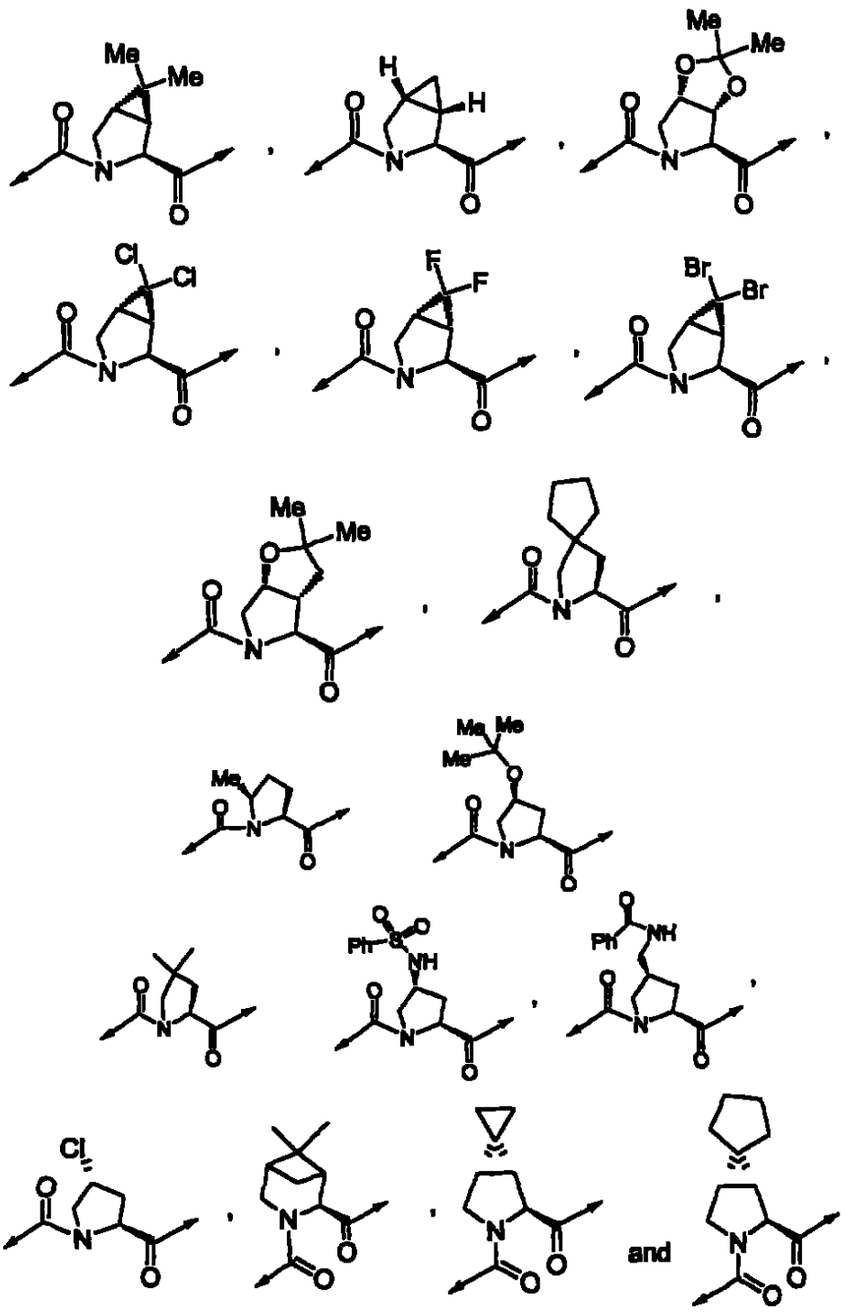




11 The compound of claim 10, wherein the moiety



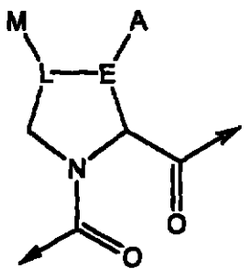
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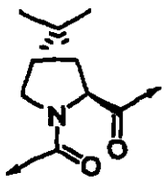
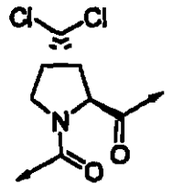
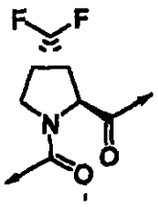
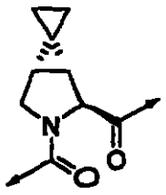
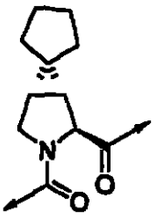
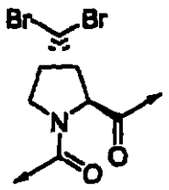
and

12 The compound of claim 11, wherein the moiety

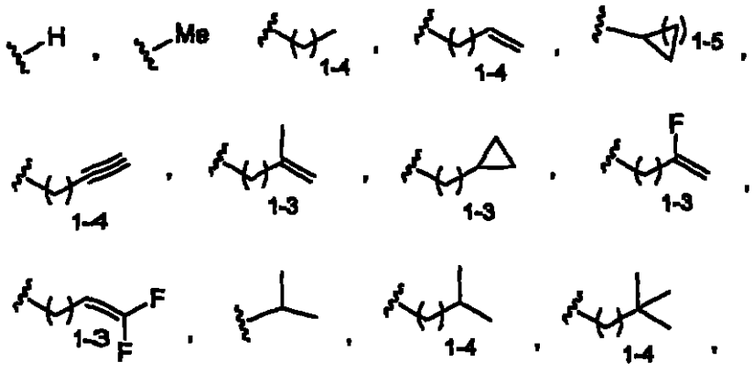
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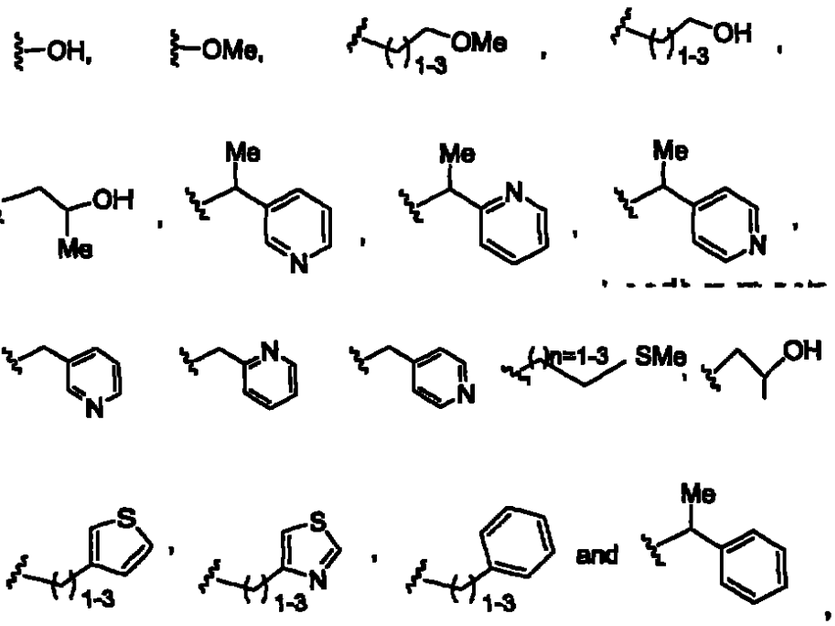


is selected from the following structures

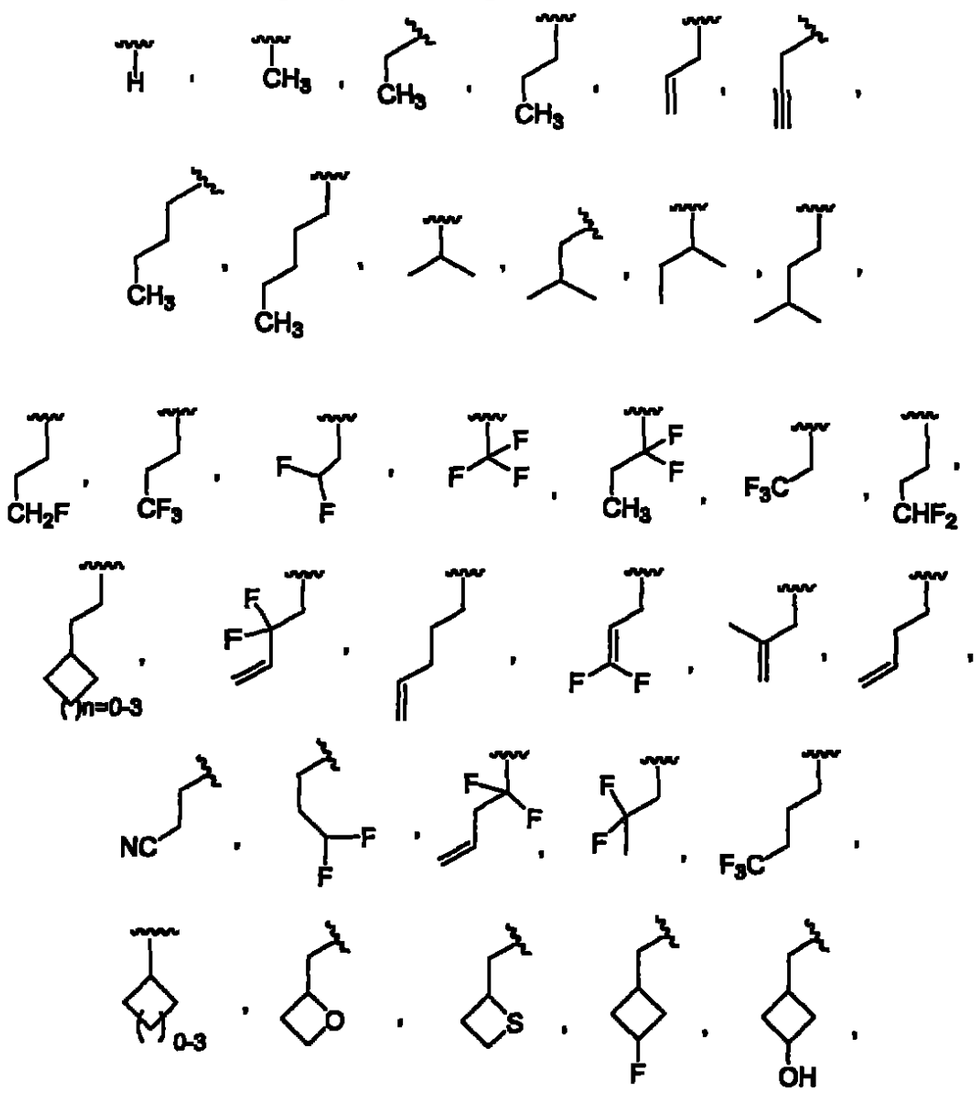





and


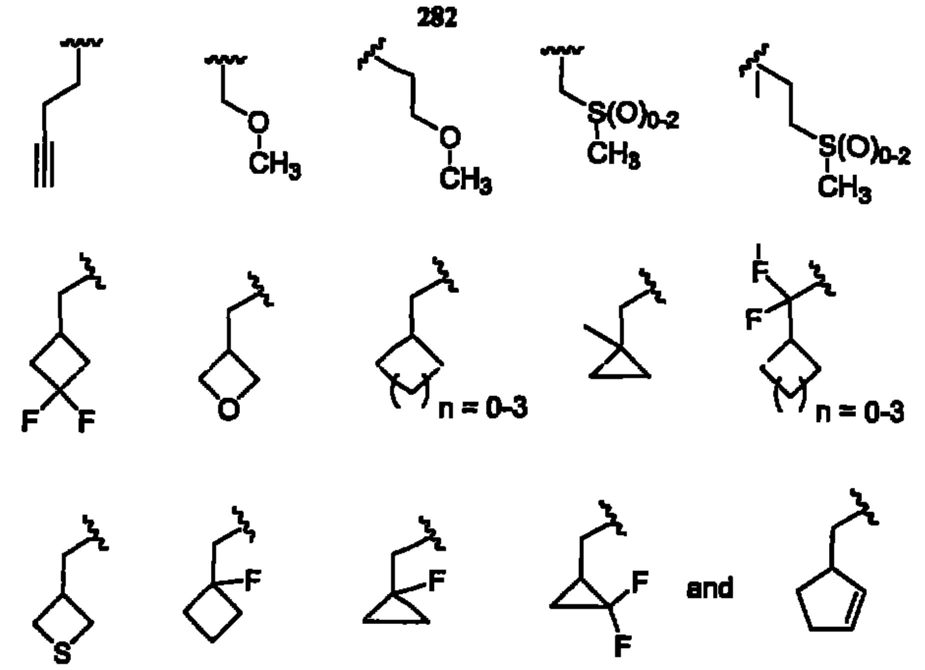
13 The compound of claim 1, wherein R^1 is NHR^{14}, where R^{14} is selected from the group consisting of



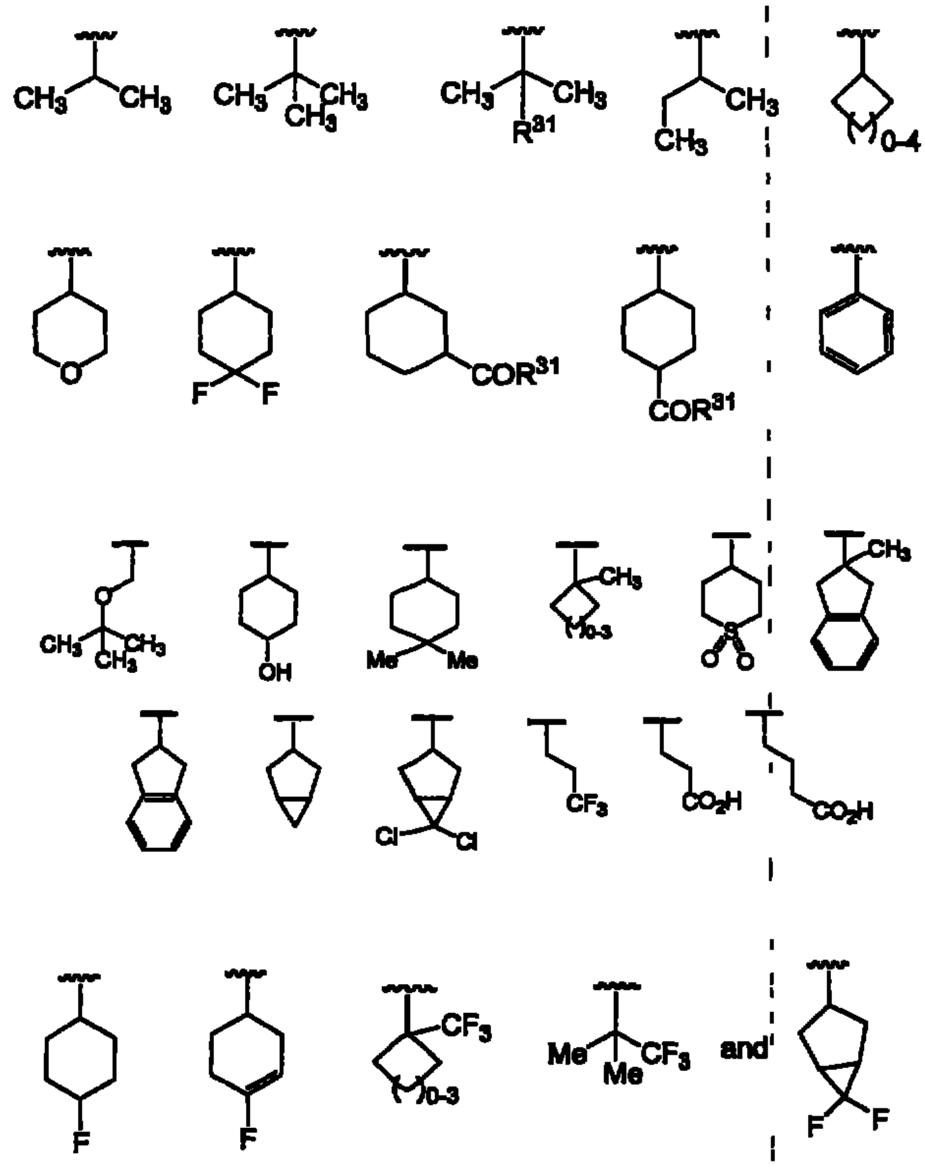


R^2 is selected from the group consisting of the following moieties

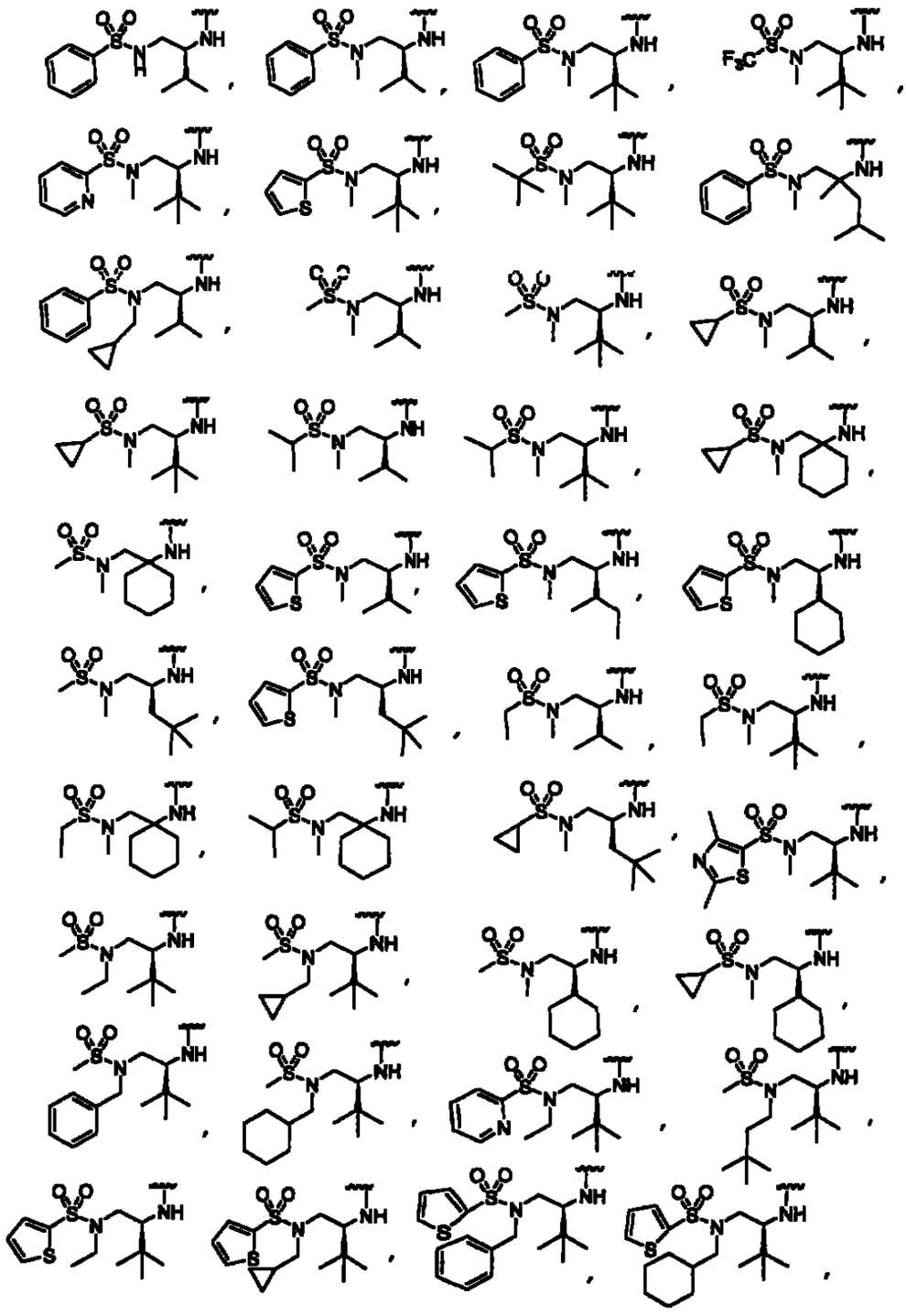


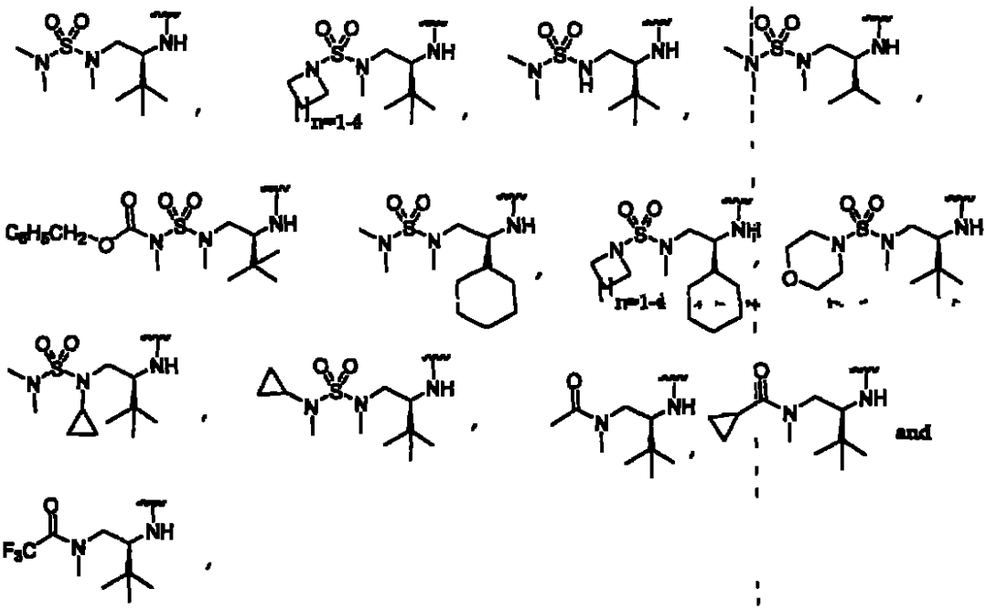


R^3 is selected from the group consisting of the following moieties

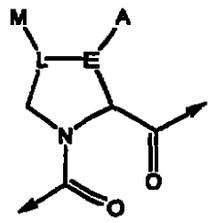


Y is selected from the group consisting of

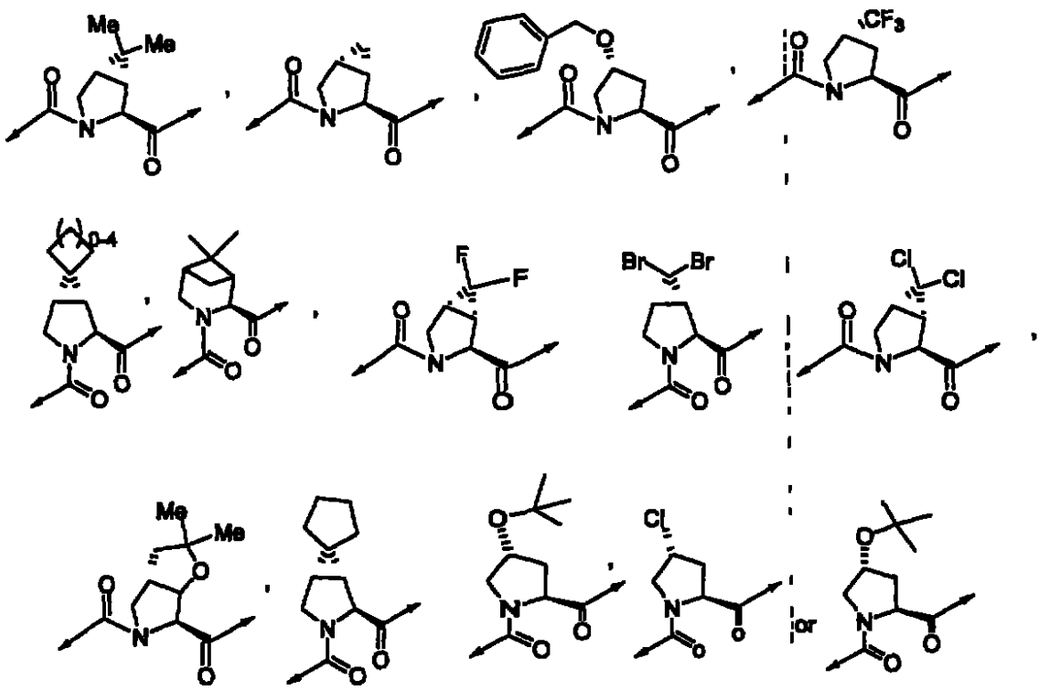




and the moiety



1S



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

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15 The pharmaceutical composition of claim 14 for use in treating disorders associated with Hepatitis C Virus ("HCV")

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

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

18 The pharmaceutical composition of claim 17, additionally containing at least one interferon

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

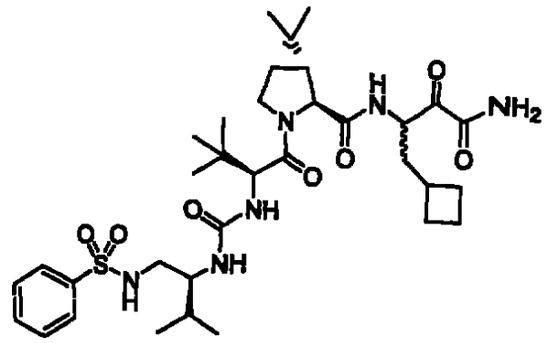
20 A method of treating disorders associated with the HCV, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound of claim 1

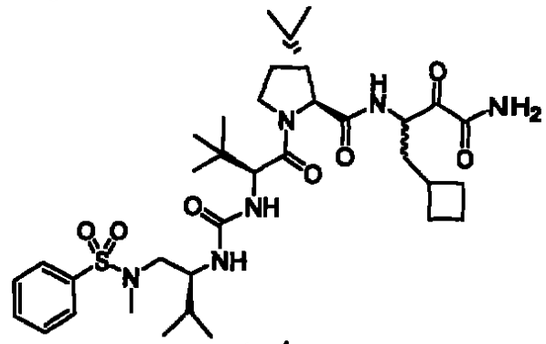
21 The method of claim 20, wherein said administration is oral or subcutaneous

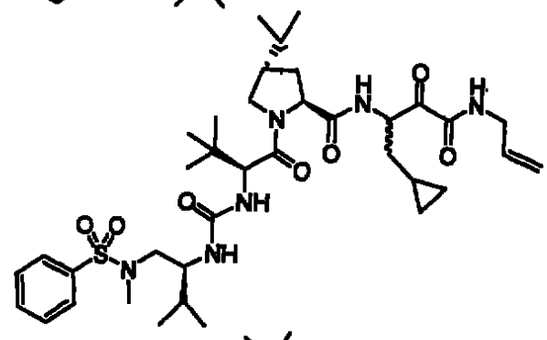
22 The use of a compound of claim 1 for the manufacture of a medicament to treat disorders associated with the HCV

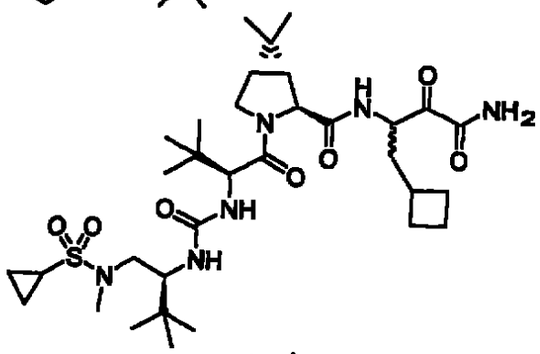
23 A method of preparing a pharmaceutical composition for treating the disorders associated with the HCV, said method comprising bringing into intimate physical contact at least one compound of claim 1 and at least one pharmaceutically acceptable carrier

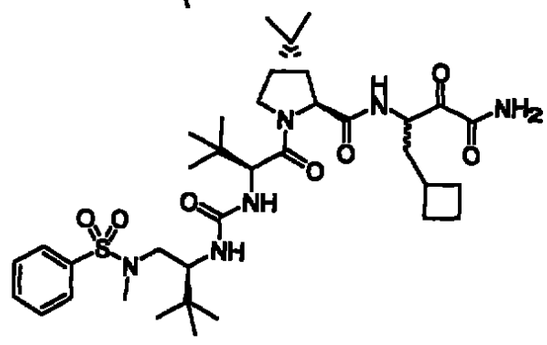
24 A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, diastereomers, and racemates of said compound, or a pharmaceutically acceptable salt, solvate or ester of said compound, said compound being selected from the compounds of structures listed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



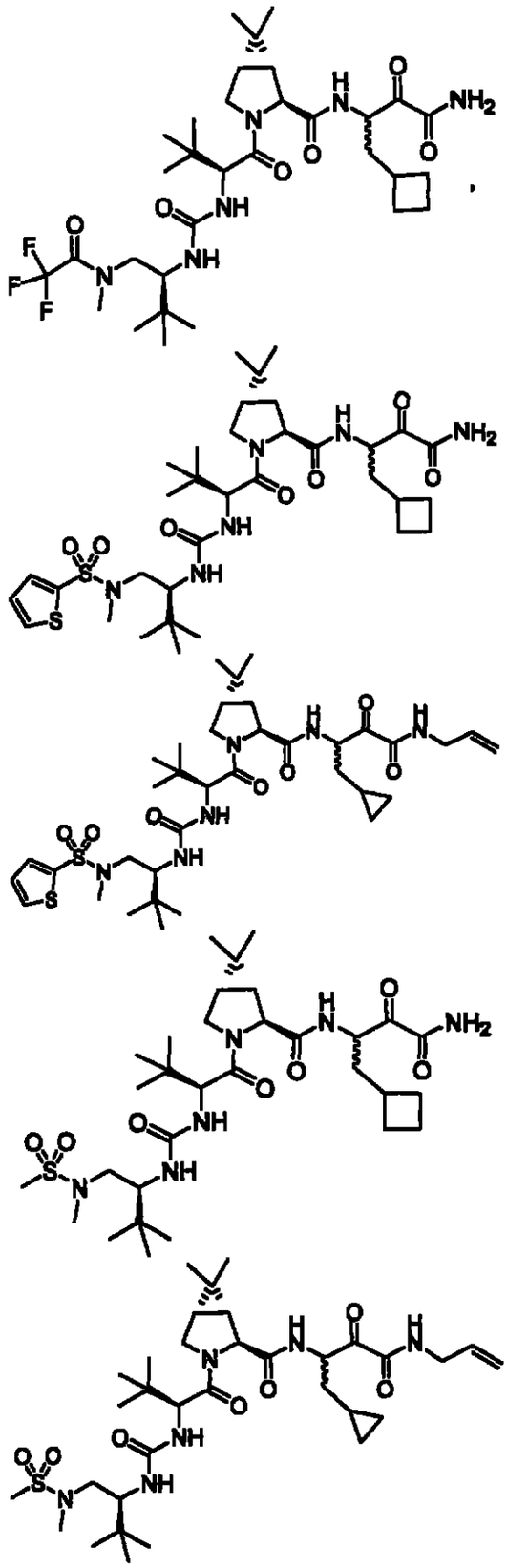


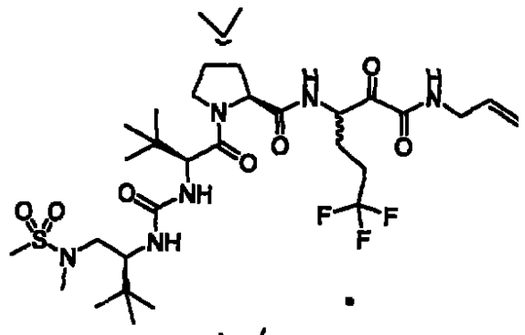


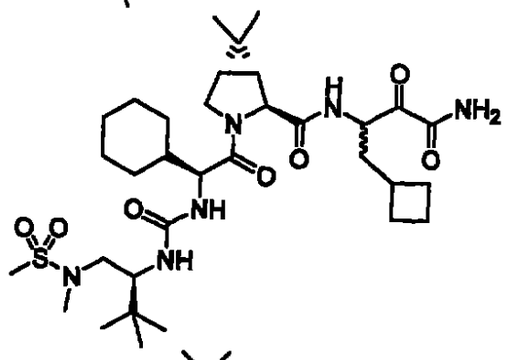


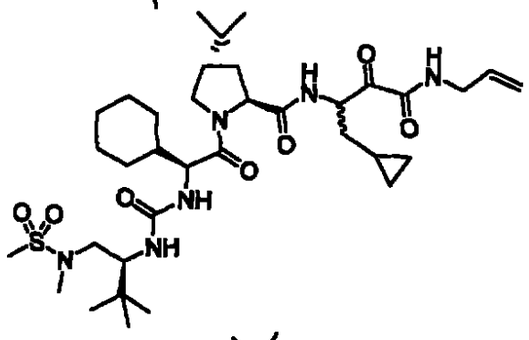


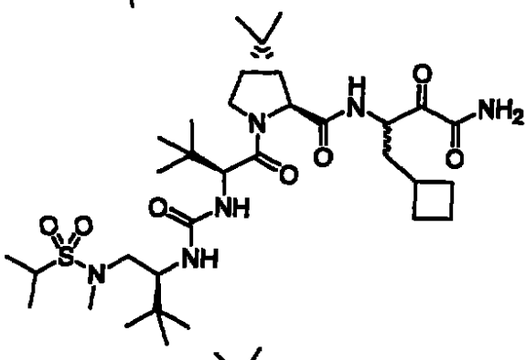
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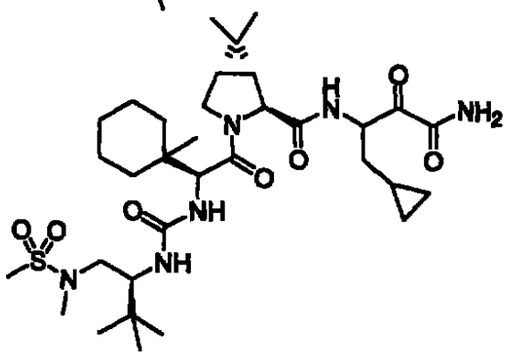




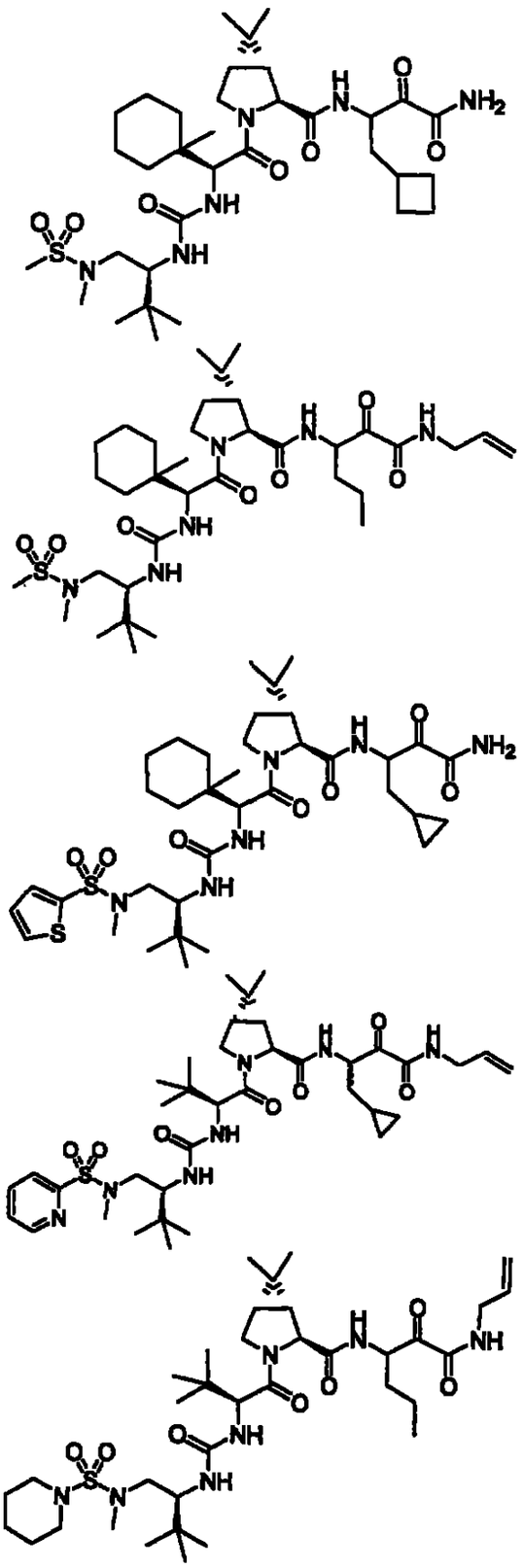




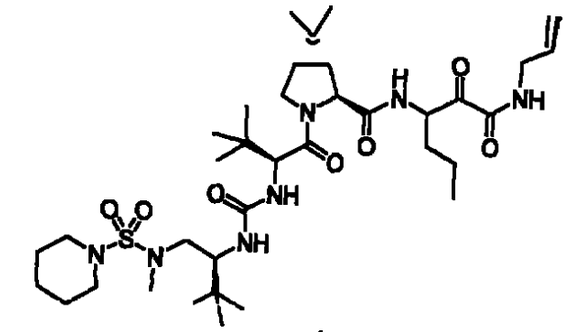


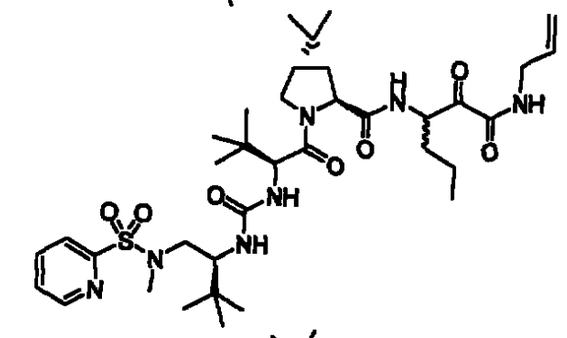


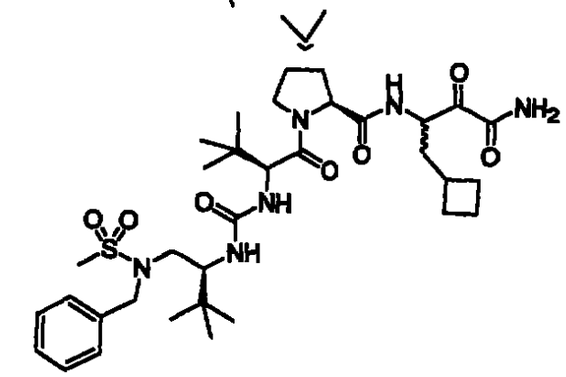
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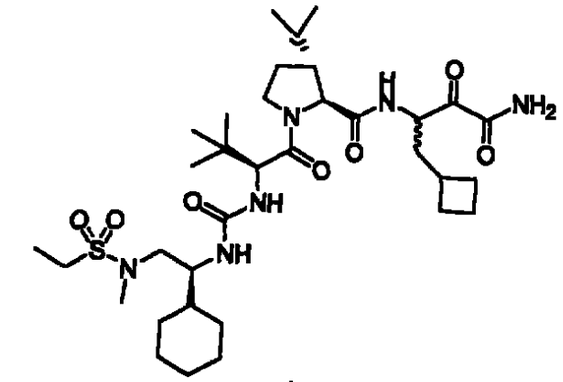


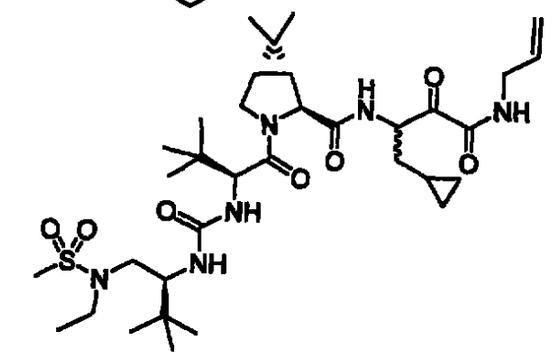
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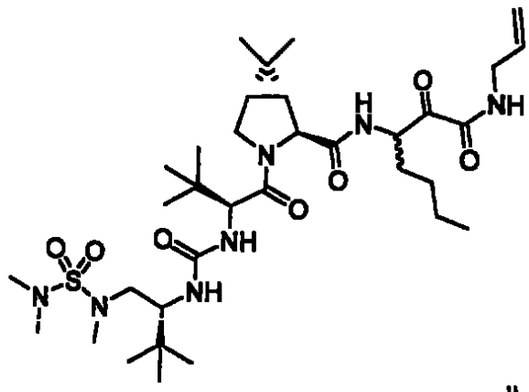


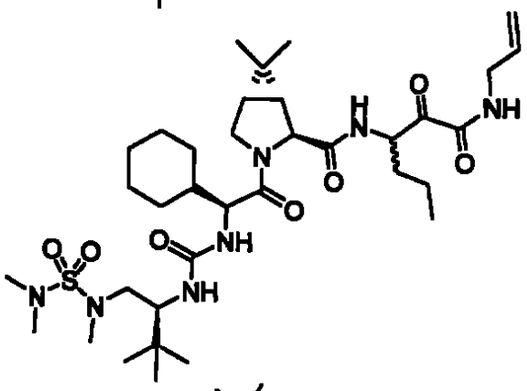


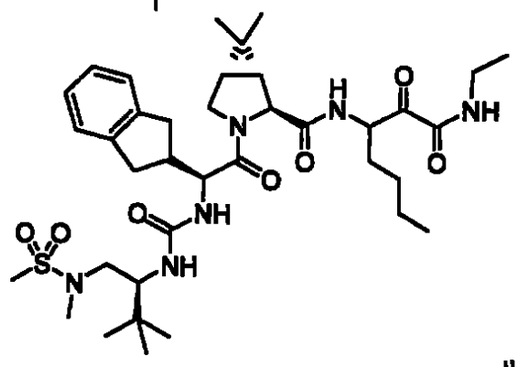


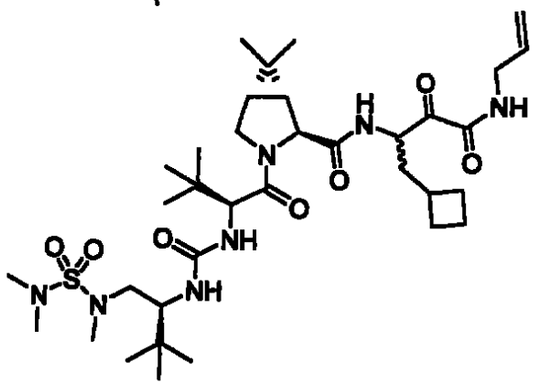


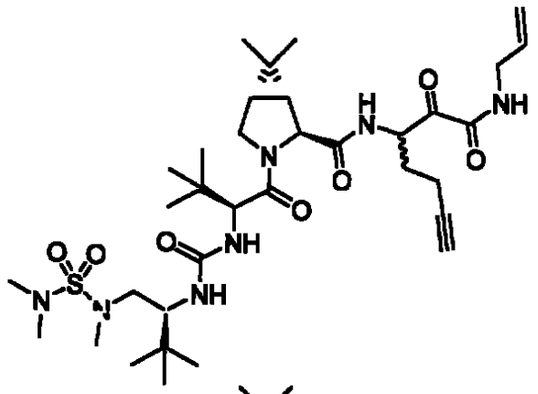
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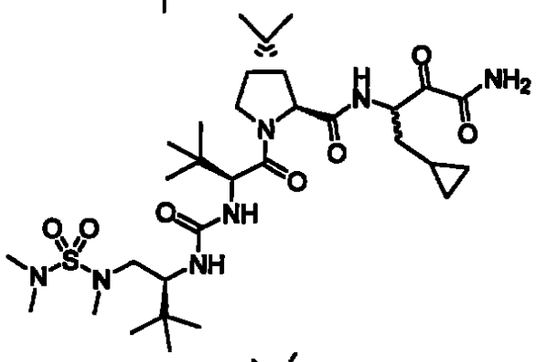


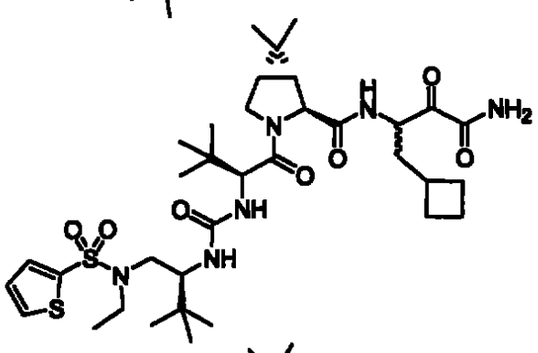


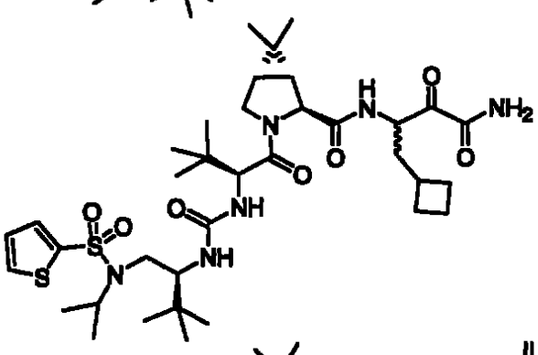


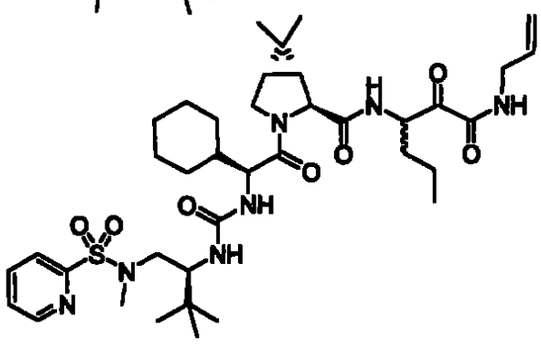




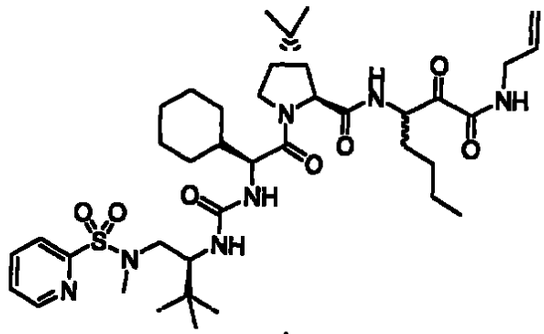


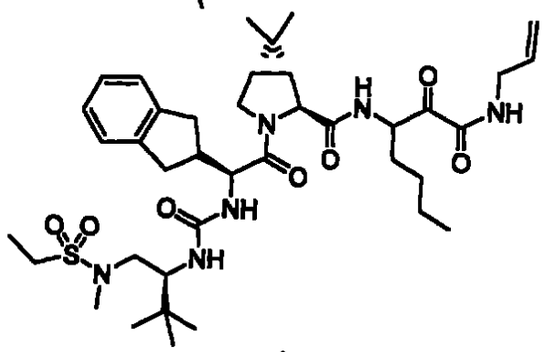


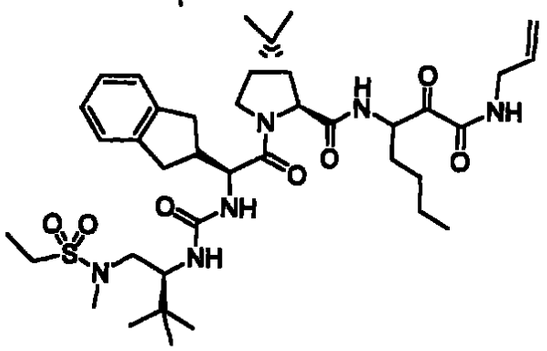


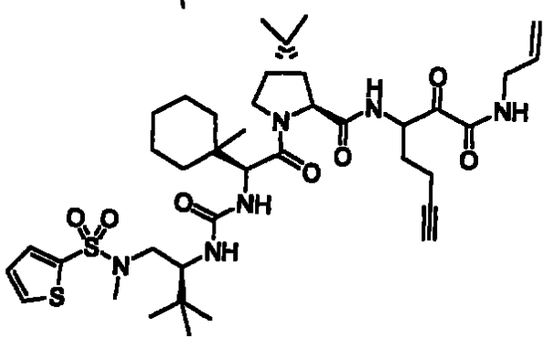


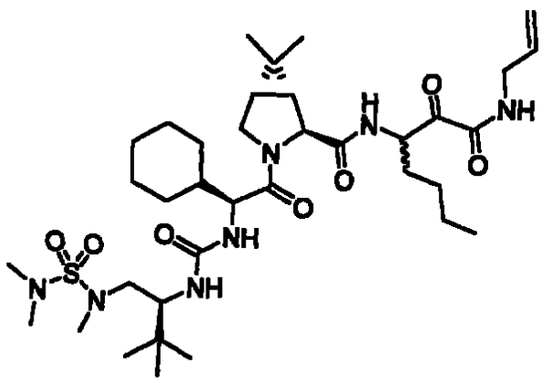
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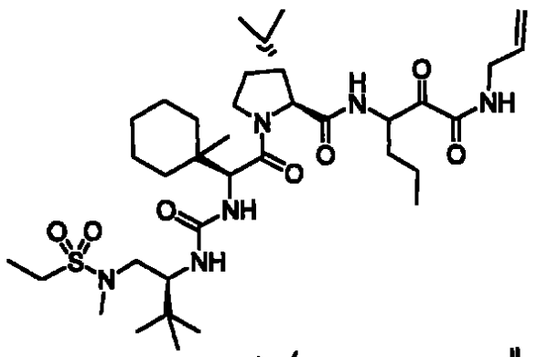


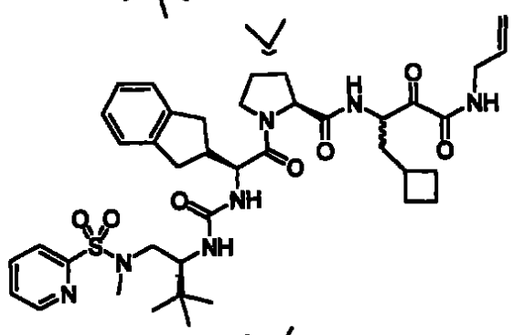


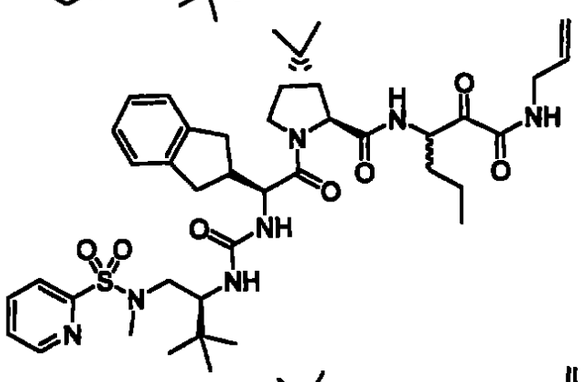


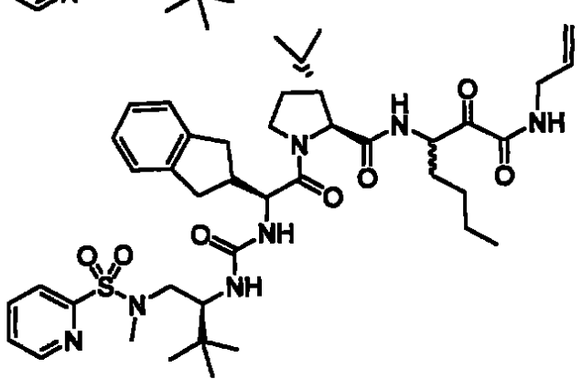


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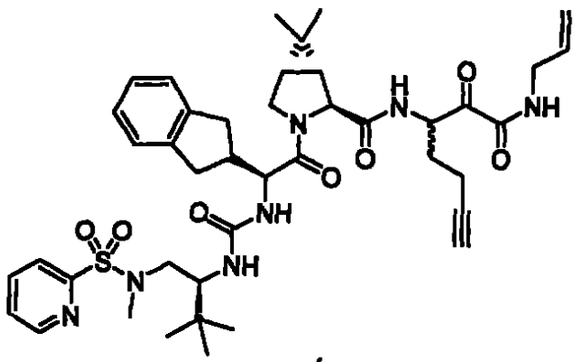


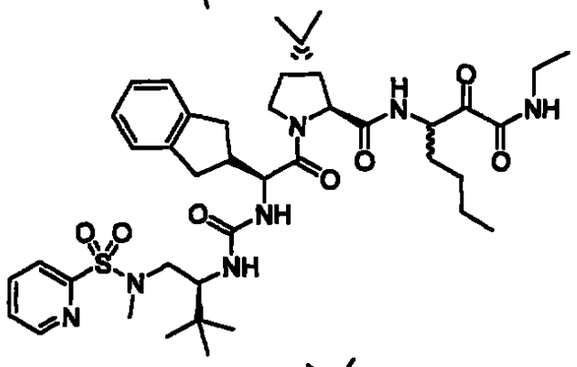


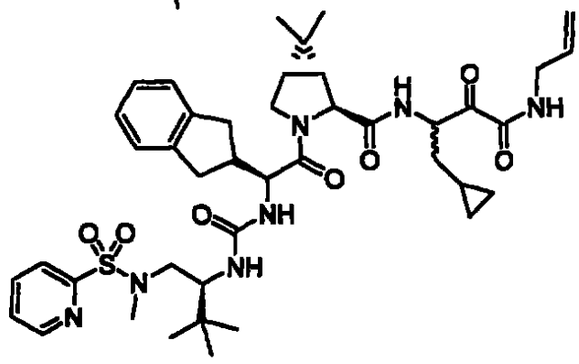




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and

25 A pharmaceutical composition for treating disorders associated with the HCV, said composition comprising therapeutically effective amount of one or more compounds in claim 24 and a pharmaceutically acceptable carrier

26 The pharmaceutical composition of claim 25, additionally containing at least one antiviral agent

27 The pharmaceutical composition of claim 26, additionally containing at least one interferon or PEG-interferon alpha conjugate ("pegylated interferon")

28 The pharmaceutical composition of claim 27, wherein said at least one antiviral agent is ribavirin and said at least one interferon is α-interferon or pegylated interferon

29 A method of treatment of a hepatitis C virus associated disorder, comprising administering an effective amount of one or more compounds of claim 24

30 A method of modulating the activity of hepatitis C virus (HCV) protease, comprising contacting HCV protease with one or more compounds of claim 24

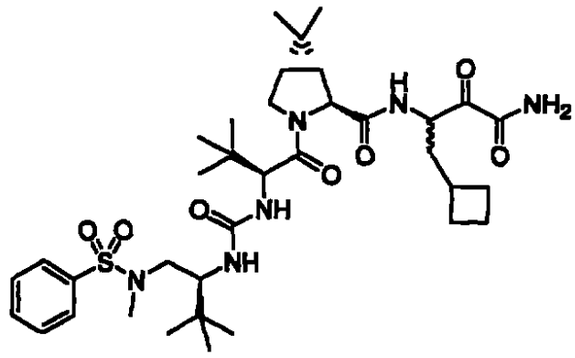
31 A method of treating, preventing, or ameliorating one or more symptoms of hepatitis C, comprising administering a therapeutically effective amount of one or more compounds of claim 24

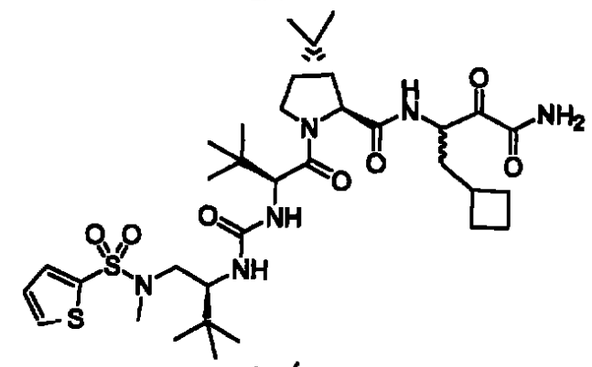
32 The method of claim 31, wherein the HCV protease is the NS3/NS4a protease

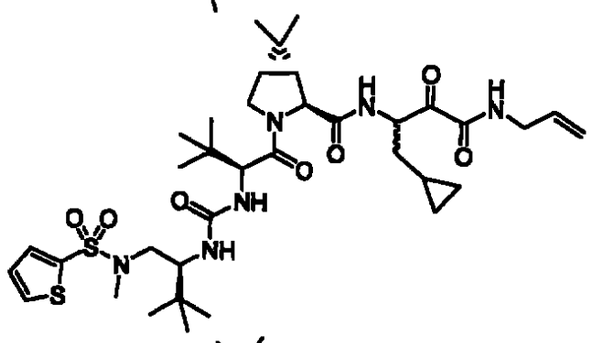
33 The method of claim 32, wherein the compound or compounds inhibit HCV NS3/NS4a protease

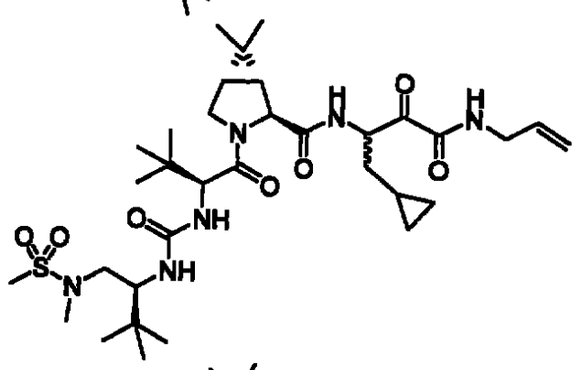
34 A method of modulating the processing of hepatitis C virus (HCV) polypeptide, comprising contacting a composition containing the HCV polypeptide under conditions in which said polypeptide is processed with one or more compounds of claim 24

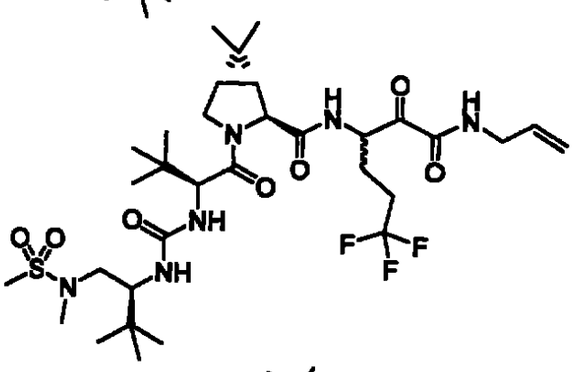
35 A method of treating disorders associated with the HCV, said method comprising administering to a patient in need of such treatment, a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound, or enantiomers, stereoisomers, rotamers, tautomers, diastereomers,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

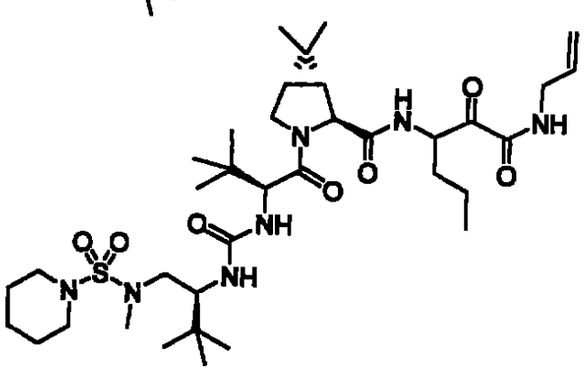


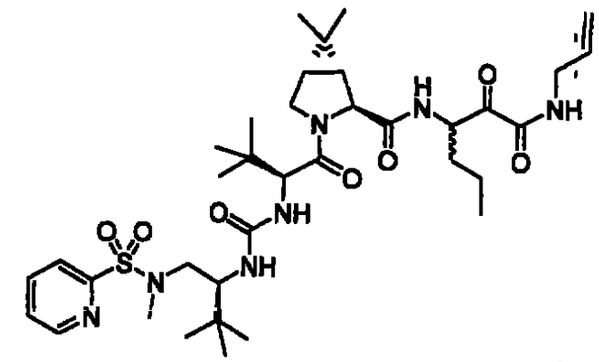


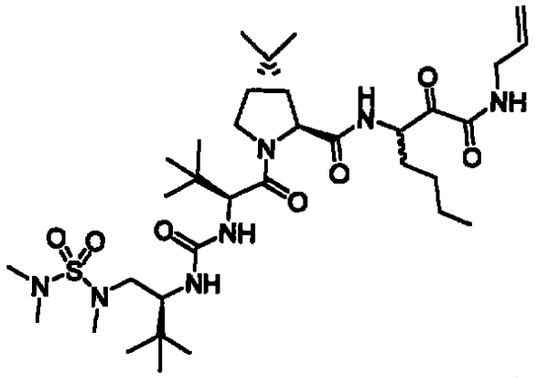


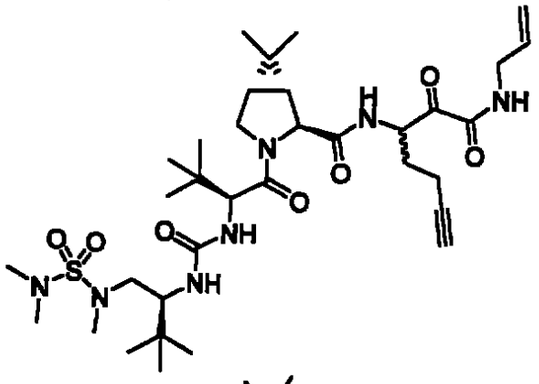


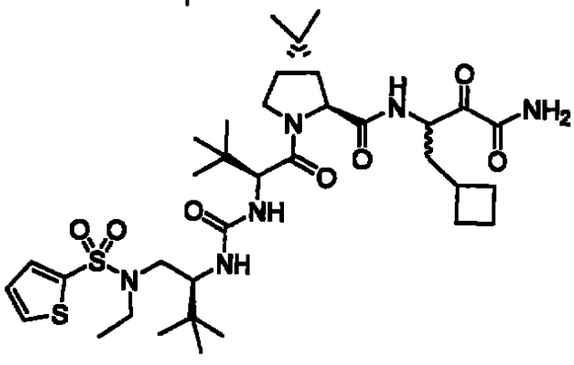


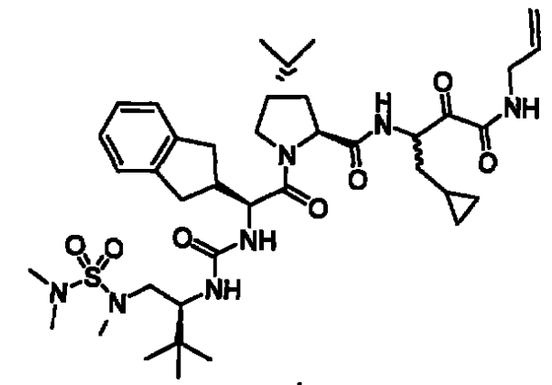


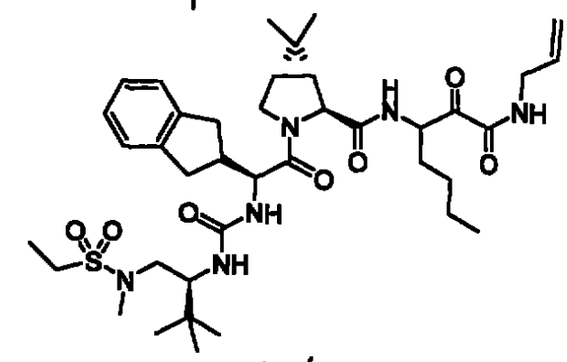


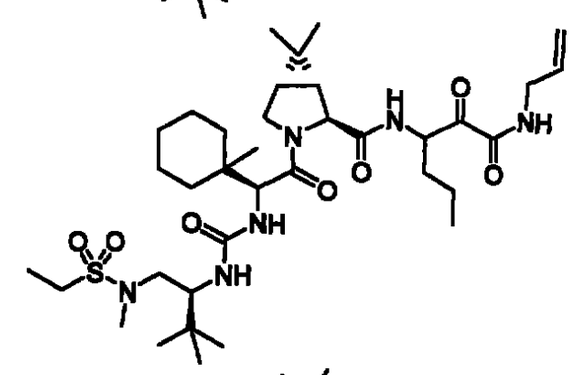


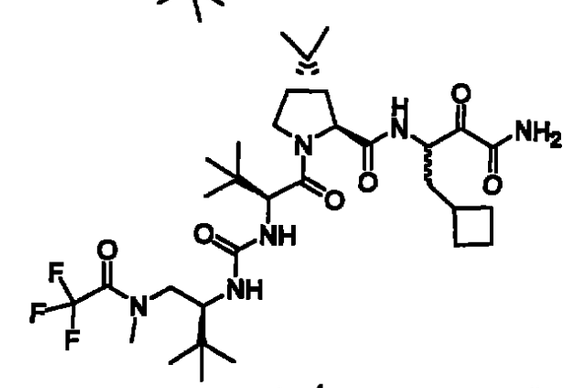


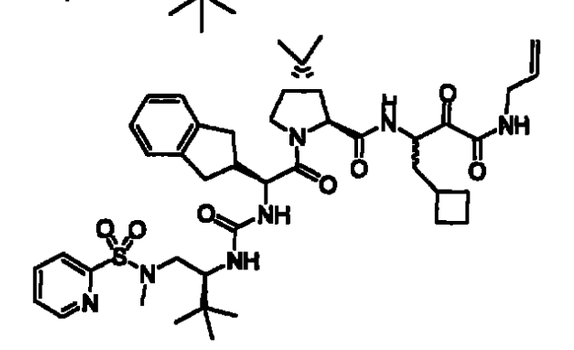




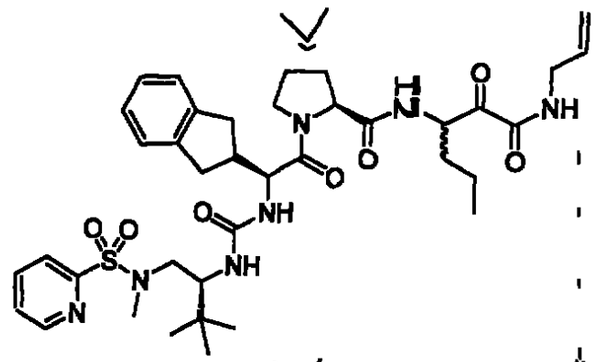


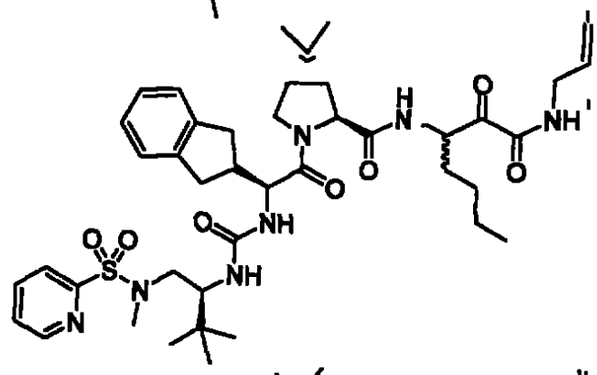


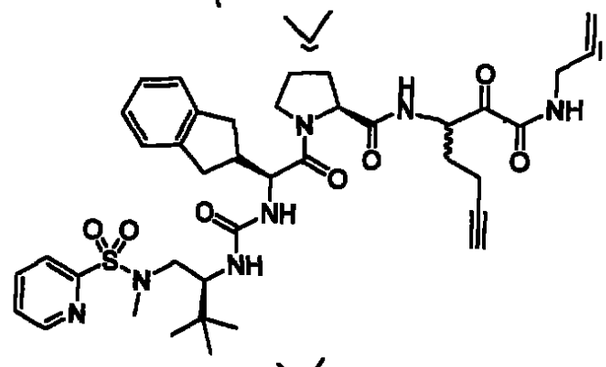


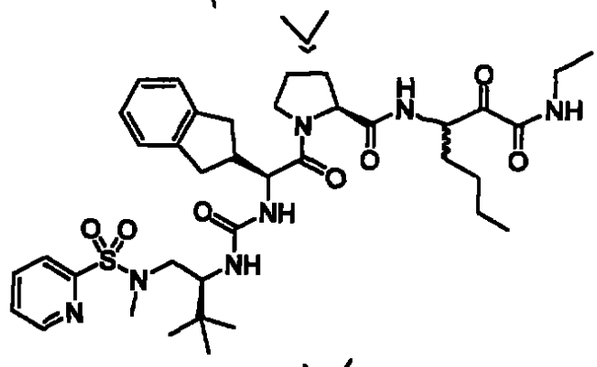


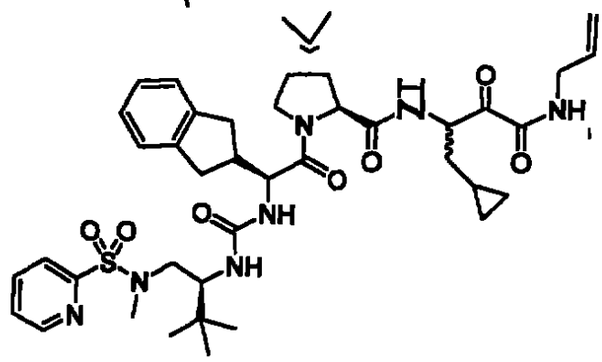
300











and

36 A compound of claim 1 in purified form

I N0 6132 - AR ref

163

Memoria Descriptiva

de la

Patente de Invención

Sobre

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

Solicitada por:

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

212128
US/PV

COMPUESTOS NOVEDOSOS COMO INHIBIDORES DE NS3 SERINA PROTEASA DEL VIRUS DE HEPATITIS C

Campo de la Invención

La presente invención se refiere a novedosos inhibidores de proteasa del virus de hepatitis C ("VHC"), composiciones farmacéuticas que contienen uno o más de tales inhibidores, métodos para preparar ese tipo de inhibidores y métodos para utilizar ese tipo de inhibidores para tratar la hepatitis C y trastornos relacionados Esta invención describe además novedosos compuestos como inhibidores de la serina proteasa NS3/NS4a del VHC Esta solicitud reivindica prioridad con respecto a la solicitud de patente provisoria estadounidense Numero de Acta 60/548 507 presentada el 27 de febrero, 2004

Antecedentes de la Invención

El virus de la hepatitis C (VHC) es un virus de ARN de una sola hebra de sentido (+) que ha sido implicado como el principal agente causante en la hepatitis no A, no B (NANBH), particularmente en NANBH asociada con la sangre (BB-NANBH) (ver, la Publicación de Solicitud de Patente Internacional No WO 89/04669 y Publicación de Solicitud de Patente Europea No EP 381 216) NANBH debe distinguirse de otros tipos de enfermedad del hígado inducida por virus, tales como el virus de la hepatitis A (VHA), virus de hepatitis B (VHB), virus hepatitis delta (VHD), citomegalovirus (CMV) y virus Epstein-Barr (VEB), así como también de otras formas de enfermedad de hígado tales como alcoholismo y cirrosis biliar primaria

Recientemente, se ha identificado, clonado y expresado una proteasa de VHC necesaria para el procesamiento polipeptídico y replicación viral (Véase, por ejemplo, Patente de los Estados Unidos No 5 712 145) Esta poliproteína de aproximadamente 3000 aminoácidos contiene, desde el término amino al término

carboxi, una proteína de nucleocápside (C), proteína de cubierta (E1 y E2) y varias proteínas no estructurales (NS1, 2, 3, 4a, 5a y 5b) NS3 es una proteína de aproximadamente 68 kda, codificada por aproximadamente 1893 nucleótidos del genoma de VHC, y tiene dos dominios distintos (a) un dominio de serina proteasa que consiste en aproximadamente 200 de los aminoácidos de terminal N, y (b) un dominio de ATPasa ARN-dependiente en el término C de la proteína La proteasa NS3 es considerada un miembro de la familia de quimotripsina debido a similitudes en la secuencia proteica, estructura tridimensional total y mecanismo de catálisis Otras enzimas del tipo quimotripsina son elastasa, factor Xa, trombina, tripsina, plasmina, uroquinasa, tPA y PSA La serina proteasa NS3 de VHC es responsable de la proteólisis del polipéptido (poliproteína) en las uniones NS3/NS4a, NS4a/NS4b, NS4b/NS5a y NS5a/NS5b y es así responsable de generar cuatro proteínas virales durante la replicación viral Esto ha hecho de la serina proteasa NS3 de VHC un objetivo atractivo para la quimioterapia antiviral Los compuestos de la invención pueden inhibir ese tipo de proteasa También pueden modular el procesamiento del polipéptido 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 serina proteasa de NS3 La autodisociación de la unión NS3/NS4a por la serina proteasa NS3/NS4a ocurre intramolecularmente (es decir, *cis*) mientras que los otros sitios de disociación son procesados intermolecularmente (es decir, *trans*)

El análisis de los sitios de disociación naturales para la proteasa de VHC reveló la presencia de cisteína en P1 y serina en P1' y que estos residuos son estrictamente conservados en las uniones NS4a/NS4b, NS4b/NS5a y NS5a/NS5b La unión NS3/NS4a contiene una treonina en P1 y una serina en P1' Se presume

que la sustitución Cys→Thr en NS3/NS4a es responsable del requerimiento de procesamiento de *cis* más que *trans* en esta unión Véase, por ej., Pizzi et al (1994) Proc Natl. Acad Sci (USA) 91 888-892, Failla et al. (1996) Folding & Design 1,35-42 El sitio de disociación NS3/NS4a es también más tolerante de la mutagénesis que los otros sitios Véase, por ejemplo, Kollykhalov et al. (1994) J. Virol 68 7525-7533 También se ha descubierto que los residuos ácidos en la región corriente arriba del sitio de disociación son necesarios para la disociación eficaz. Véase, por ejemplo, Komoda et al (1994) J Virol. 68 7351-7357

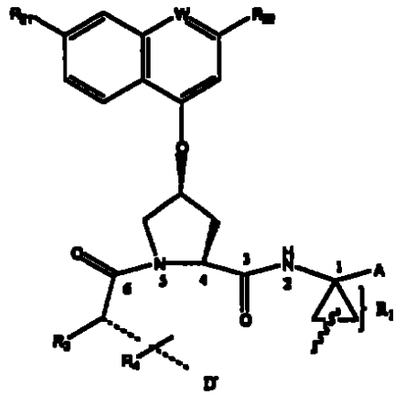
Los inhibidores de la proteasa de VHC que han sido reportados incluyen antioxidantes (véase, la Publicación de la Solicitud de Patente Internacional No WO 98/14181), ciertos péptidos y análogos peptídicos (véase, la Publicación de Solicitud de Patente Internacional No WO 98/17679, Landro et al. (1997) 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 de afinidad seleccionados de inhibidor de 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) Protein Eng 10 607-614), y α1-antiquimotripsina (ACT) (Elzouki et al) (1997) J. Hepat 27 42-28) Una ribozima diseñada para destruir selectivamente ARN del virus de la hepatitis C ha sido descrita recientemente (véase, *BioWorld Today* 9(217) 4 (10 de Noviembre, 1998))

También se hace referencia a las Publicaciones PCT, No WO 98/17679, publicadas el 30 de abril, 1998 (Vertex Pharmaceuticals Incorporated), WO 98/22496,

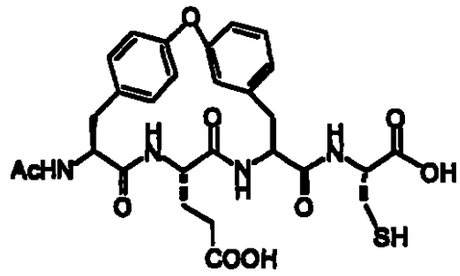
publicada el 28 de mayo, 1998 (F Hoffmann-La Roche AG), y WO 99/07734, publicada el 18 de febrero, 1999 (Boehringer Ingelheim Canada Ltd)

El VHC ha sido involucrado en la cirrosis hepática y en la inducción de carcinoma hepatocelular El pronóstico para los pacientes que sufren de la infección por VHC es actualmente pobre La infección de VHC es más difícil de tratar que otras formas de hepatitis debido a la falta de inmunidad o remisión asociada con la infección del VHC Los datos actuales indican una tasa de supervivencia inferior al 50% en cuatro años posteriores al diagnóstico de cirrosis Los pacientes diagnosticados con carcinoma hepatocelular resecable localizado tienen una tasa de supervivencia de cinco años de 10-30%, mientras que aquellos con carcinoma hepatocelular no resecable localizado tienen una tasa de supervivencia de cinco años inferior al 1%

Se hace referencia a WO 00/59929 (Patente de los Estados Unidos 6 608 027, Cesionario Boehringer Ingelheim (Canada) Ltd , Publicada el 12 de Octubre, 2000) la cual describe derivados peptídicos de la fórmula

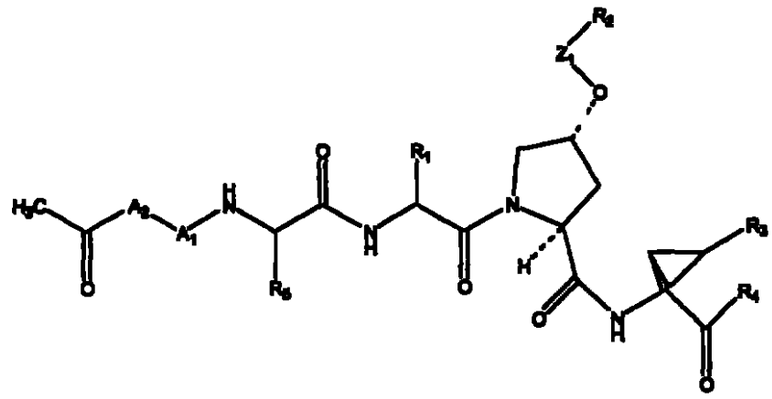


Se hace referencia a A Marchetti *et al*, *Synlett*, S1, 1000-1002 (1999) que describe la síntesis de análogos bicíclicos de un inhibidor de proteasa NS3 de VHC Un compuesto descrito allí tiene la fórmula

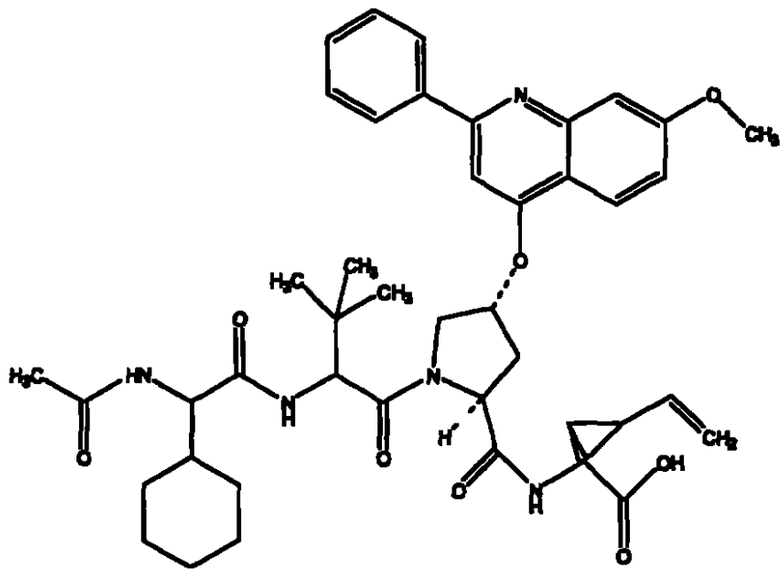


También se hace referencia a W Han *et al*, *Bioorganic & Medicinal Chem Lett*, (2000) 10, 711-713, la cual describe la preparación de ciertas α-cetoamidas, α-cetoésteres y α-dicetonas que contienen funcionalidades alílicas y etílicas

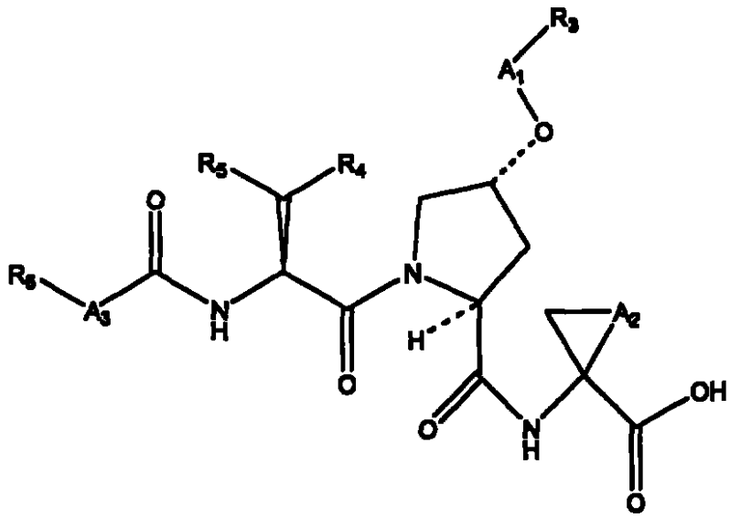
También se hace referencia a WO 00/09558 (Cesionario Boehringer Ingelheim Limited, Publicado el 24 de febrero, 2000) la cual describe derivados peptídicos de la fórmula



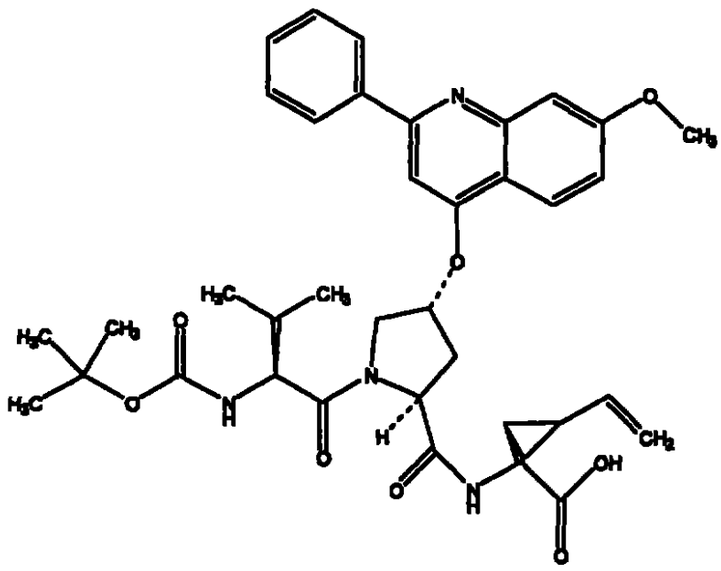
donde los diversos elementos son definidos allí Un compuesto ilustrativo de esa serie es



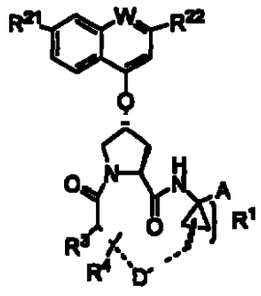
También se hace referencia a WO 00/09543 (Cesionario Boehringer Ingelheim Limited, Publicada el 24 de febrero, 2000) la cual describe derivados peptídicos de la fórmula



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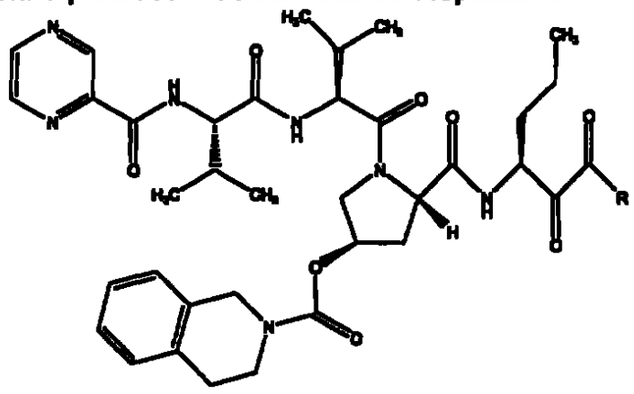
Tambien se hace referencia a la Patente de los Estados Unidos 6 608 027 (Boehringer Ingelheim, Canadá) la cual describe inhibidores de la proteasa NS3 del tipo



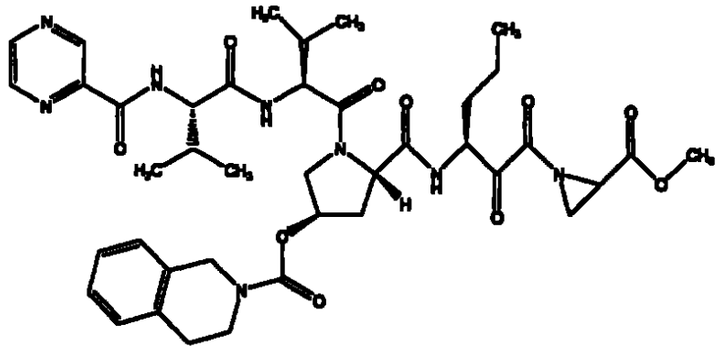
en donde las diversas porciones son definidas en la misma

Las terapias actuales para la hepatitis C incluyen interferón-α (INF_α) y terapia de combinación con ribavirina e interferón Véase, por ejemplo, Beremguer et al (1998) Proc. Assoc Am Physicians 110(2) 98-112 Estas terapias sufren de un bajo índice de respuesta sostenida y frecuentes efectos colaterales Véase por ejemplo, Hoofnagle et al, (1997) N. Engl. J Med 336 347 Actualmente, no se encuentra disponible ninguna vacuna para la infección por VHC

Se hace referencia adicionalmente a WO 01/74768 (Cesionario Vertex Pharmaceuticals Inc) publicada el 11 de Octubre, 2001, la cual describe ciertos compuestos de la siguiente fórmula general (R es definida en la misma) como inhibidores de la serina proteasa NS3 del virus de Hepatitis C



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



Las Publicaciones PCT WO 01/77113, WO 01/081325, WO 02/08198, WO 02/08256, WO 02/08187, WO 02/08244, WO 02/48172, WO 02/08251, y solicitud de Patente de los Estados Unidos pendiente, Acta No 10/052 386, presentada el 18 de enero, 2002, describen diversos tipos de péptidos y/u otros compuestos como inhibidores de serina proteasa NS-3 del virus de la hepatitis C Las descripciones de

aquellas solicitudes se incorporan en la presente memoria descriptiva por referencia a las mismas

Existe la necesidad de nuevos tratamientos y terapias para la infección del VHC Existe la necesidad de compuestos útiles en el tratamiento o prevención o mejora de uno o más síntomas de la hepatitis C

Existe la necesidad de métodos para el tratamiento o prevención o mejora de uno o más síntomas de la hepatitis C

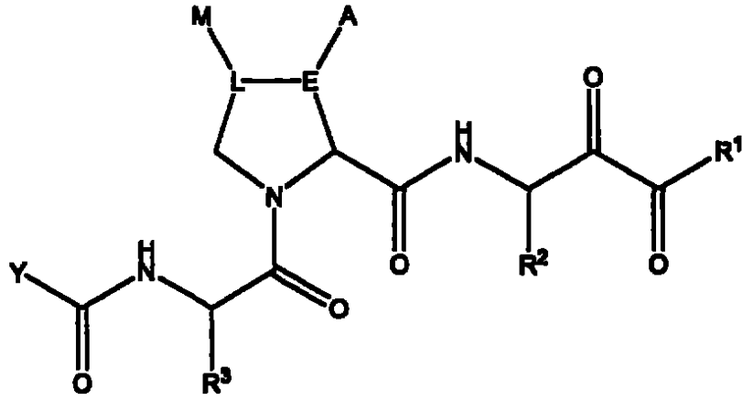
Existe la necesidad de métodos para modular la actividad de serina proteasas, particularmente la serina proteasa NS3/NS4a del VHC, utilizando los compuestos provistos en la presente memoria descriptiva

Existe la necesidad de métodos para modular el procesamiento del polipéptido del VHC utilizando los compuestos provistos en la presente memoria descriptiva

Síntesis de la Invención

En sus muchas realizaciones, la presente invención proporciona una clase novedosa 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 esos compuestos, y métodos de tratamiento o prevención del VHC o mejora de uno o más de los síntomas de la hepatitis C utilizando uno o más de ese tipo de compuestos o una o más de ese tipo de formulaciones También se proporcionan métodos para modular la interacción de un polipéptido de VHC con proteasa de VHC Entre los compuestos proporcionados en la presente memoria descriptiva, los compuestos que inhiben la actividad de la serina proteasa NS3/NS4a del VHC son preferidos La presente invención describe compuestos, o enantiómeros, estereoisómeros, rotámeros, tautómeros, diastereómeros y racematos de dichos compuestos, o una sal farmacéuticamente

aceptable, solvato o éster de dichos compuestos, teniendo dichos compuestos la estructura general mostrada en la Fórmula estructural 1

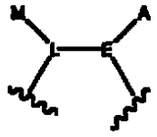


Fórmula I

en la cual

R^1 es H, OR^8, NR^9R^{10}, o CHR^9R^{10}, en la cual R^8, R^9 y R^{10} pueden ser iguales o diferentes, siendo cada uno seleccionado independientemente del grupo formado por H, alquil-, alquenil-, alquinil-, aril-, heteroalquil-, heteroaril-, cicloalquil-, heterocicil-, arialquil-, y heteroarilalquilo,

A y M pueden ser iguales o diferentes, siendo cada uno seleccionado independientemente entre R, NR^9R^{10}, SR, SO_2R, y halo, o A y M están conectados entre si de modo que la porción



que se muestra más arriba en la Fórmula I (es decir, M-L-E-A tomados juntos) forma ya sea un cicloalquilo de tres, cuatro, seis, siete u ocho miembros, un heterocicilo de cuatro a ocho miembros, un arilo de seis a diez miembros o un heteroarilo de cinco a diez miembros,

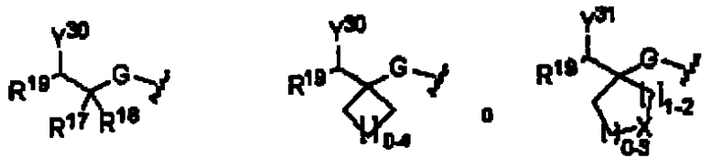
E es C(H) o C(R),

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

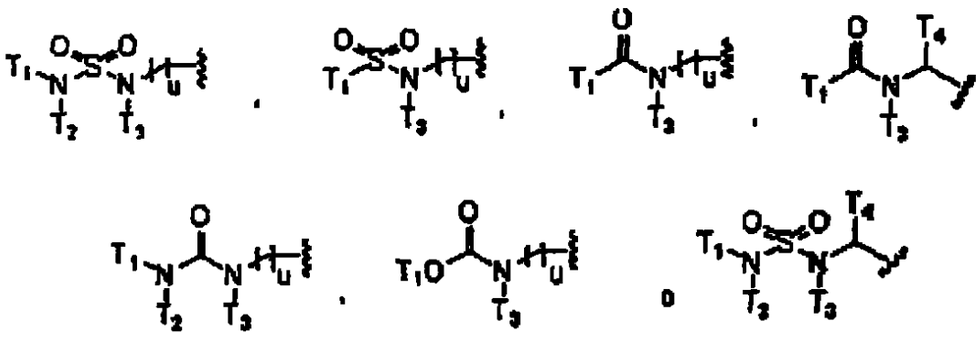
474
179

R, R', R^2, y R^3 pueden ser iguales o diferentes, siendo cada uno seleccionado independientemente del grupo formado por H, alquil-, alquenil-, alquinil-, cicloalquil-, heteroalquil-, heterociclil-, aril-, heteroaril-, (cicloalquil)alquil-, (heterociclil)alquil-, aril-alquil-, y heteroaril-alquil-, o alternativamente R y R' en NRR' están conectados entre sí de modo que NR^9R^{10} forma un heterociclilo de cuatro a ocho miembros,

Y se selecciona de las siguientes porciones



donde Y^{30} e Y^{31} se seleccionan entre



donde u es un N° 0-6

X se selecciona entre O, NR^{15}, $NC(O)R^{16}$, S, S(O) y SO_2,

G es NH o O, y

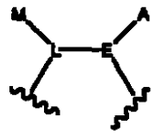
R^{15}, R^{16}, R^{17} , R^{18}, R^{19}, T_1, T_2, T_3 y T_4 pueden ser iguales o diferentes, siendo cada uno seleccionado independientemente del grupo formado por H, alquilo, heteroalquilo, alquenilo, heteroalquenilo, alquinilo, heteroalquinilo, cicloalquilo,

175
175

heterociclilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, o alternativamente, R^{17} y R^{18} están conectados entre si para formar un cicloalquilo o heterociclilo de tres a ocho miembros,

donde cada uno de dicho alquilo, arilo, heteroarilo, cicloalquilo o heterociclilo puede estar no sustituido u opcionalmente independientemente sustituidos con una o más porciones seleccionadas del grupo formado por hidroxi, alcoxi, ariloxi, tio, alquiltio, aniilo, amino, amido, alquilamino, arilamino, alquilsulfonilo, arilsulfonilo, sulfonamido, alquilo, arilo, heteroarilo, alquilsulfonamido, arilsulfonamido, ceto, carboxi, carbalcoxi, carboxamido, alcoxicarbonilamino, alcoxicarboniloxi, alquilureido, arilureido, halo, ciano, y nitro

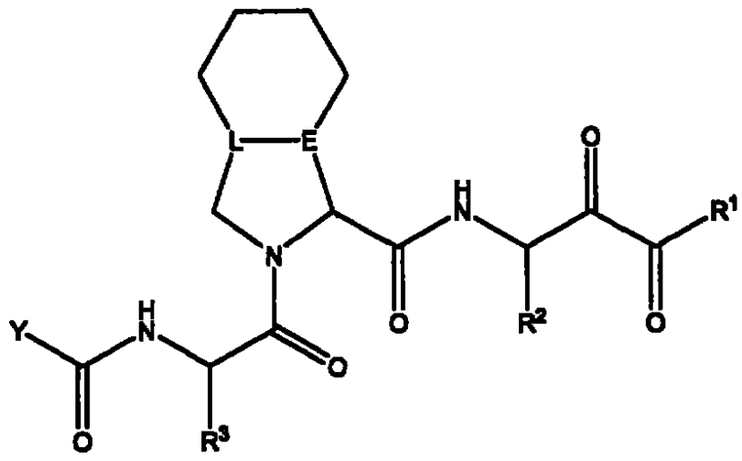
La indicación antes mencionada "A y M están conectados entre sí de modo que la porción



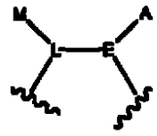
que se muestra anteriormente en la Fórmula I forma ya sea un cicloalquilo de tres, cuatro, seis, siete u ocho miembros, un heterociclilo de cuatro a ocho miembros, un arilo de seis a diez miembros, o un heteroanlo de cinco a diez miembros" puede ser ilustrada de manera no limitativa de la siguiente manera Por lo tanto, por ejemplo, en el caso en que A y M están conectados de modo que la porción



que se muestra anteriormente en la Fórmula I forma un cicloalquilo (ciclohexilo) de seis miembros, La Fórmula I puede ser ilustrada como



Un experto en la técnica apreciará que puede ambarse á descripciones similares para la Fórmula I cuando A y M que se muestran más arriba en la porción



(M-L-E-A tomados en forma conjunta) están conectados para formar un cicloalquilo de tres, cuatro, siete u ocho miembros, un heterocicilo de cuatro a ocho miembros, un anlo de seis a diez miembros, o un heteroarilo de cinco a diez miembros

En las definiciones antes señaladas de R, R', R^2, y R^3 alquilo preferido está hecho de uno a diez átomos de carbono, alquenilo o alquinilo preferido está hecho de dos a diez átomos de carbono, cicloalquilo preferido está hecho de tres a ocho átomos de carbono, y heteroalquilo, heteroarilo o heterocicloalquilo (heterocicilo) preferido tiene uno a seis átomos de oxígeno, nitrógeno, azufre o fósforo

Los compuestos representados por la Fórmula I, por si mismos o en combinación con uno o más agentes adecuados diferentes descritos en la presente memoria descriptiva, pueden ser útiles para el tratamiento de enfermedades tales como, por ejemplo, VHC, HIV, SIDA (Síndrome de Inmunodeficiencia Adquirida), y trastornos relacionados, así como también para modular la actividad de la proteasa

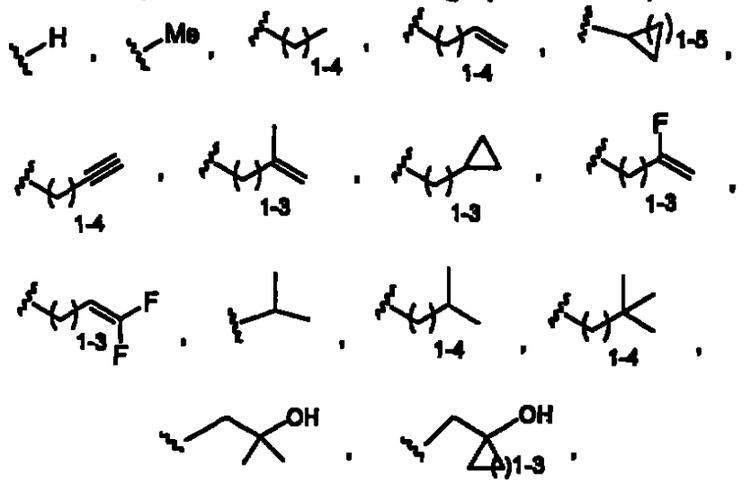
del virus de la hepatitis C (VHC), para prevenir el VHC, o aliviar uno o más síntomas de la hepatitis C Tal modulación, tratamiento, prevención o alivio puede realizarse con los compuestos de la invención así como también con composiciones o formulaciones farmacéuticas que comprenden tales compuestos Sin estar limitados por la teoría, se cree que la proteasa del VHC puede ser la proteasa NS3 o NS4a Los compuestos de la invención pueden inhibir ese tipo de proteasa También pueden modular el procesamiento del polipéptido del virus de la hepatitis C (VHC)

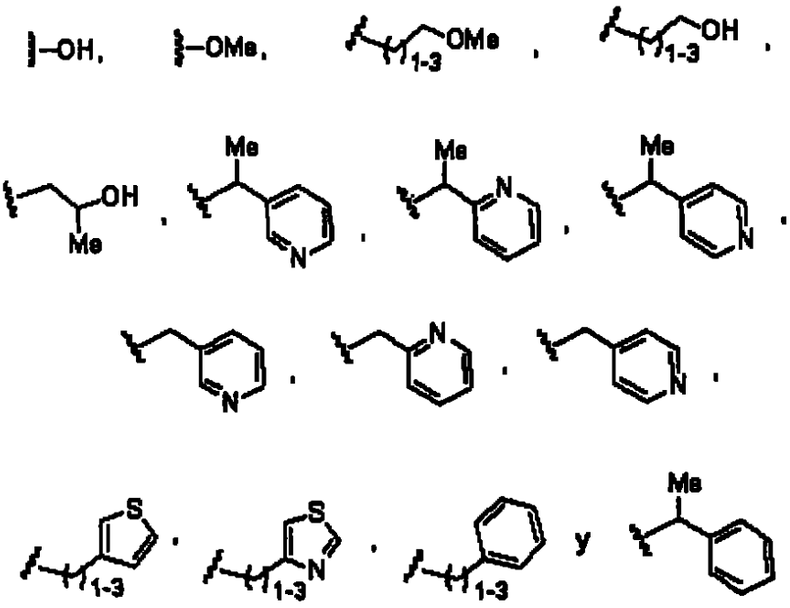
Descripción Detallada

En una realización, la presente invención describe compuestos los cuales son representados mediante la Fórmula estructural 1 o una sal, solvato o éster de los mismos farmacéuticamente aceptables, en donde las diversas porciones son según lo definido anteriormente

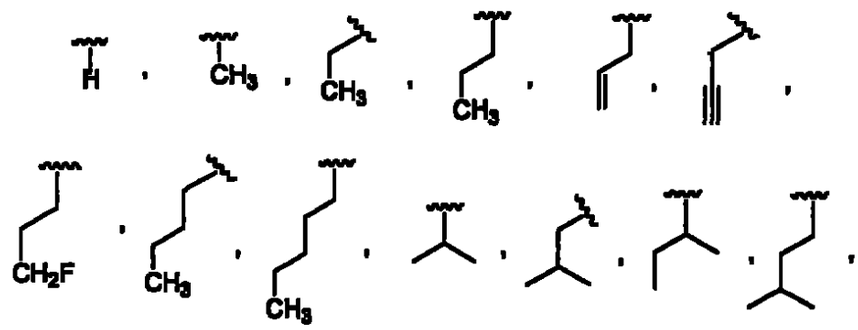
En otra realización, R^1 es NR^9R^{10}, y R^9 es H, R^{10} es H, o R^{14} donde R^{14} es H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, alquil-arilo, alquil-heteroarilo, aril-alquilo, alquenilo, alquinilo o heteroaril-alquilo

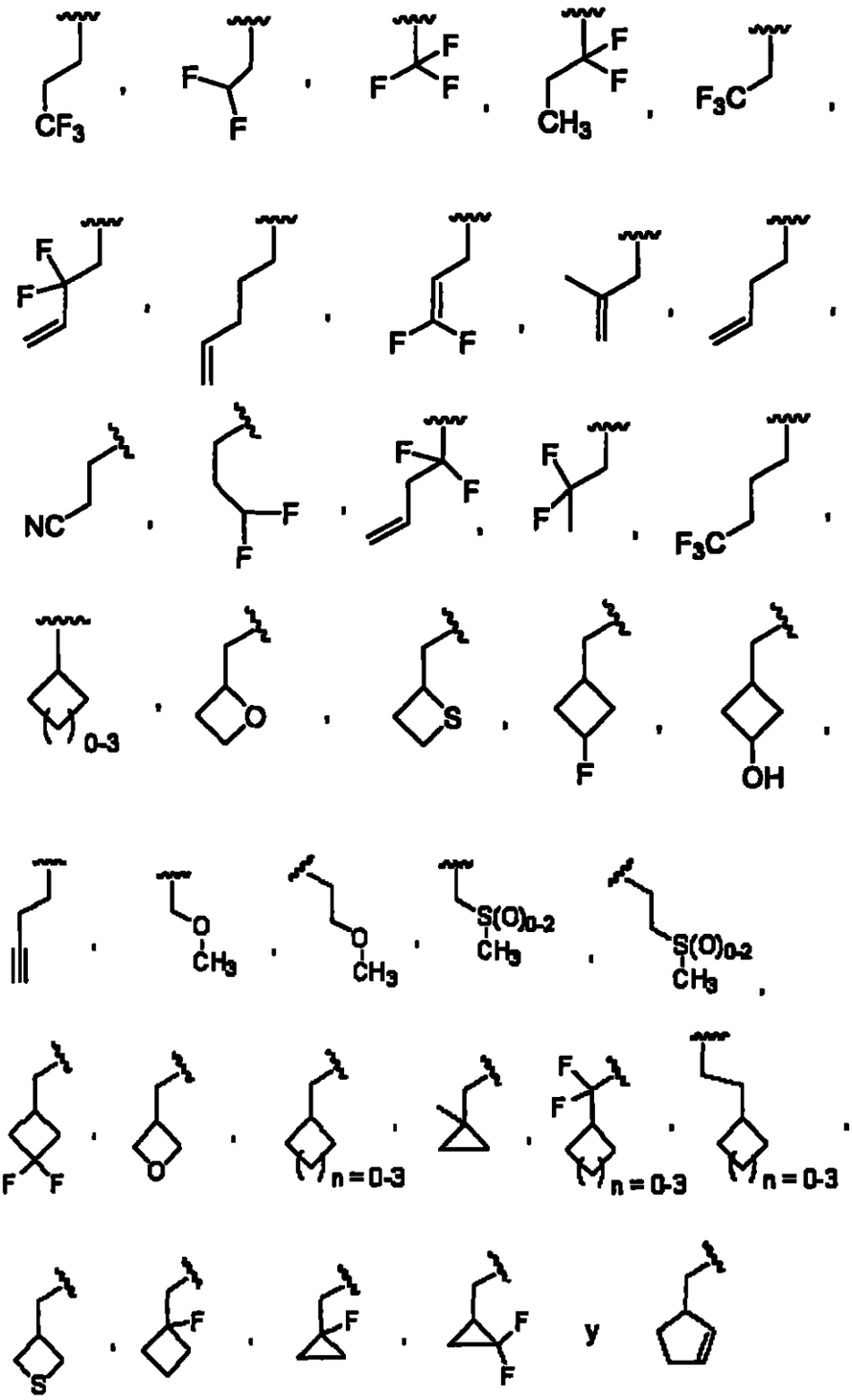
En otra realización, R^{14} se selecciona del grupo formado por



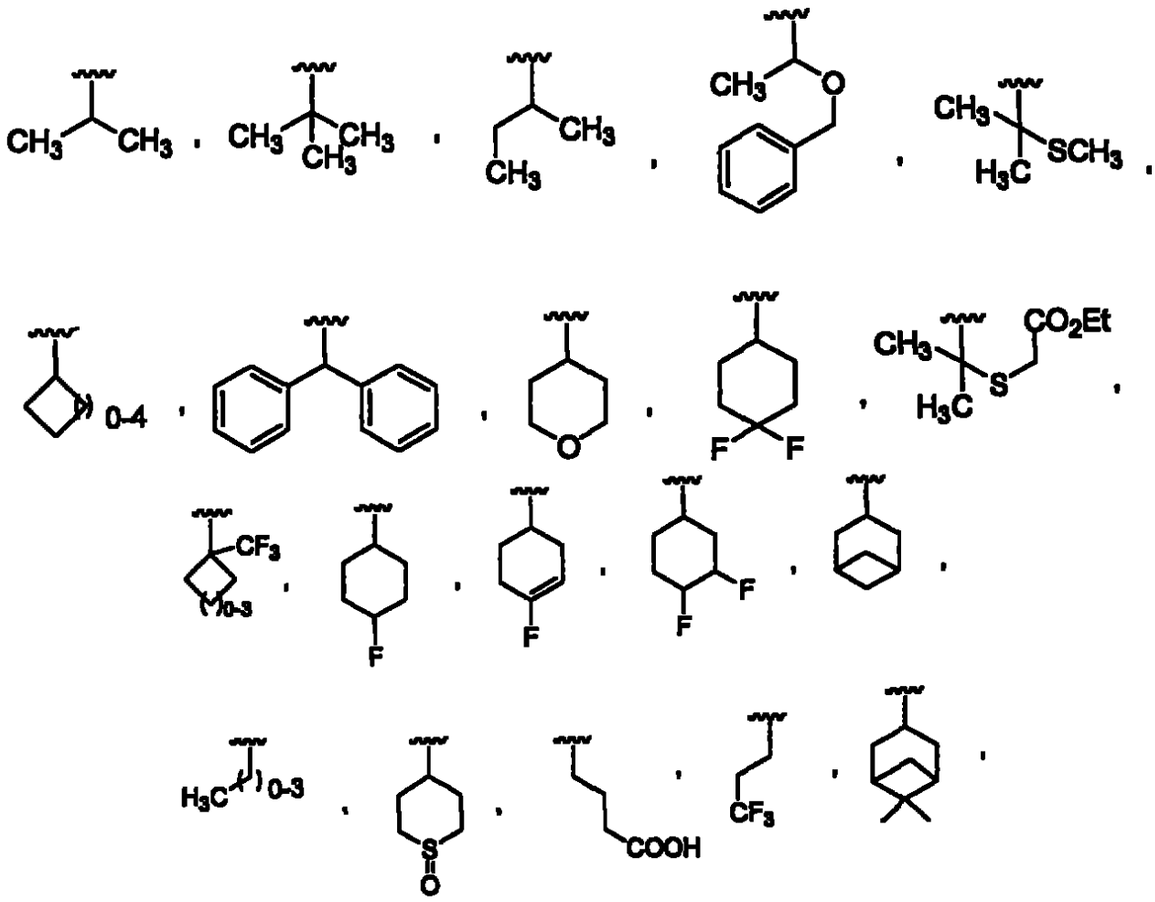


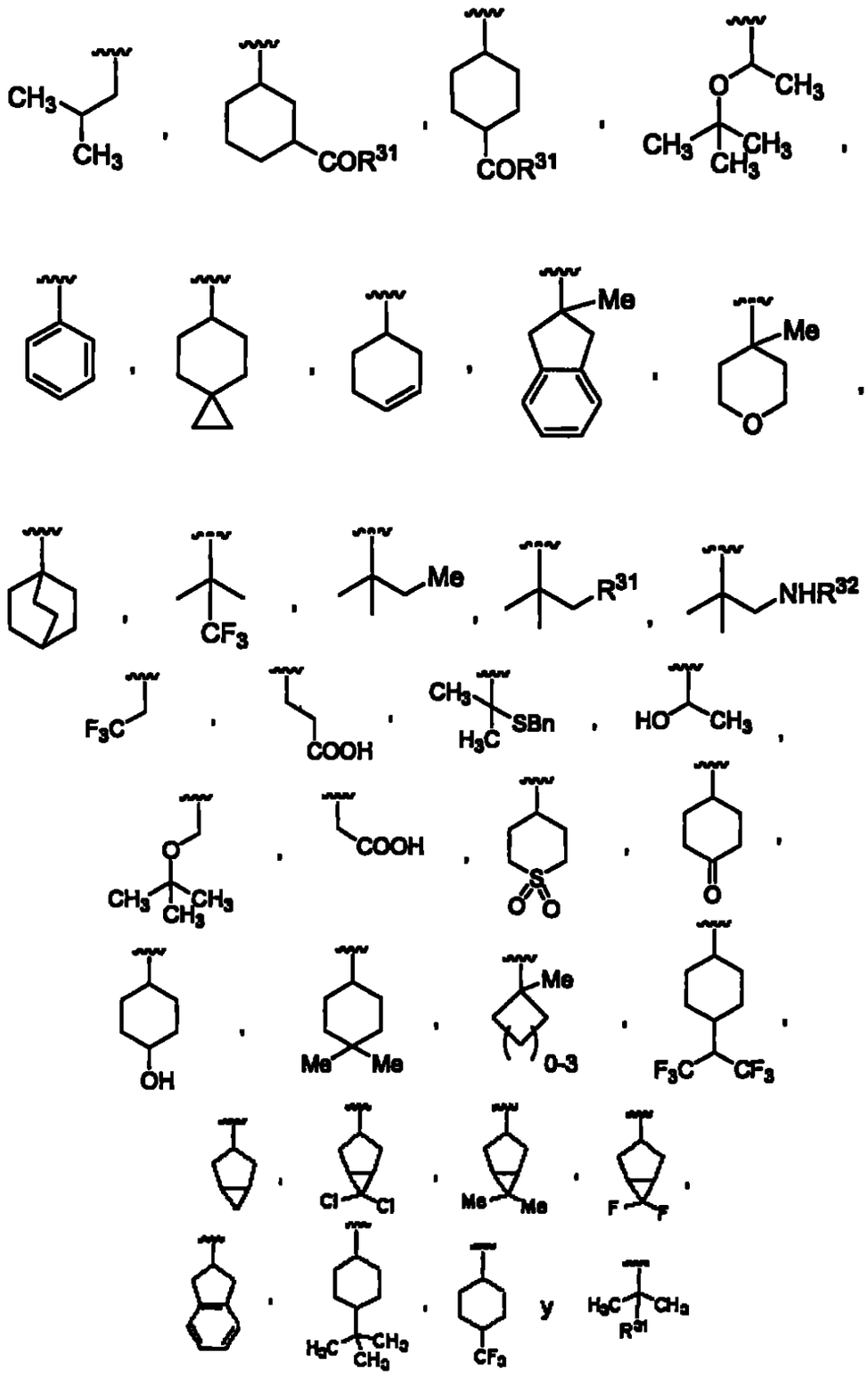
En otra realización, R^2 se selecciona del grupo formado por las siguientes porciones





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

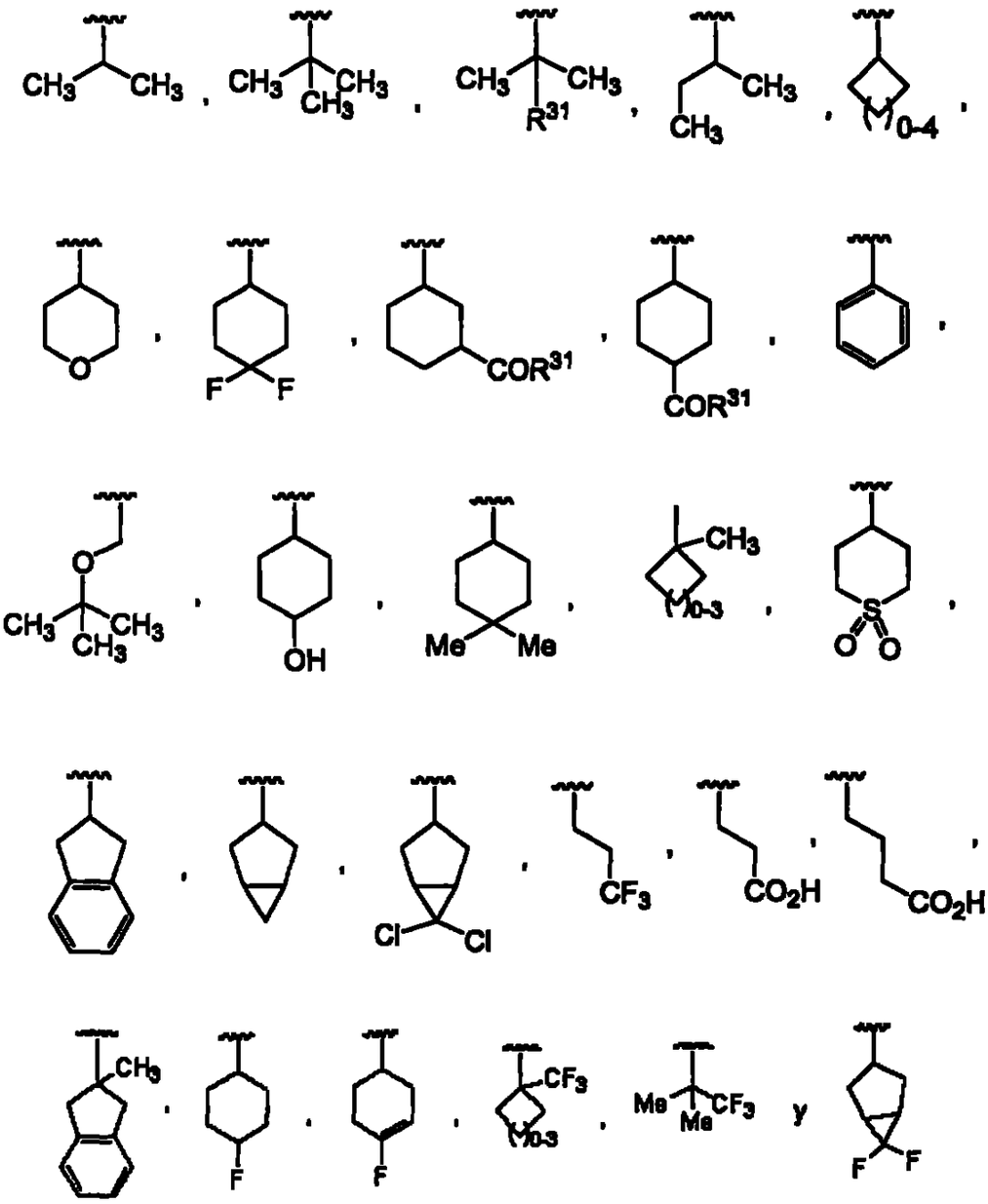



CH3
CH3
COR31
COR31
O
CH3
CH3
CH3
CH3
Me
Me
O
CF3
Me
R31
NHR32
F3C
COOH
CH3
SBn
H3C
HO
CH3
O
CH3
CH3
CH3
COOH
S
O
O
O
OH
Me
Me
Me
0-3
F3C
CF3
Cl
Cl
Me
Me
F
F
H3C
CH3
CH3
CF3
y
H3C
CH3
R31

en donde R^{31} es OH o O-alquilo, y

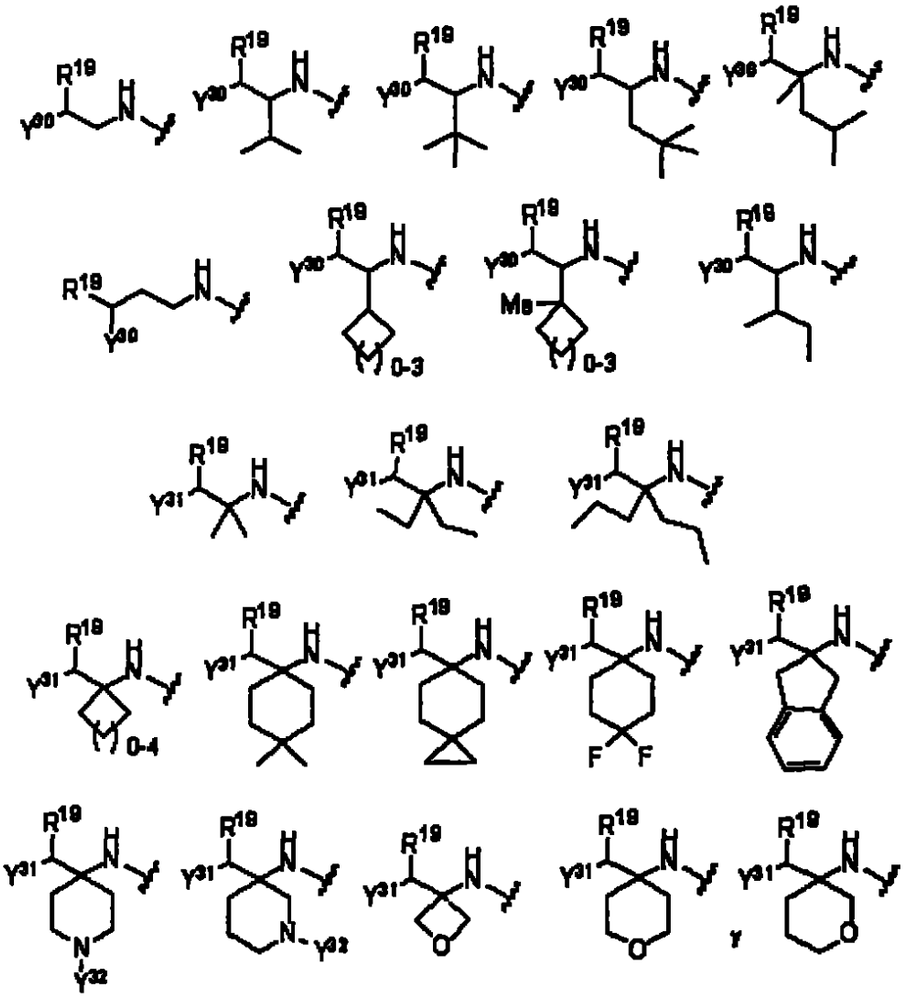
R^{32} es H, $C(O)CH_3$, C(O)OtBu o C(O)N(H)tBu

En una realización adicional, R^3 se selecciona del grupo formado por las siguientes porciones

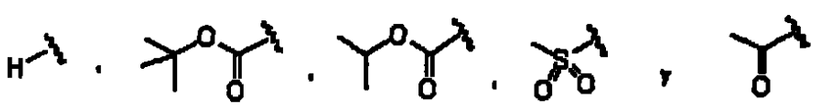


En otra realización, G es NH

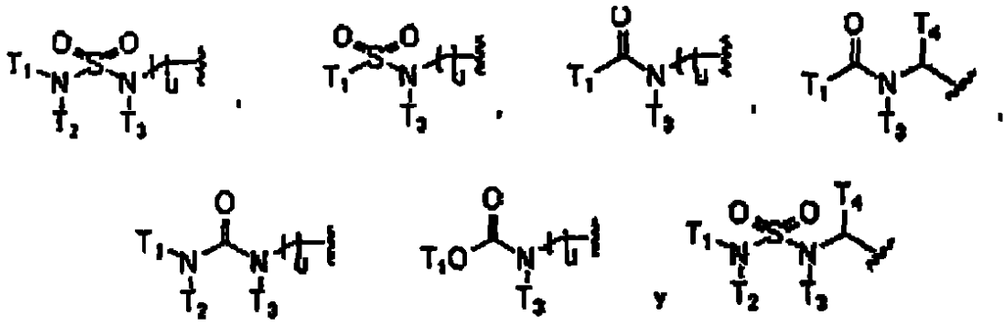
En otra realización, Y se selecciona de las siguientes porciones



donde Y^{32} se selecciona entre el grupo que consiste en



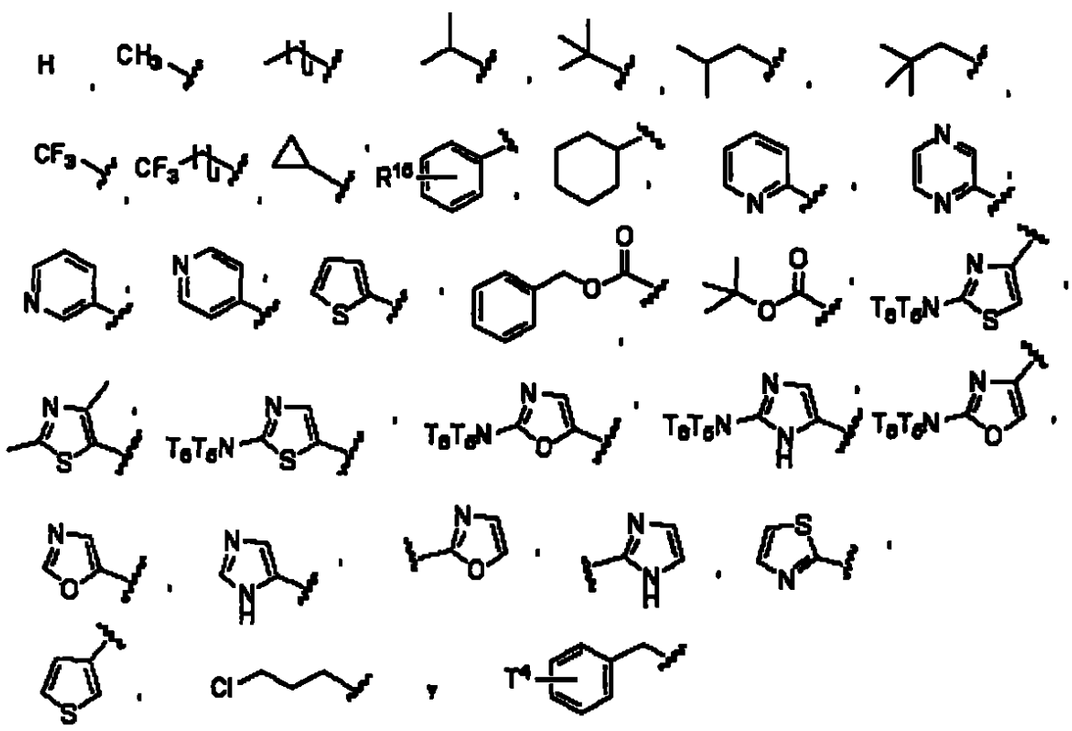
Y^{30} e Y^{31} se selecciona entre



donde v es N= 0-6

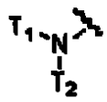
y R^{16} se selecciona entre H, alquilo, fenilo o bencilo

En otra realización, T_1 y T_2 pueden ser iguales o diferentes, siendo cada uno seleccionado en forma independiente entre el grupo que consiste en

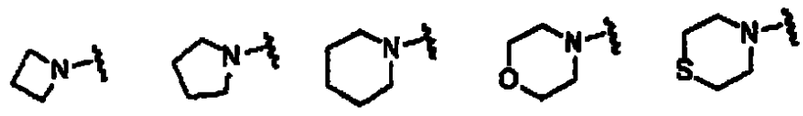


en la cual T_5 y T_6 pueden ser iguales o diferentes, siendo cada uno seleccionado en forma independiente entre el grupo que consiste en alquilo, arilo, cicloalquilo, heteroarilo y heterociclilo,

o la porción

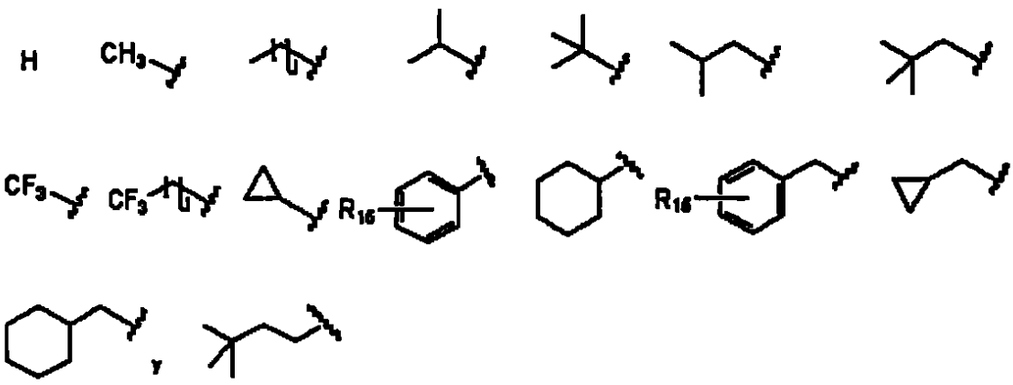


en forma conjunta representar



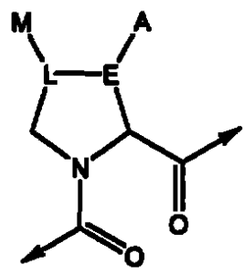
y

T_3 y T_4 pueden ser iguales o diferentes, cada uno se selecciona independientemente entre

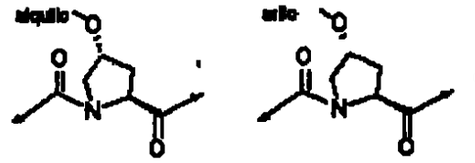


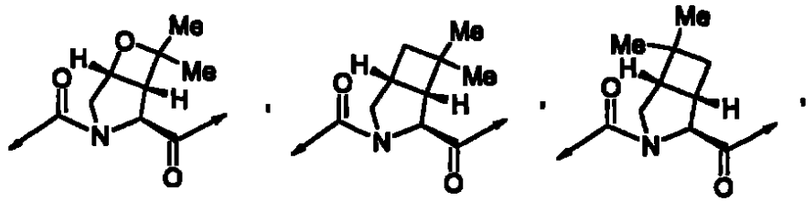
o T_3 y T_4 tomados en forma conjunta pueden formar parte de un anillo heterocíclico de cuatro a siete miembros, en otras palabras, la porción T_3-N-C-T_4 puede formar parte de un anillo heterocíclico de cuatro a siete miembros

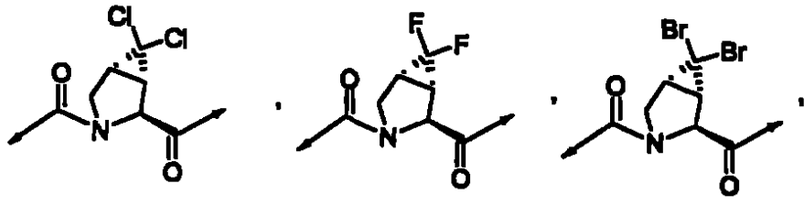
En otra realización la porción

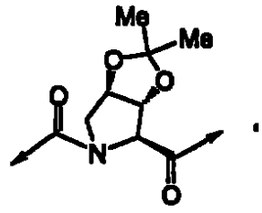


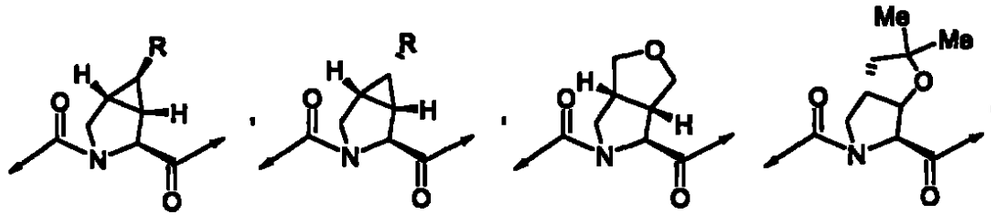
se selecciona de las siguientes estructuras

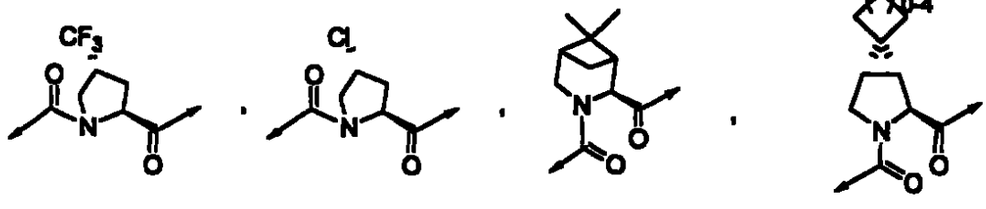


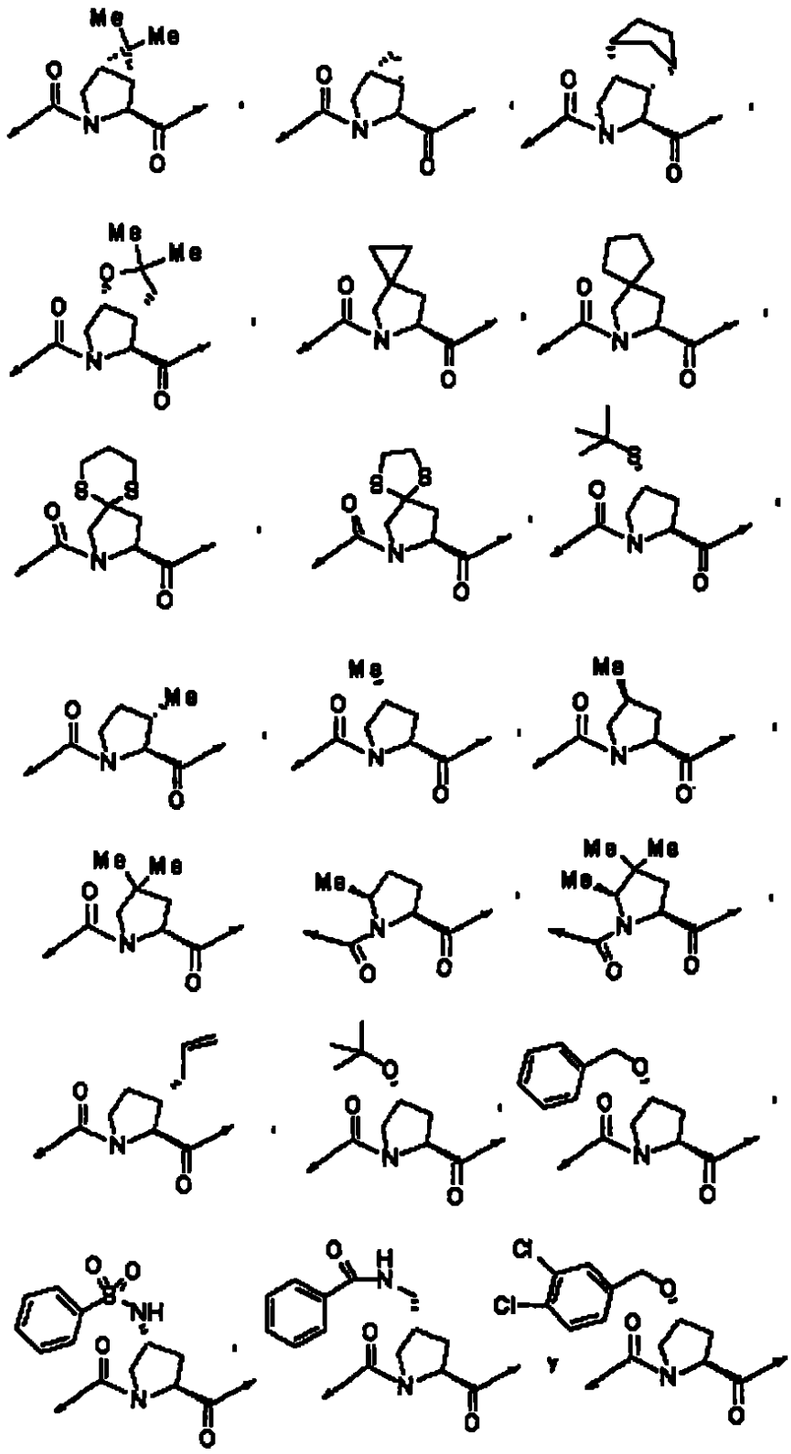




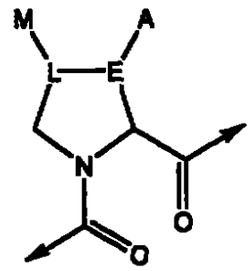




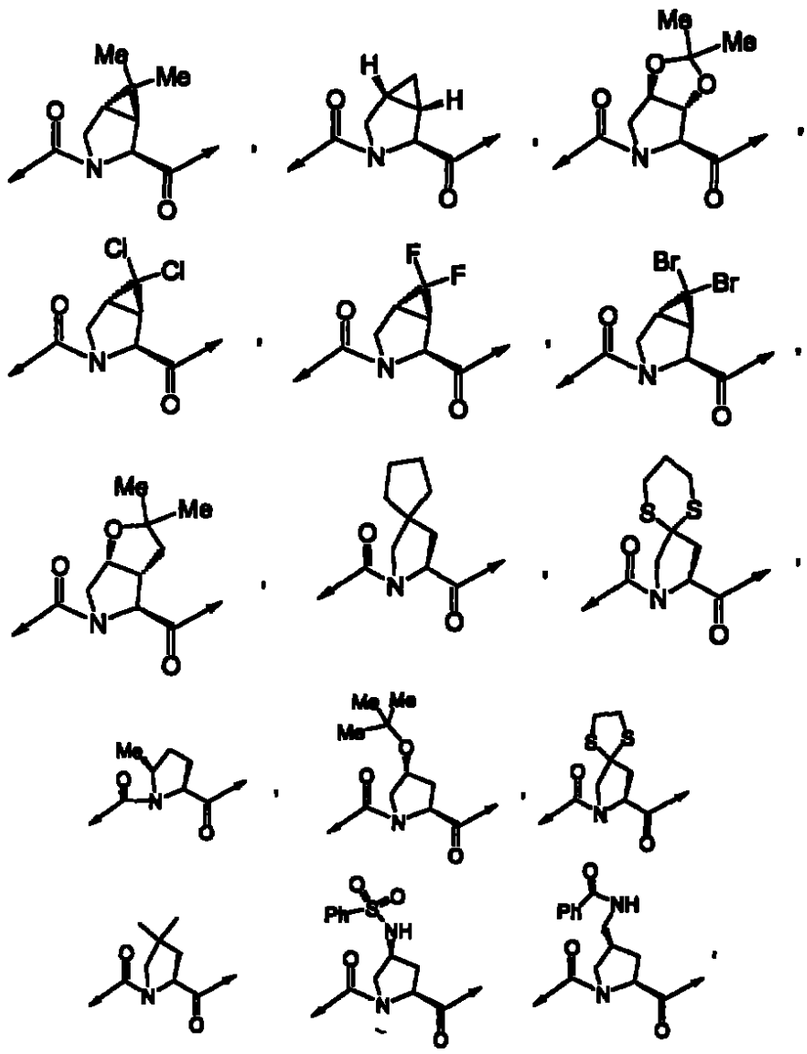


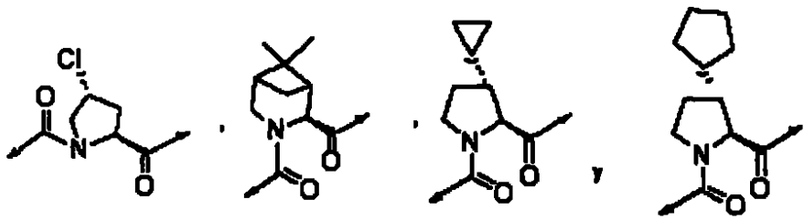


En una realización adicional, la porción

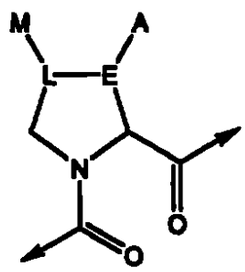


se selecciona de las siguientes estructuras

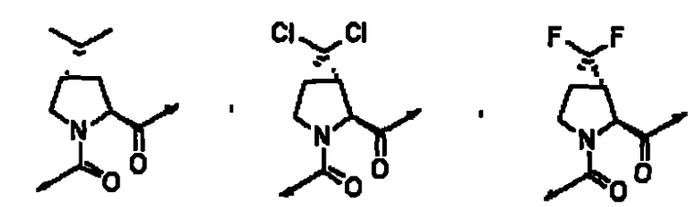


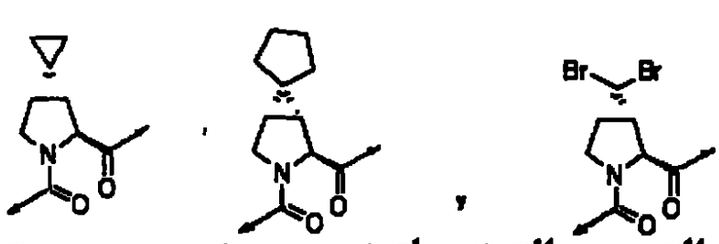


En aun una realización adicional, la porción

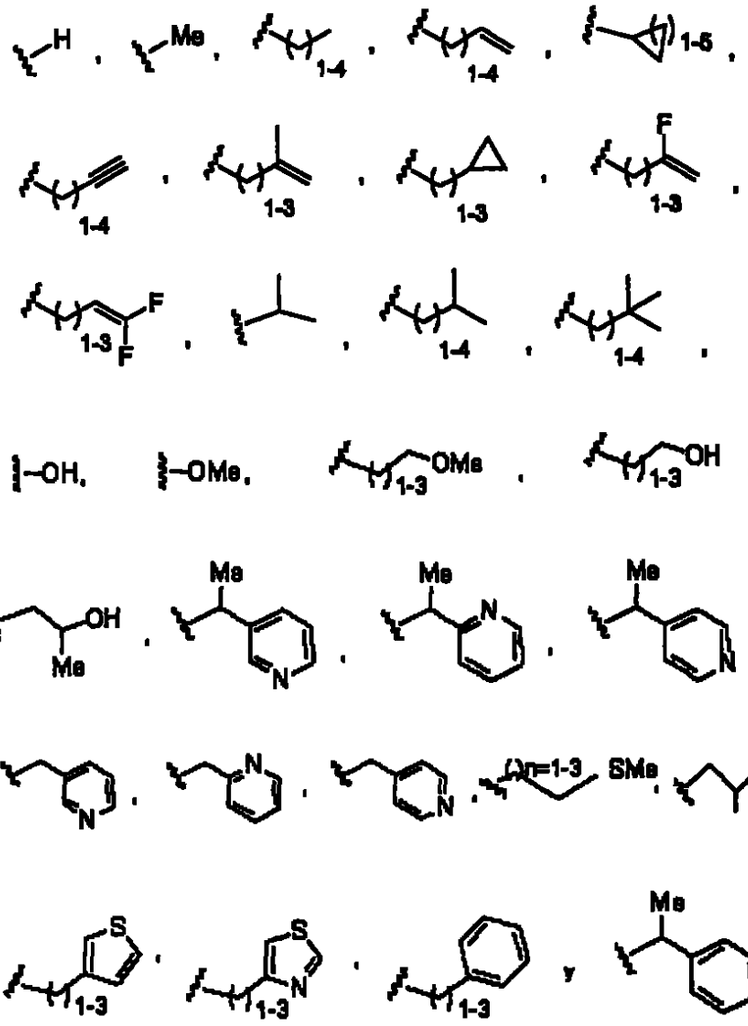


se selecciona de las siguientes estructuras

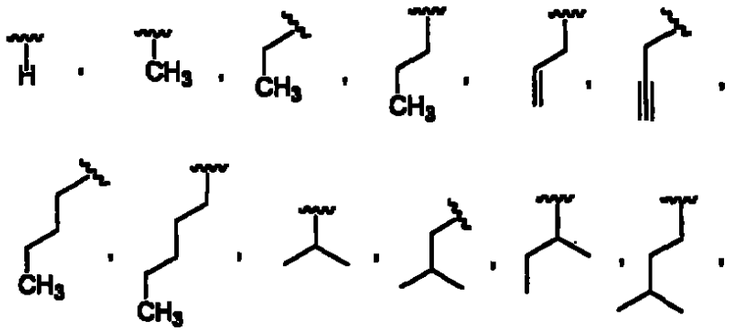


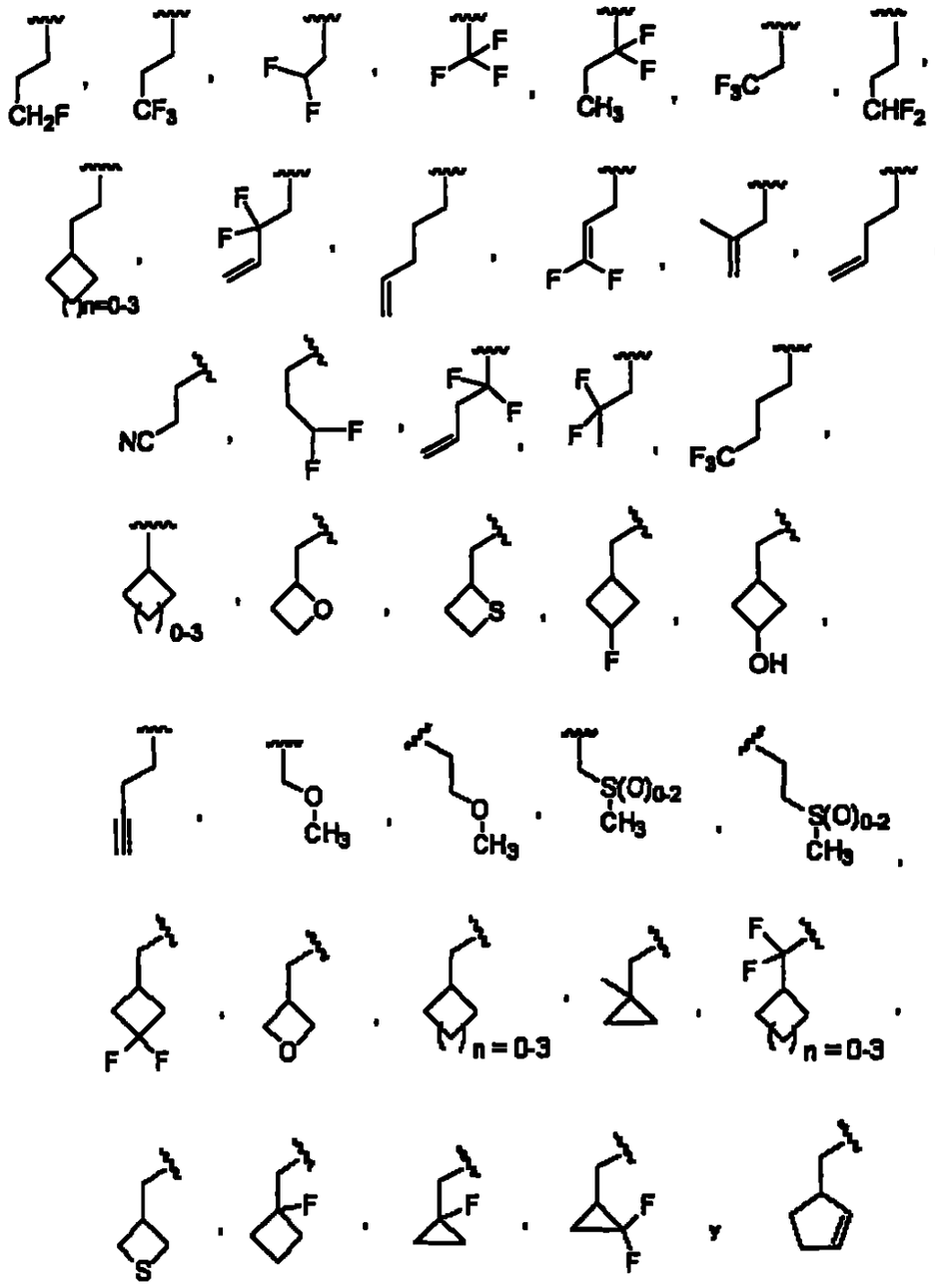


En una realización adicional, R^1 es NHR^{14}, donde R^{14} se selecciona entre el grupo que consiste en

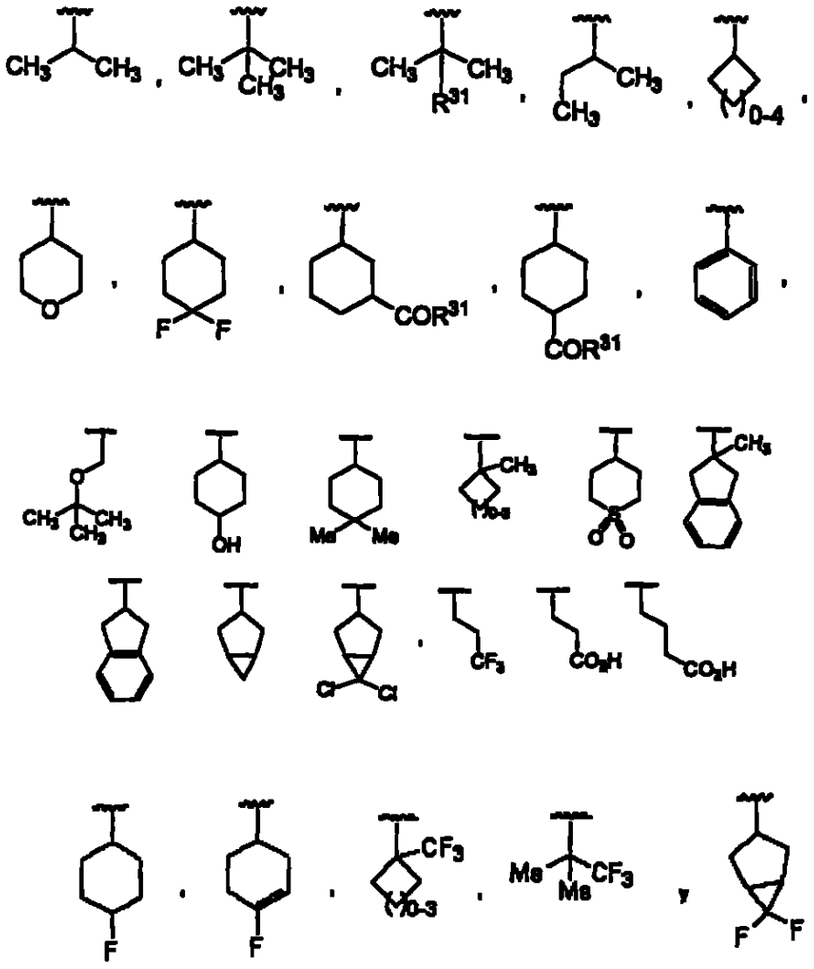


R^2 se selecciona del grupo que consiste en las siguientes porciones



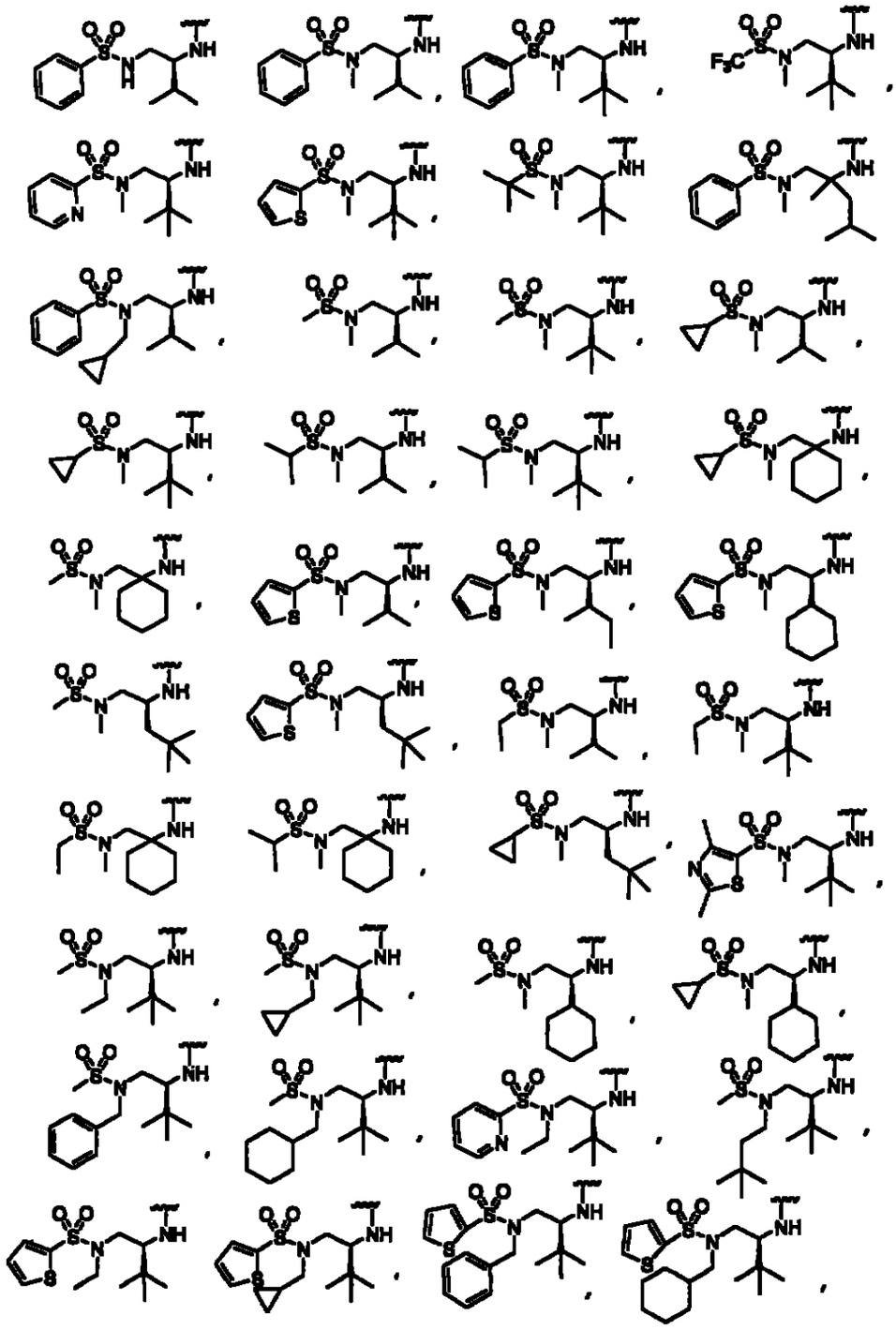


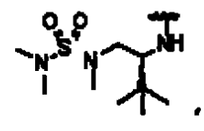
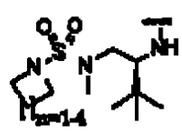
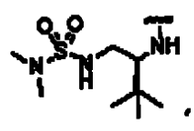
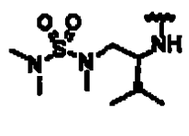
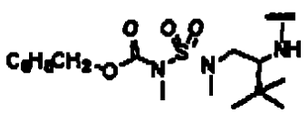
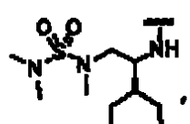
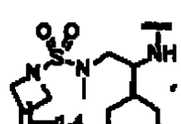
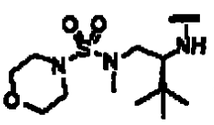
R^3 se selecciona entre el grupo que consiste en las siguientes porciones

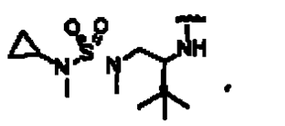
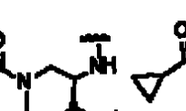


Y se selecciona entre el grupo que consiste en

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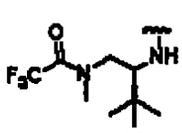
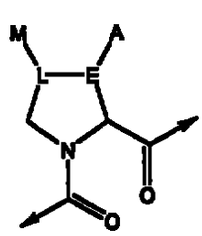
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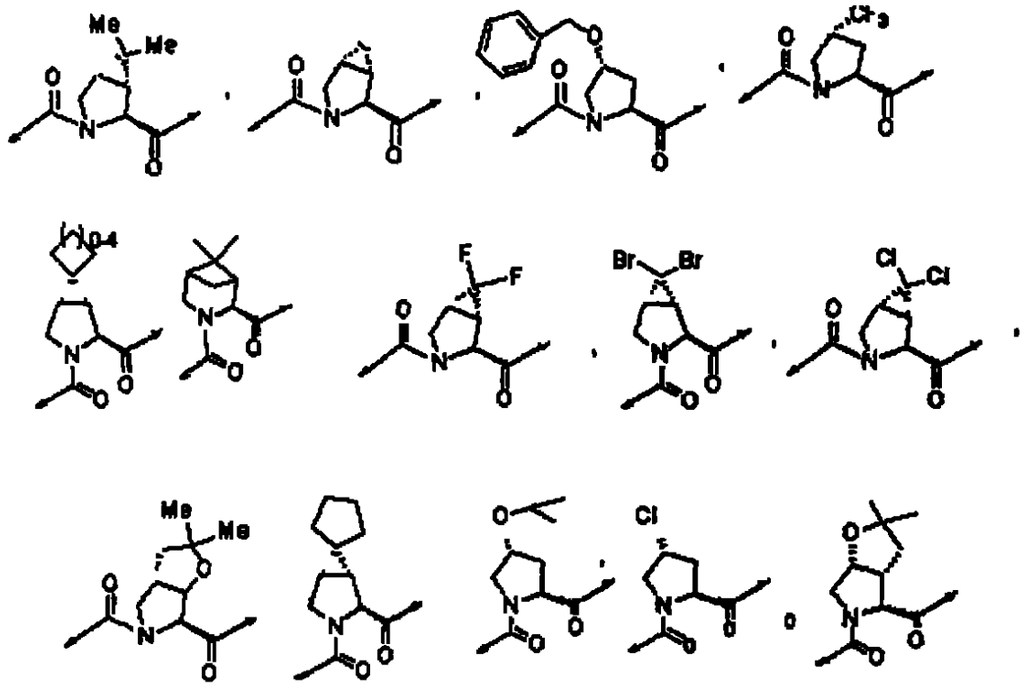
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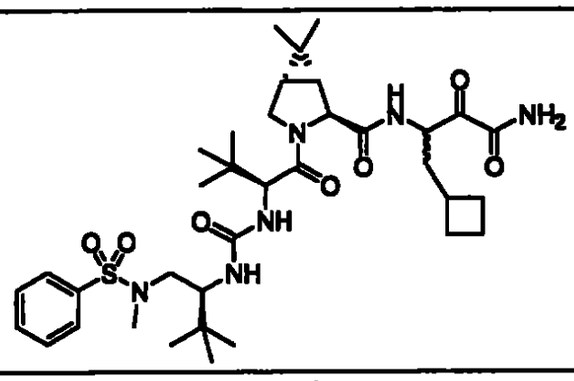
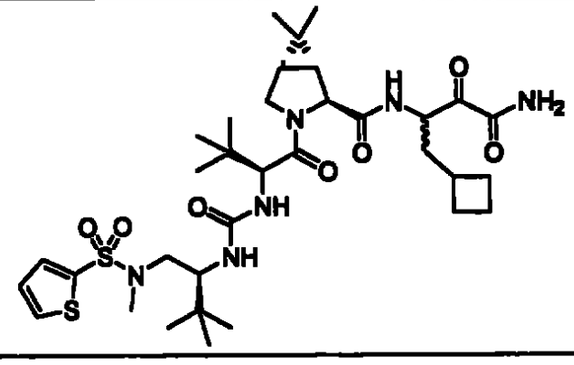
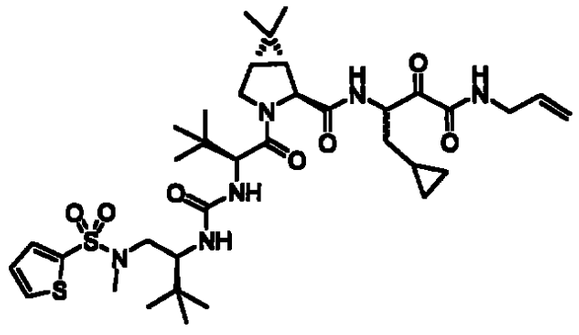
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y la porción

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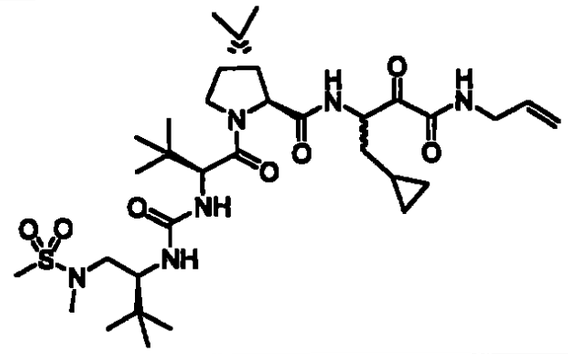
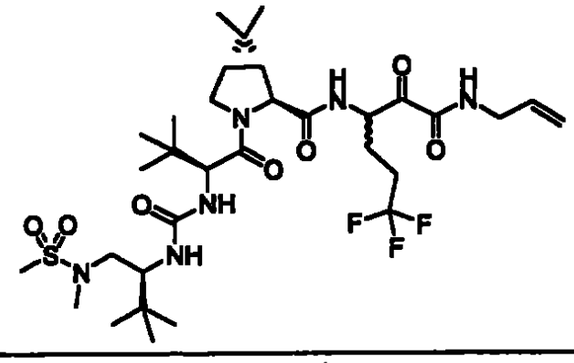
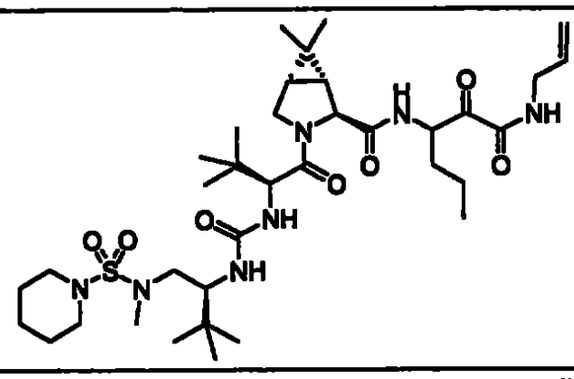
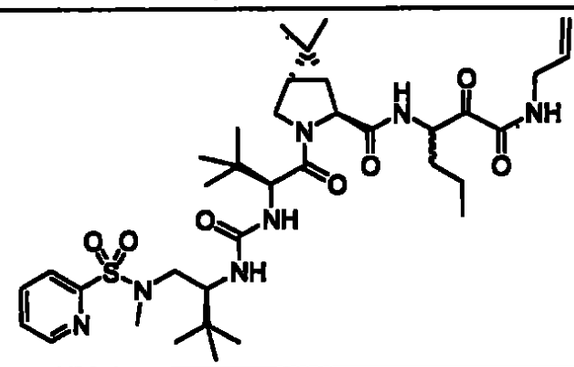
Aun otra realización de la invención describe compuestos mostrados en la Tabla 1, Tabla 2, Tabla 3, Tabla 4 y Tabla 5 más adelante en esta Descripción También se muestra en las Tablas las actividades biológicas de diversos compuestos de la invención (como valores Ki* en nanoMolar)

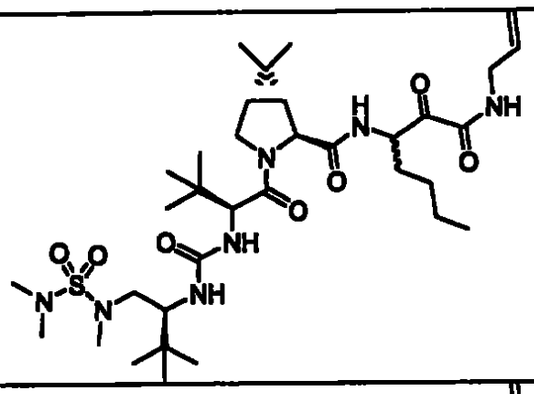
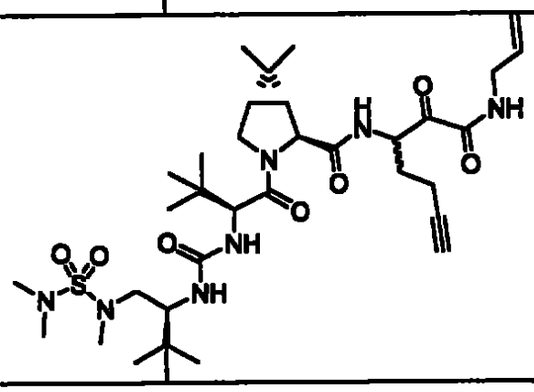
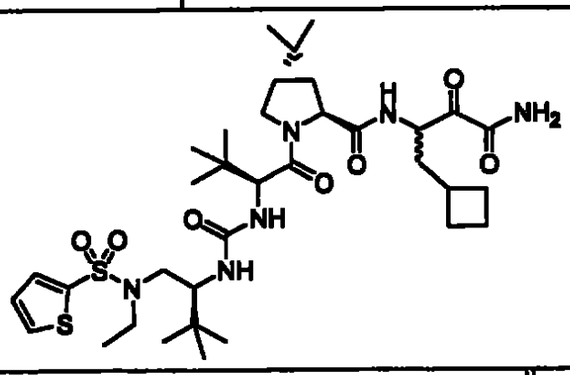
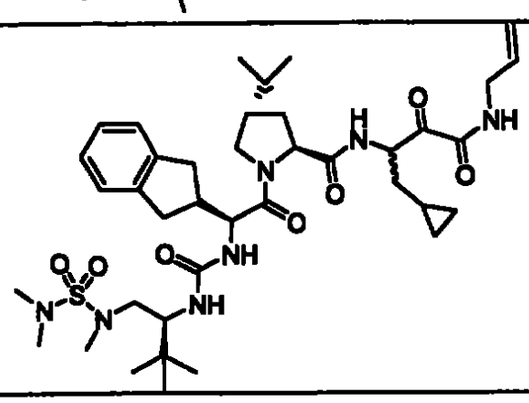
En aun otra realización, esta invención describe los siguientes compuestos en la Tabla 6

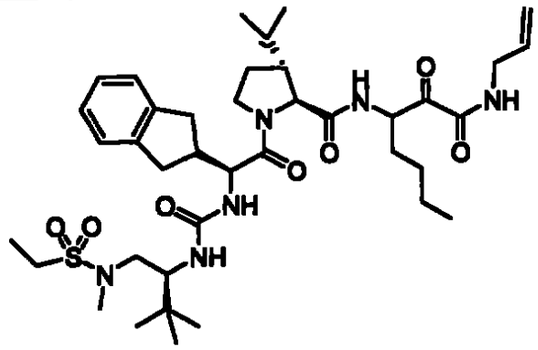
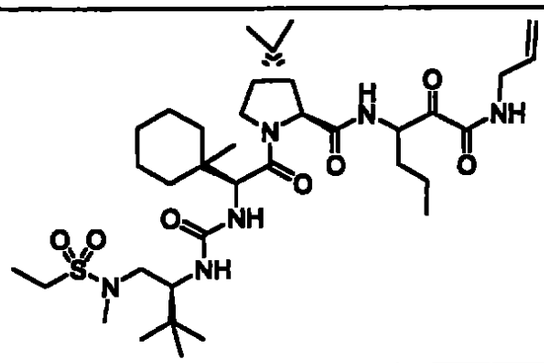
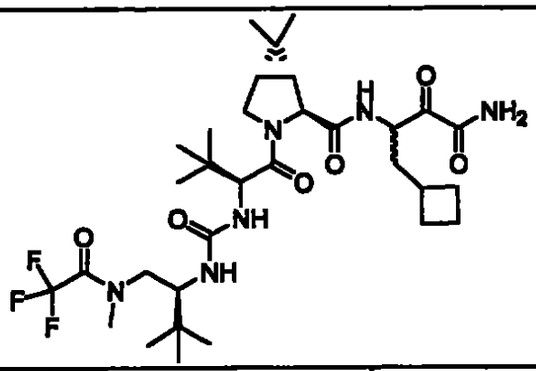
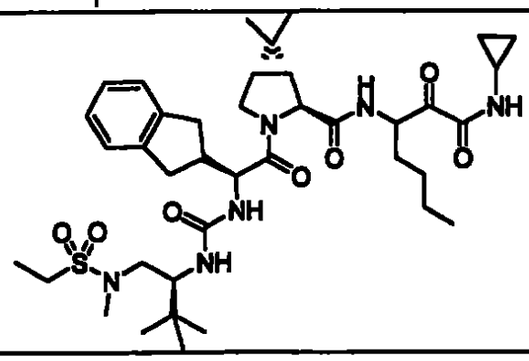
Tabla 6

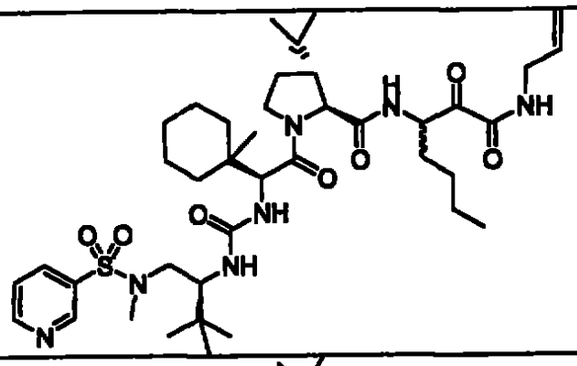
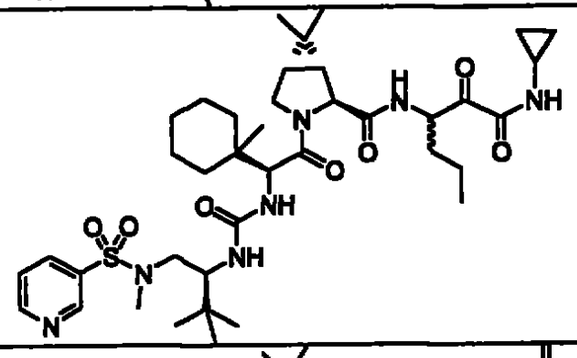
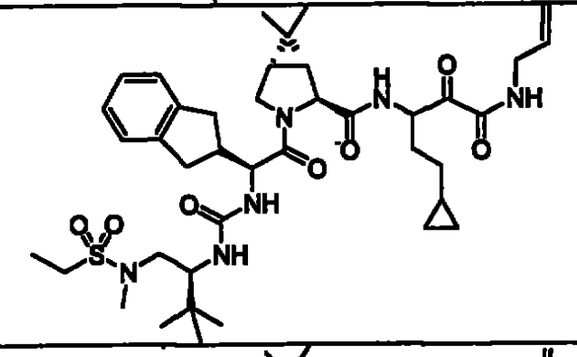
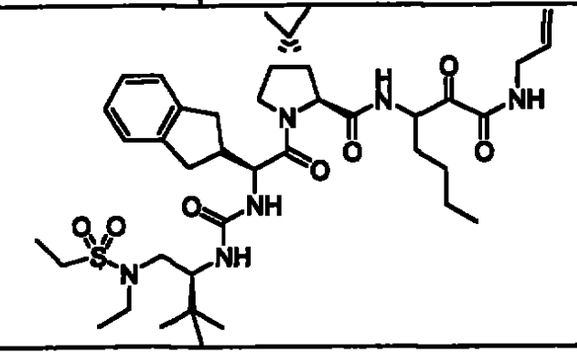
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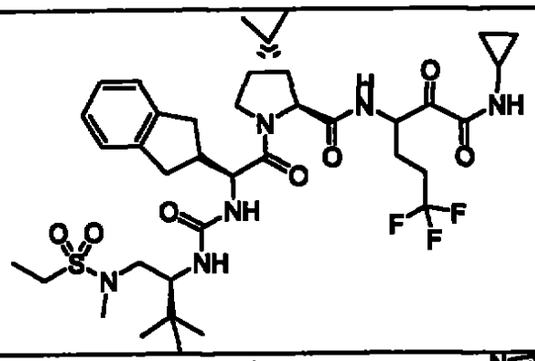
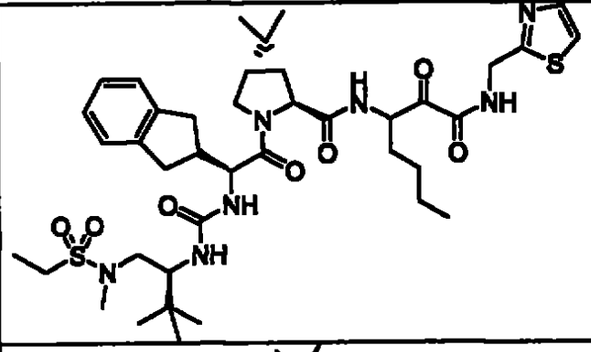
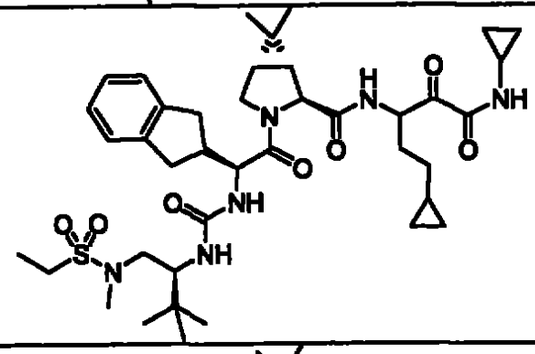
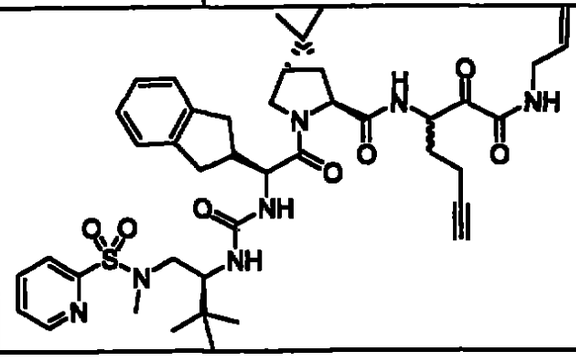
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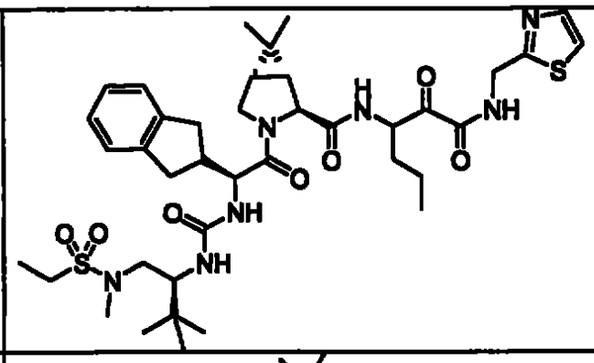
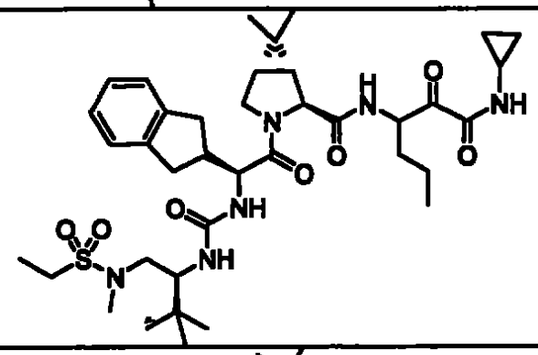
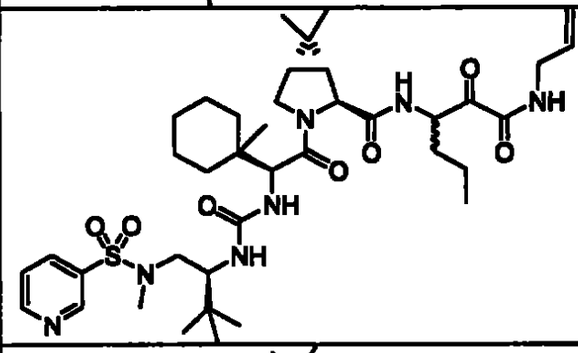
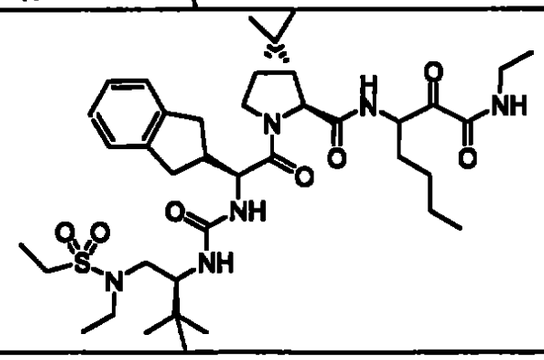
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11417		6
11401		6

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11418		7
11421		7
11395		8

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Como se utiliza en lo que antecede, y a lo largo de esta descripción, los siguientes términos, a menos que se indique lo contrario, se entenderán como que tienen los siguientes significados

"Paciente" incluye tanto humano como animales

"Mamífero" significa humanos y otros animales mamíferos

"Alquilo" significa un grupo hidrocarburo alifático el cual puede ser recto o ramificado y que comprende aproximadamente 1 a aproximadamente 20 átomos de carbono en la cadena Los grupos alquilo preferidos contienen aproximadamente 1 a aproximadamente 12 átomos de carbono en la cadena Los grupos alquilo más preferidos contienen de aproximadamente 1 a 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 alquílica lineal "Alquilo inferior" significa un grupo que tiene aproximadamente 1 a aproximadamente 6 átomos de carbono en la cadena la cual puede ser recta o ramificada El término "alquilo sustituido" significa que el grupo alquilo puede estar sustituido con uno o más sustituyentes los cuales pueden ser iguales o diferentes, siendo cada sustituyente seleccionado independientemente del grupo formado por halo, alquilo, arilo, cicloalquilo, ciano, hidroxi, alcoxi, alquiltio, amino, -NH(alquilo), -NH(cicloalquilo), -N(alquilo)$_2$, -N(alquilo)$_2$, carboxi y –C(O)O-alquilo Ejemplos no limitativos de grupos alquilo adecuados incluyen metilo, etilo, n-propilo, isopropilo y t-butilo

"Alquenilo" significa un grupo hidrocarburo alifático que contiene por lo menos un enlace doble carbono- carbono y el cual puede ser recto o ramificado y que comprende aproximadamente 2 a aproximadamente 15 átomos de carbono en la cadena Los grupos alquenilo preferidos tienen aproximadamente 2 a aproximadamente 12 átomos de carbono en la cadena, y más preferentemente

aproximadamente 2 a 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 alquenilo lineal "Alquenilo inferior" significa aproximadamente 2 a aproximadamente 6 átomos de carbono en la cadena la cual puede ser recta o ramificada El término "alquenilo sustituido" significa que el grupo alquenilo puede estar sustituido con uno o más sustituyentes los cuales pueden ser iguales o diferentes, estando cada sustituyente seleccionado independientemente del grupo formado por halo, alquilo, arilo, cicloalquilo, ciano, alcoxi y –S(alquilo) Los ejemplos no limitativos de grupos alquenilo adecuados incluyen etenilo, propenilo, n-butenilo, 3-metilbut-2-enilo, n-pentenilo, octenilo y decenilo

"Alquinilo" significa un grupo hidrocarburo alifático que contiene por lo menos un triple enlace carbono- carbono y el cual puede ser recto o ramificado y que comprende aproximadamente 2 a aproximadamente 15 átomos de carbono en la cadena Los grupos alquinilo preferidos tienen aproximadamente 2 a aproximadamente 12 átomos de carbono en la cadena, y más preferentemente aproximadamente 2 a 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" significa aproximadamente 2 a aproximadamente 6 átomos de carbono en la cadena la cual puede ser recta o ramificada Los ejemplos no limitativos de grupos alquinilo adecuados incluyen etinilo, propinilo, 2-butinilo y 3-metilbutinilo El término "alquinilo sustituido" significa que el grupo alquinilo puede ser sustituido con uno o más sustituyentes los cuales pueden ser iguales o diferentes, cada sustituyente es seleccionado independientemente del grupo formado por alquilo, arilo y cicloalquilo

"Arilo" significa un sistema de anillos monocíclico o multicíclico aromático que comprende aproximadamente 6 a aproximadamente 14 átomos de carbono, preferentemente aproximadamente 6 a aproximadamente 10 átomos de carbono El grupo arilo puede estar opcionalmente sustituido con uno o más "sustituyentes en el sistema de anillos" los cuales pueden ser iguales o diferentes, y son según lo definido en la presente Los ejemplos no limitativos de grupos arilo adecuados incluyen fenilo y naftilo

"Heteroarilo" significa un sistema de anillos monocíclico o multicíclico aromático que comprende aproximadamente 5 a aproximadamente 14 átomos en el anillo, preferentemente aproximadamente 5 a aproximadamente 10 átomos en el anillo, en los cuales uno o más de los átomos en el anillo es un elemento diferente a carbono, por ejemplo, nitrógeno, oxígeno o azufre, solo o en combinación Los heteroarilos preferidos contienen aproximadamente 5 a aproximadamente 6 átomos en el anillo El "heteroanlo" puede ser opcionalmente sustituido con uno o más "sustituyentes en el sistema de anillos" los cuales pueden ser iguales o diferentes, y son segun lo definido en la presente memoria descriptiva El prefijo aza, oxa o tia delante del nombre de raíz heteroarilo significa que por lo menos un átomo de nitrógeno, oxígeno o azufre respectivamente, está presente como un átomo en el anillo Un átomo de nitrógeno de un heteroanlo puede ser opcionalmente oxidado al correspondiente N-óxido Los ejemplos no limitativos de los heteroarilos adecuados incluyen piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, pindona (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,

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quinazolinilo, tienopirimidilo, pirrolopindilo, imidazopiridilo, isoquinolinilo, benzoazaindolilo, 1,2,4-triazinilo, benzotiazolilo y similares El término "heteroarilo" también se refiere a porciones heteroanlo parcialmente saturadas tales como, por ejemplo, tetrahidroisoquinolilo, tetrahidroquinolilo y similares

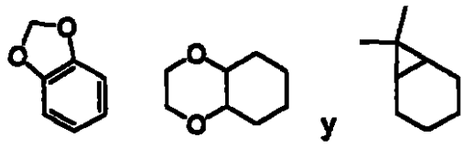
"Aralquilo" o "arilalquilo" significa un grupo aril-alquilo en el cual el arilo y el alquilo son segun lo descrito previamente Los aralquilos preferidos comprenden un grupo alquilo inferior Los ejemplos no limitativos de grupos aralquilo adecuados incluyen benzilo, 2-fenetilo y naftalénilmetilo. El enlace a la porción madre es a través del alquilo

"Alquilarilo" significa un grupo alquil-aril- en el cual el alquilo y el arilo son como se describió previamente Los alquilanlos preferidos comprenden un grupo alquilo inferior El ejemplo no limitativo de un grupo alquilanlo adecuado es tolilo El enlace a la porción madre es a través del arilo

"Cicloalquilo" significa un sistema de anillos mono- o multicíclico no aromático que comprende aproximadamente 3 a aproximadamente 10 átomos de carbono, preferentemente aproximadamente 5 a aproximadamente 10 átomos de carbono Los anillos cicloalquilo prefendos contienen entre aproximadamente 5 y aproximadamente 7 átomos en el anillo El cicloalquilo puede ser opcionalmente sustituido con uno o más "sustituyentes en el sistema de anillos" los cuales pueden ser iguales o diferentes, y son segun lo definido anteriormente Los ejemplos no limitativos de cicloalquilos monocíclicos adecuados incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo y similares Los ejemplos no limitativos de cicloalquilos multicíclicos adecuados incluyen 1-decalinilo, norbornilo, adamantilo y similares, así como también especies parcialmente saturadas tales como, por ejemplo, indanilo, tetrahidronaftilo y similares

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

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

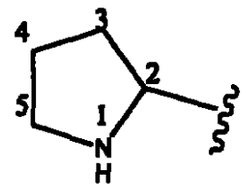


"Heterociclilo" significa un sistema de anillos monocíclico o multicíclico saturado no aromático que comprende aproximadamente 3 a aproximadamente 10 átomos en el anillo, preferentemente aproximadamente 5 a aproximadamente 10

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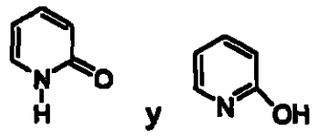
átomos en el anillo, en el cual uno o más de los átomos en el sistema de anillos es un elemento distinto a carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o en combinación No hay átomos de oxígeno y/o azufre adyacentes presentes en el sistema de anillos Los heterociclilos preferidos contienen aproximadamente 5 a aproximadamente 6 átomos en el anillo El prefijo aza, oxa o tia antes del nombre de raíz heterociclilo significa que al menos un átomo de nitrógeno, oxígeno azufre respectivamente está presente como un átomo en el 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, tales protecciones son también consideradas parte de esta invención El heterociclilo puede estar opcionalmente sustituido por uno o más "sustituyentes en el sistema de anillos" los cuales pueden ser iguales o diferentes, y son segun lo definido en la presente memona descriptiva El átomo de nitrógeno o azufre del heterociclilo puede ser opcionalmente oxidado al correspondiente N-óxido, S-óxido o S,S-dióxido Los ejemplos no limitativos de anillos heterociclilo monocíclicos adecuados incluyen piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,4-dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, lactama, lactona, y similares

Debería señalarse que en sistemas de anillos que contienen heteroátomos de esta invención, no hay grupos hidroxilo en átomos de carbono adyacentes a un N, O o S, así como también no hay grupos N o S en carbono adyacente a otro heteroátomo Por lo tanto, por ejemplo, en el anillo



no hay -OH adherido directamente a carbonos marcados 2 y 5

También debería señalarse que formas tautoméncas tales como, por ejemplo, las porciones



son consideradas equivalentes en ciertas realizaciones de esta invención

"Alquinilalquilo" significa un grupo alquinil-alquil- en el cual el alquinilo y el alquilo son según lo descrito previamente Los alquinilalquilos preferidos contienen un grupo alquinilo inferior y un alquilo inferior El enlace a la porción madre es a través del alquilo Los ejemplos no limitativos de grupos alquinilalquilo adecuados incluyen propargilmetilo

"Heteroaralquilo" significa un grupo heteroaril-alquil- en el cual el heteroarilo y el alquilo son según lo descrito previamente Los heteroaralquilos preferidos contienen un grupo alquilo inferior Los ejemplos no limitativos de grupos aralquilo adecuados incluyen piridilmetilo, y quinolin-3-ilmetilo El enlace a la porción madre es a través del alquilo

"Hidroxialquilo" significa un grupo HO-alquil- en el cual alquilo es según lo definido previamente Los hidroxialquilos preferidos contienen alquilo inferior

Los ejemplos no limitativos de grupos hidroxialquilo adecuados incluyen hidroximetilo y 2-hidroxietilo

"Acilo" significa un grupo H-C(O)-, alquil-C(O)- o cicloalquil-C(O)-, en el cual los diversos grupos son según lo descrito previamente El enlace a la porción madre es a través del carbonilo Los acilos preferidos contienen un alquilo inferior Los ejemplos no limitativos de grupos acilo adecuados incluyen formilo, acetilo y propanoílo

"Aroílo" significa un grupo aril-C(O)- en el cual el grupo arilo es según lo descrito previamente El enlace a la porción madre es a través del carbonilo Los ejemplos no limitativos de grupos adecuados incluyen benzoílo y 1- naftoílo

"Alcoxi" significa un grupo alquil-O- en el cual el grupo alquilo es según lo descrito previamente Los ejemplos no limitativos de grupos alcoxi adecuados incluyen metoxi, etoxi, n-propoxi, isopropoxi y n-butoxi El enlace a la porción madre es a través del oxígeno de éter

"Ariloxi" significa un grupo aril-O- en el cual el grupo arilo es según lo descrito previamente Los ejemplos no limitativos de grupos ariloxi adecuados incluyen fenoxi y naftoxi El enlace a la porción madre es a través del oxígeno de éter

"Aralquiloxi" significa un grupo aralquil-O- en el cual el grupo aralquilo es según lo descrito previamente Los ejemplos no limitativos de grupos aralquiloxi adecuados incluyen benciloxi y 1- o 2-naftalenmetoxi El enlace a la porción madre es a través del óxigeno de éter

"Alquiltio" significa un grupo alquil-S- en el cual el grupo alquilo es según lo descrito previamente Los ejemplos no limitativos de grupos alquiltio adecuados incluyen metiltio y etiltio El enlace a la porción madre es a través del azufre

"Ariltio" significa un grupo aril-S- en el cual el grupo arilo es según lo descrito previamente Los ejemplos no limitativos de grupos ariltio adecuados incluyen feniltio y naftiltio El enlace a la porción madre es a través del azufre

"Aralquiltio" significa un grupo aralquil-S- en el cual el grupo aralquilo es según lo descrito previamente Un ejemplo no limitativo de un grupo aralquiltio adecuado es bencíltio El enlace a la porción madre es a través del azufre

"Alcoxicarbonilo" significa un grupo alquil-O-CO- Los ejemplos no limitativos de grupos alcoxicarbonilo adecuados incluyen metoxicarbonilo y etoxicarbonilo El enlace a la porción madre es a través del carbonilo

"Ariloxicarbonilo" significa un grupo aril-O-C(O)- Los ejemplos no limitativos de grupos ariloxicarbonilo adecuados incluyen fenoxicarbonilo y naftoxicarbonilo El enlace a la porción madre es a través del carbonilo

"Aralcoxicarbonilo" significa un grupo aralquil-O-C(O)- Un ejemplo no limitativo de un grupo aralcoxicarbonilo adecuado es benciloxicarbonilo El enlace a la porción madre es a través del carbonilo

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

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

El término "sustituido" significa que uno o más hidrógenos en el átomo designado es reemplazado con una selección del grupo indicado, siempre que la valencia normal del átomo designado bajo las circunstancias existentes no sea excedida, y que la sustitución de como resultado un compuesto estable Las combinaciones de sustituyentes y/o variables son permisibles solamente si tales combinaciones dan como resultado compuestos estables Por "compuesto estable" o "estructura estable" se quiere decir un compuesto que es suficientemente fuerte como para sobrevivir al aislamiento hasta un grado útil de pureza de una mezcla de reacción, y formulación en un agente terapéutico eficaz

El término "uno o más" o "al menos uno", cuando indica la cantidad de sustituyentes, compuestos, agentes de combinación y similares, se refiere a por lo

menos uno, y hasta el número máximo de sustituyentes, compuestos, agentes de combinación y similares, químicamente y físicamente permisibles, que están presentes o que son agregados, dependiendo del contexto Tales técnicas y conocimiento son bien conocidos por el experto en la técnica

El término "opcionalmente sustituido" significa sustitución opcional con los grupos, radicales o porciones especificados

El término "aislado" o "en forma aislada" para un compuesto se refiere al estado físico de dicho compuesto después de ser aislado de un proceso sintético o fuente natural o su combinación El término "purificado" o "en forma purificada" para un compuesto se refiere al estado físico de dicho compuesto después de ser obtenido de un proceso o procesos de purificación descritos en la presente memoria descriptiva o bien conocidos por el experto en la técnica, en suficiente pureza para ser caracterizable por técnicas analíticas estándares descritas en la presente memoria descriptiva o bien conocidas por el experto en la técnica

También debería señalarse que cualquier heteroátomo con valencias no satisfactorias en el texto, esquemas, ejemplos y Tablas de la presente invención se presume que tiene el o los átomos de hidrógeno para satisfacer las valencias

Cuando un grupo funcional en un compuesto es descrito como "protegido", esto quiere decir que el grupo está en forma modificada para evitar reacciones colaterales no deseadas en el sitio protegido cuando el compuesto es sometido a una reacción Los grupos protectores adecuados serán reconocidos por aquellos expertos en la técnica así como también por referencia a libros de texto estándares tales como, por ejemplo, T W Greene *et al*, *Protective Groups In organic Synthesis* (1991), Wiley, Nueva York.

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

Como se utiliza en la presente memoria descriptiva, el término "composición" tiene el propósito de abarcar un producto que comprende los ingredientes especificados en las cantidades especificadas, así como también cualquier producto el cual es el resultado, directa o indirectamente, de la combinación de los ingredientes especificados en las cantidades especificadas

Los profármacos y solvatos de los compuestos de la invención son también contemplados en la presente memoria descriptiva El término "profármaco", como se emplea en la presente memoria descriptiva, denota un compuesto que es un precursor de un fármaco el cual, luego de la administración a un sujeto, sufre la conversión química mediante procesos metabólicos o químicos para dar un *compuesto de Fórmula 1 o su sal y/o solvato* Una descripción de *profármacos* es provista en T Higuchi y V Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 de la Serie de Simposios A C S (A C S Symposium Series), y en *Bioreversible Carriers in Drug Design,* (1987) Edward B Roche, ed , American Pharmaceutical Association and Pergamon Press, ambos son incorporados en la presente memoria descriptiva como referencia

"Solvato" significa una asociación física de un compuesto de esta invención con una o más moléculas solventes Esta asociación física involucra grados variables de unión iónica y covalente, incluyendo unión con hidrógeno En ciertos casos, el solvato será capaz de aislamiento, por ejemplo, cuando una o más moléculas solventes son incorporadas en la red cristalina del sólido cristalino "Solvato" abarca tanto los solvatos de fase en solución y los solvatos aislables Los ejemplos no

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limitativos de solvatos adecuados incluyen etanolatos, metanolatos y similares "Hidrato" es un solvato en el cual la molécula solvente es H_2O

"Cantidad eficaz" o "cantidad terapéuticamente eficaz" tiene el propósito de describir una cantidad de compuesto o una composición de la presente invención eficaz para inhibir el CDK(s) y así producir el efecto terapéutico, aliviador, inhibitorio o preventivo deseado

Los compuestos de Fórmula 1 pueden formar sales las cuales también se encuentran dentro del alcance de esta invención La referencia a un compuesto de Fórmula 1 en la presente memoria descriptiva se entiende que incluye las referencias a sus sales, a menos que se indique lo contrario El término "sal(es)", como se emplea en la presente memoria descriptiva, denota sales ácidas formadas con ácidos inorgánicos y/u orgánicos, así como también sales básicas formadas con bases inorgánicas y/u orgánicas Adicionalmente, cuando un compuesto de la Fórmula 1 contiene tanto una porción básica, tal como, aunque sin limitarse a una pindina o imidazol, y una porción ácida, tal como, aunque sin limitarse a un ácido carboxílico, zwitteriones ("sales internas") pueden formarse y son incluidas dentro del término "sal(es)" como se utiliza en la presente memoria descriptiva Las sales farmacéuticamente aceptables (es decir, no tóxicas, fisiológicamente aceptables) son preferidas, si bien también son útiles otras sales Pueden formarse sales de los compuestos de la Fórmula 1, por ejemplo, haciendo reaccionar un compuesto de Fórmula 1 con una cantidad de ácido o base, tal como una cantidad equivalente, en un medio tal como uno en el cual la sal precipita o en un medio acuoso seguido por liofilización

Las sales de adición de ácido ejemplares incluyen acetatos, ascorbatos, benzoatos, bencensulfonatos, bisulfatos, boratos, butiratos, citratos, canforatos,

canforsulfonatos, fumaratos, clorhidratos, bromhidratos, yodhidratos, lactatos, maleatos, metansulfonatos, naftalensulfonatos, nitratos, oxalatos, fosfatos, propionatos, salicilatos, succinatos, sulfatos, tartaratos, tiocianatos, toluensulfonatos (también conocidos como tosilatos,) y similares Adicionalmente, los ácidos los cuales son generalmente considerados adecuados para la formación de sales farmacéuticamente útiles de compuestos farmacéuticos básicos son descritos, por ejemplo, por P Stahl *et al*, Camille G (eds) *Handbook of Pharmaceutical Salts Properties, Selection and Use* (2002) Zurich Wiley-VCH, S Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19, P Gould, *International J of Pharmaceutics* (1986) 33 201-217, Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, Nueva York, y en *The Orange Book* (Food & Drug Administration, Washington, D C en su sitio en la web) Estas descripciones son incorporadas a la presente invención por referencia a las mismas

Las sales básicas ejemplares incluyen sales de amonio, sales de metales alcalinos, tales como, sales de sodio, litio y potasio, sales de metales alcalinotérreos tales como sales de calcio y magnesio, sales con bases orgánicas (por ejemplo, aminas orgánicas) tales como diciclohexilaminas, t-butilaminas, y sales con aminoácidos tales como arginina, lisina y similares Los grupos que contienen nitrógeno básicos pueden ser cuaternizados con agentes tales como haluros de alquilo inferior (por ejemplo, cloruros, bromuros y yoduros metílicos, etílicos y butílicos), dialquilsulfatos (por ejemplo, dimetil, dietil, y dibutilsulfatos), haluros de cadena larga (por ejemplo, cloruros, bromuros y yoduros de decilo, laurilo y estearilo), haluros de aralquilo (por ejemplo, bromuros de bencilo y fenetilo), y otros

Todas las sales de ácidos de ese tipo y las sales de bases tienen el propósito de ser sales farmacéuticamente aceptables dentro del alcance de la invención y

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todas las sales de ácido y de base son consideradas equivalentes a las formas libres de los compuestos correspondientes para los propósitos de la invención

Los ésteres farmacéuticamente aceptables de los presentes compuestos incluyen a los siguientes grupos (1) ésteres de ácido carboxílico obtenidos mediante esterificación de los grupos hidroxi, en los cuales la porción no carbonilo de la porción ácido carboxílico del grupo éster se selecciona de alquilo de cadena recta o ramificada (por ejemplo, acetilo, n-propilo, t-butilo, o n-butilo), alcoxialquilo (por ejemplo, metoximetilo), aralquilo (por ejemplo, bencilo), arilexialquilo (por ejemplo, fenoximetilo), arilo (por ejemplo, fenilo opcionalmente sustituido 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 ser adicionalmente esterificados por, por ejemplo, un alcohol C_{1-20} o su derivado reactivo, o mediante un 2,3-di acil(C_{6-24}) glicerol

Los compuestos de Fórmula 1, y sus sales, solvatos y profármacos, pueden existir en su forma tautomérica (por ejemplo, como una amida o imino éter) Todas las formas tautoméricas de ese tipo son contempladas en la presente memoria descriptiva 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, solvatos, y profármacos de los compuestos así como también las sales y solvatos de los profármacos), tales como aquellas que pueden existir debido a carbonos asimétricos en diversos sustituyentes, incluyendo las formas enantioméricas (las cuales pueden existir aun en ausencia de carbonos asimétricos), formas rotaméricas,

atropisómeros, y formas diastereoméricas, son contempladas dentro del alcance de esta invención, como son los isómeros posicionales (tales como, por ejemplo, 4-piridilo y 3-piridilo) Los estereoisómeros individuales de los compuestos de la invención pueden estar, por ejemplo, sustancialmente libres de otros isómeros, o pueden estar mezclados, por ejemplo, como racematos o con todos los otros estereoisómeros, u otros estereoisómeros seleccionados Los centros quirales de la presente invención pueden tener la configuración S o R según lo definido mediante las Recomendaciones de *IUPAC* 1974 El uso de los términos "sal", "solvato", "profármaco" y similares, se entiende que son igualmente aplicables a la sal, solvato y profármaco de enantiómeros, estereoisómeros, rotámeros, tautómeros, isómeros posicionales, racematos o profármacos de los compuestos de la invención

Las formas polimórficas de los compuestos de Fórmula I, y de las sales, solvatos y profármacos de los compuestos de Fórmula I, tienen el propósitos de estar incluidas en la presente invención

Debe entenderse que la utilidad de los compuestos de Fórmula 1 para las aplicaciones terapéuticas descritas en la presente memoria descriptiva es aplicable a cada compuesto por si mismo o a la combinación o combinaciones de uno o más compuestos de Fórmula 1 según lo ilustrado, por ejemplo, en el párrafo próximo inmediato El mismo criterio es también aplicable a composicion(es) farmacéutica(s) que comprende(n) ese tipo de compuesto o compuestos y método(s) de tratamiento que involucra(n) ese tipo de compuesto o compuestos

Los compuestos de acuerdo con la invención pueden tener propiedades farmacológicas, en particular, los compuestos de Fórmula 1 pueden ser inhibidores de la proteasa de VHC, cada compuesto por si mismo o uno o más compuestos de Fórmula 1 pueden combinarse con uno o más compuestos seleccionados de la

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Fórmula 1 El o los compuestos pueden ser útiles para el tratamiento de enfermedades tales como, por ejemplo, VHC, HIV, (SIDA, Síndrome de Inmunodeficiencia Adquirida), y trastornos relacionados, así como también para modular la actividad de la proteasa del virus de la hepatitis C (VHC), previniendo el VHC, o aliviando uno o más síntomas de la hepatitis C

Los compuestos de la Fórmula 1 pueden utilizarse para la manufactura de un medicamento para tratar trastornos asociados con la proteasa de VHC, por ejemplo, el método comprende poner en contacto íntimo un compuesto de Fórmula 1 y un portador farmacéuticamente aceptable

En otra realización, esta invención proporciona composiciones farmacéuticas que comprenden el compuesto o compuestos de la invención como un ingrediente activo Las composiciones farmacéuticas generalmente comprenden además al menos un diluyente portador, excipiente o portador farmacéuticamente aceptable (denominados colectivamente en la presente memoria descriptiva materiales portadores) Debido a su actividad inhibitoria del VHC, tales composiciones farmacéuticas poseen utilidad en el tratamiento de la hepatitis C y trastornos relacionados

En aun otra realización, la presente invención describe métodos para preparar composiciones farmacéuticas que comprenden los compuestos de la invención como un ingrediente activo En las composiciones farmacéuticas y métodos de la presente invención, los ingredientes activos típicamente serán administrados en mezcla con materiales portadores adecuados seleccionados adecuadamente con respecto a la forma pretendida de administración, es decir, tabletas orales, cápsulas (ya sea cargadas con sólido, cargadas con semisólido o cargadas con líquido), polvos para constitución, geles orales, elíxires, gránulos dispersables, jarabes, suspensiones y

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similares, y consistentes con las prácticas farmacéuticas convencionales Por ejemplo, para la administración oral en la forma de tabletas o cápsulas, el componente farmacológico activo puede ser combinado con cualquier portador inerte farmacéuticamente aceptable, no tóxico, oral, tal como lactosa, almidón, sacarosa, celulosa, estearato de magnesio, fosfato dicálcico, sulfato de calcio, talco, manitol, alcohol etílico (formas líquidas) y similares Asimismo, cuando se desee o sea necesario, también pueden incorporarse en la mezcla aglutinantes, lubricantes, agentes desintegrantes y agentes colorantes adecuados Los polvos y tabletas pueden comprender entre aproximadamente 5 y aproximadamente 95 por ciento de la composición de la invención

Los aglutinantes adecuados incluyen almidón, gelatina, azúcares naturales, edulcorantes de maíz, gomas naturales y sintéticas tales como acacia, alginato de sodio, carboximetilcelulosa, polietilenglicol y ceras Entre los lubricantes pueden mencionarse para utilizarse en estas formas de dosificación, el ácido bórico, benzoato de sodio, acetato de sodio, cloruro de sodio y similares Los desintegrantes incluyen almidón, metilcelulosa, goma de guar y similares

También pueden incluirse agentes edulcorantes y saborizantes y conservantes cuando fuese apropiado Algunos de los términos antes señalados, básicamente desintegrantes, diluyentes, lubricantes, aglutinantes y similares, son descritos con más detalle más adelante

Adicionalmente, las composiciones de la presente invención pueden ser formuladas en forma de liberación sostenida para proporcionar el índice de liberación controlada de cualquiera de uno o más de los componentes o ingredientes activos para optimizar los efectos terapéuticos, es decir, la actividad inhibitoria de VHC y similares Las formas de dosificación adecuadas para la liberación sostenida incluyen

tabletas estratificadas que contienen capas de índices de desintegración variables o matrices poliméricas de liberación controlada impregnadas con los componentes activos y conformadas en forma de tableta o cápsulas que contienen tales matrices poliméricas porosas impregnadas o encapsuladas

Las preparaciones en forma líquida incluyen soluciones, suspensiones y emulsiones Como un ejemplo pueden mencionarse soluciones acuosas o de agua-propilenglicol para inyecciones parenterales o adición de edulcorantes y pacificadores para soluciones orales, suspensiones y emulsiones Las preparaciones en forma líquida también pueden incluir soluciones para administración intranasal

Las preparaciones en aerosol adecuadas para inhalación pueden incluir soluciones y sólidos en forma de polvo, las cuales pueden estar en combinación con un portador farmacéuticamente aceptable tal como un gas comprimido inerte, por ejemplo, nitrógeno

Para la preparación de supositorios, una cera de bajo punto de fusión tal como una mezcla de glicéridos de ácidos grasos tal como manteca de cacao es primero fundida, y el ingrediente activo es dispersado de manera homogénea en la misma agitando o mezclando similarmente Luego, la mezcla homogénea fundida es vertida en moldes de tamaño conveniente, se deja enfriar y así solidificar

También se incluyen las preparaciones en forma sólida las cuales tienen el propósito de ser convertidas, brevemente antes de su utilización, en preparaciones en forma líquida para la administración oral o parenteral Tales formas líquidas incluyen soluciones, suspensiones y emulsiones

Los compuestos de la invención también pueden ser administrados por vía transdérmica Las composiciones transdérmicas pueden adoptar la forma de cremas, lociones, aerosoles y/o emulsiones y pueden ser incluidas en un parche transdérmico

del tipo matriz o depósito de acuerdo con los convencionales en la técnica para este propósito

Los compuestos de la invención también pueden ser administrados oralmente, intravenosamente, intranasalmente o subcutáneamente

Los compuestos de la invención también pueden comprender preparaciones las cuales están en forma de dosificación unitaria En tal forma, la preparación es subdividida en dosis unitarias con tamaño adecuado que contienen cantidades apropiadas de los componentes activos, por ejemplo, una cantidad eficaz para lograr el propósito deseado

La cantidad de la composición activa de la invención en una dosis unitaria de preparación puede variar generalmente o ajustarse entre aproximadamente 1,0 miligramo y aproximadamente 1 000 miligramos, preferentemente entre aproximadamente 1,0 y aproximadamente 950 miligramos, más preferentemente entre aproximadamente 1,0 y aproximadamente 500 miligramos, y típicamente entre aproximadamente 1 y aproximadamente 250 miligramos, de acuerdo con la aplicación en particular La dosis real empleada puede variar dependiendo de la edad, sexo, peso del paciente y de la gravedad de la afección que se está tratando Tales técnicas son bien conocidas por los expertos en la técnica

Generalmente, la forma de dosificación oral humana que contiene los ingredientes activos puede ser administrada 1 o 2 veces por día La cantidad y frecuencia de la administración serán reguladas de acuerdo con el criterio del clínico interviniente Un régimen de dosificación diaria generalmente recomendado para la administración oral puede oscilar entre aproximadamente 1,0 miligramo y aproximadamente 1 000 miligramos por día, en dosis unica o en dosis divididas

A continuación se describen algunos términos útiles

Cápsula – se refiere a un envase o encerramiento especial hecho de meticelulosa, alcoholes polivinílicos, o gelatinas desnaturalizada o almidón para sostener o contener composiciones que comprenden los ingredientes activos Las cápsulas de vaina dura están tipicamente preparadas de mezclas de gelatinas de piel porcina y hueso con resistencia al gel relativamente elevada La cápsula misma puede contener pequeñas cantidades de tintes, agentes opacantes, plastificantes y conservantes

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

Gel oral – se refiere a los ingredientes activos dispersados o solubilizados en una matriz semisólida hidrófila

Polvo para constitución se refiere a mezclas en polvo que contienen los ingredientes activos y diluyentes adecuados los cuales pueden ser suspendidos en agua o jugos

Diluyente – se refiere a sustancias que generalmente forman la porción principal de la composición o forma de dosificación Los diluyentes adecuados incluyen azúcares tales como lactosa, sacarosa, manitol y sorbitol, almidones derivados de trigo, maíz, arroz y papa, y celulosas tales como celulosa microcristalina La cantidad de diluyente en la composición puede oscilar entre aproximadamente 10 y aproximadamente 90% en peso de la composición total, preferentemente entre aproximadamente 25 y aproximadamente 75%, más preferentemente entre aproximadamente 30 y aproximadamente 60% en peso, aun más preferentemente entre aproximadamente 12 y aproximadamente 60%

Desintegrante – se refiere a materiales agregados a la composición para ayudarla a desintegrarse y liberar los medicamentos Los desintegrantes adecuados incluyen almidones, almidones modificados "solubles en agua fría" tales como almidón de carboximetilo de sodio, gomas naturales y sintéticas tales como algarrobilla, goma karaya, guar, tragacanto y agar; derivados de celulosa tales como metilcelulosa y carboximetilcelulosa de sodio, celulosas microcristalinas 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 oscilar entre aproximadamente 2 y aproximadamente 15% en peso de la composición, más preferentemente entre aproximadamente 4 y aproximadamente 10% en peso

Aglutinante – se refiere a sustancias que unen o "pegan" polvos entre si y los hacen cohesivos mediante la formación de gránulos, sirviendo de ese modo como el "adhesivo" en la formulación Los aglutinantes agregan fuerza cohesiva ya disponible en el diluyente o agente que otorga densidad ("bulking agent") Los aglutinantes adecuados incluyen azúcares tales como sacarosa, almidones derivados de trigo, maíz, arroz y papa, gomas naturales tales como goma de acacia, gelatina y tragacanto, derivados de algas manitas tales como ácido algínico, alginato de sodio y alginato de calcio y amonio, materiales celulósicos tales como metilcelulosa y carboximetilcelulosa de sodio e hidroxipropilmetilcelulosa, polivinilpirrolidona, y materiales inorgánicos tales como silicato de magnesio aluminio La cantidad de aglutinante en la composición puede oscilar entre aproximadamente 2 y aproximadamente 20% en peso de la composición, más preferentemente entre aproximadamente 3 y aproximadamente 10% en peso, aun más preferentemente entre aproximadamente 3 y aproximadamente 6% en peso

Lubricante – se refiere a una sustancia agregada a la forma de dosificación para permitir que la tableta, gránulos, etc después de haberse comprimido, se libere del molde o matriz reduciendo la fricción o el desgaste Los lubricantes adecuados 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 hidrosolubles tales como cloruro de sodio, benzoato de sodio, acetato de sodio, oleato de sodio, polietilenglicoles y d'l-leucina Los lubricantes son generalmente agregados en el último paso antes de la compresión, puesto que deben estar presentes sobre las superficies de los gránulos y entre medio de los mismos y las partes de la prensa de tableteado La cantidad de lubricante en la composición puede oscilar entre aproximadamente 0,2 y aproximadamente 5% en peso de la composición, preferentemente entre aproximadamente 0,5 y aproximadamente 2%, más preferentemente entre aproximadamente 0,3 y aproximadamente 1,5% en peso

Agente del deslizamiento – material que evita la aglomeración y mejora las características de fluidez de las granulaciones, de modo que el flujo sea suave y uniforme Los agentes del deslizamiento adecuados incluyen dióxido de silicio y talco La cantidad de agente de deslizamiento en la composición puede oscilar entre aproximadamente 0,1% y aproximadamente 5% en peso de la composición total, preferentemente entre aproximadamente 0,5 y aproximadamente 2% en peso

Agentes colorantes – excipientes que proporcionan coloración a la composición o a la forma de dosificación Tales excipientes pueden incluir tintes para alimento y tintes para alimento adsorbidos sobre un adsorbente adecuado tal como arcilla u óxido de aluminio La cantidad del agente colorante puede variar entre aproximadamente 0,1 y aproximadamente 5% en peso de la composición, preferentemente entre aproximadamente 0,1 y aproximadamente 1%

Biodisponibilidad – se refiere al índice y grado en el cual el ingrediente farmacológico activo o porción terapéutica es absorbida en la circulación sistémica desde una forma de dosificación administrada en comparación con un patrón o control

Los métodos convencionales para preparar tabletas son conocidos Tales métodos incluyen métodos secos tales como compresión directa y compresión de granulación producida por compactación, o métodos húmedos u otros procedimientos especiales Los métodos convencionales para preparar otras formas para administración tales como, por ejemplo, cápsulas, supositorios y similares son también bien conocidos

Otra realización de la invención describe el uso de los compuestos de la invención o composiciones farmacéuticas descritas anteriormente para el tratamiento de enfermedades tales como, por ejemplo, hepatitis C y similares El método comprende administrar una cantidad terapéuticamente eficaz del compuesto de la invención o composición farmacéutica a un paciente que tiene ese tipo de enfermedad o enfermedades y que necesita ese tipo de tratamiento

En aun otra realización, los compuestos de la invención pueden utilizarse para el tratamiento del VHC en seres humanos en modalidad de monoterapia o en una modalidad de terapia de combinación (por ejemplo, combinación dual, combinación triple etc) tal como, por ejemplo, en combinación con agentes antivirales y/o inmunomoduladores Ejemplos de tales agentes antivirales y/o inmunomoduladores incluyen Ribavirina (de Schering-Plough Corporation, Madison, Nueva Jersey) y Levovirin™ (de ICN Pharmaceuticals, Costa Mesa, California), VP 50406™ (de Viropharma, Incorporated, Exton, Pensilvania), ISIS 14803™ (de ISIS Pharmaceuticals, Carlsbad, California), Heptazyme™ (de Ribozyme

Pharmaceuticals, Boulder, Colorado), VX 497™ (de Vertex Pharmaceuticals, Cambridge, Masachusets), Thymosin™ (de SciClone Pharmaceuticals, San Mateo, California), Maxamine™ (Maxim Pharmaceuticals, San Diego, California), micofenolato mofetilo (de Hoffman-LaRoche, Nutley, Nueva Jersey), interferón (tal como, por ejemplo, interferón-alfa, conjugados de PEG-alfa interferón) y similares Los "conjugados de PEG- alfa interferón" *son moléculas* de alfa interferón covalentemente unidas a una molécula de PEG Los ejemplos de conjugados de PEG-*alfa* interferón incluyen interferón alfa-2a (Roferon™, de Hoffman La-Roche, Nutley, Nueva Jersey) en la forma de interferón alfa-2a peglado (por ejemplo, como es comercializado bajo la denominación comercial Pegasys™), interferón alfa-2b (Intron™, de Schering-Plough Corporation) *en la forma de interferón alfa-2b* peglado (por ejemplo, según es comercializado bajo la denominación comercial PEG-*Intron*™), *interferón alfa*-2c (Berofor Alpha™, de Boehringer Ingelheim, Ingelheim, Alemania) o interferón de consenso según lo definido por determinación de una secuencia de consenso de interferón alfas naturales (Infergen™, de Amgen, Thousand Oaks, California)

Como se indicó anteriormente, la invención también incluye a los tautómeros, rotámeros, enantiómeros y otros estereoisómeros de los compuestos de la invención Por lo tanto, como podrá apreciar un experto en la técnica, algunos de los compuestos de la invención pueden existir en formas isoméricas adecuadas Tales variaciones son contempladas como estando dentro del alcance de la invención

Otra realización de la invención describe un método para preparar los compuestos descritos en la presente memoria descriptiva Los compuestos pueden ser preparados mediante diversas técnicas conocidas en la técnica Los procedimientos ilustrativos son descritos en los siguientes esquemas de reacción

Las ilustraciones no deberían ser interpretadas como limitando el alcance de la invención la cual es definida en las reivindicaciones adjuntas Las rutas mecanísticas y estructuras análogas alternativas serán evidentes para los expertos en la técnica

Debe entenderse que si bien los siguientes esquemas ilustrativos describen la preparación de unos pocos compuestos de la invención representativos, la sustitución adecuada de cualquiera de los dos aminoácidos naturales y no naturales dará como resultado la formación de los compuestos deseados en base a tal sustitución Se contemplan tales variaciones como estando dentro del alcance de la invención

Para los procedimientos descritos a continuación, se utilizan las siguientes abreviaturas

Abreviaturas

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

THF Tetrahidrofurano

DMF N,N-Dimetilformamida

EtOAc acetato de etilo

AcOH ácido acético

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

EDCI Clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida

NMM N-Metilmorfolina

ADDP 1,1'-(Azodicarbonil)dipiperidina

DEAD Dietilazodicarboxilato

MeOH Metanol

EtOH Etanol

Et_2O éter dietílico

DMSO Dimetilsulfóxido

HOBt N-Hidroxibenzotriazol

PyBrOP Hexafluorfosfato de bromo-tris-pirrolidinofosfonio

DCM Diclorometano

DCC 1,3-Diciclohexilcarbodiimida

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

Phg Fenilglicina

Chg Ciclohexilglicina

Bn Bencilo

Bz. Bencilo

Et: Etilo

Ph Fenilo

IBoc Isobutoxicarbonilo

iPr Isopropilo

^{t}Bu or Bu^t ter-Butilo

Boc ter-Butiloxicarbonilo

Cbz Benciloxicarbonilo

Cp Ciclopentildienilo

Ts p-toluensulfonilo

MCPBA ácido 3-cloroperbenzoico

Me Metilo

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

DMAP 4-N,N-Dimetilaminopiridina

Bop Benzotriazol-1-il-oxi-tris(dimetilamino)hexafluorfosfato

PCC clorocromato de piridinio

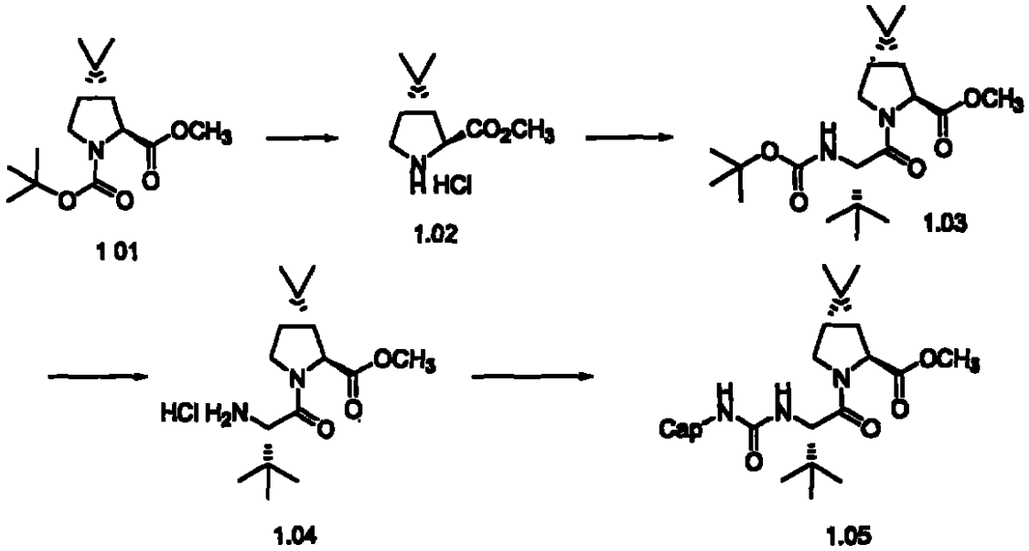
Otras abreviaturas son las abreviaturas comúnmente utilizadas tales como aquellas acorde con las pautas publicadas por Journal of Organic Chemistry

Esquemas Generales para la Preparación de Compuestos Objetivos

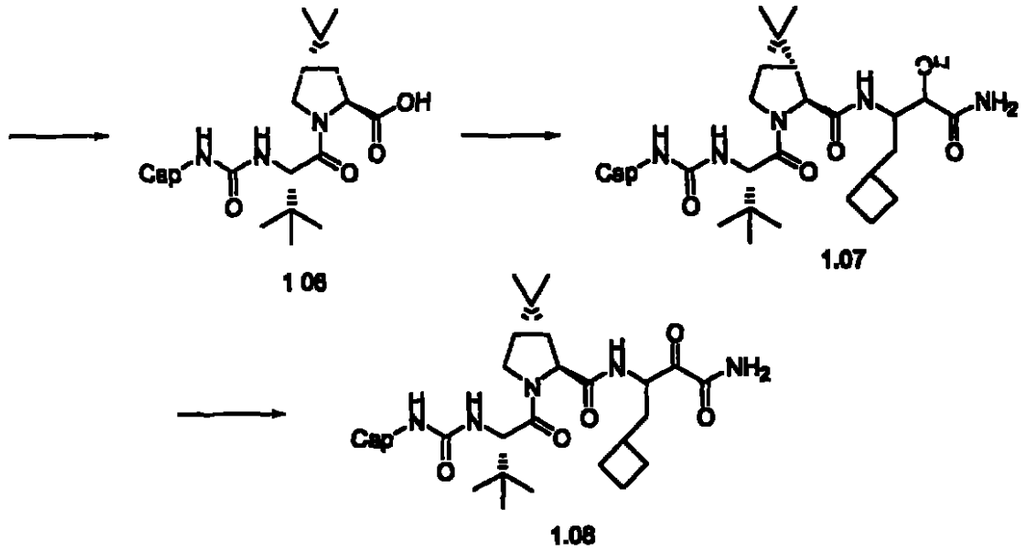
Los compuestos de la presente invención fueron sintetizados utilizando los esquemas generales (Métodos A-E) descritos a continuación

Método A.

La desprotección de la funcionalidad N-Boc de 1 01 bajo condiciones ácidas proporcionó la sal clorhidrato 1 02 la cual fue posteriormente acoplada con N-Boc-ter-leucina bajo metodología de acoplamiento peptídico (Louis A Carpino et al "*Preparation of uronium and immonium salts for peptide coupling*", WO 2002094822 página 76) para dar 1 03 La desprotección de N-Boc seguida por tratamiento con isocianato apropiado dieron la urea 1 05 La hidrólisis del éster metílico proporcionó el ácido 1 06 El acoplamiento peptídico del ácido 1 06 con la porción amida primaria P_1-P' apropiada dio la hidroxilamida 1 07 La oxidación (Moffatt o Dess-Martin's dio como resultado el compuesto objetivo 1 08



1 01 1.02 1.03 1.04 1.05

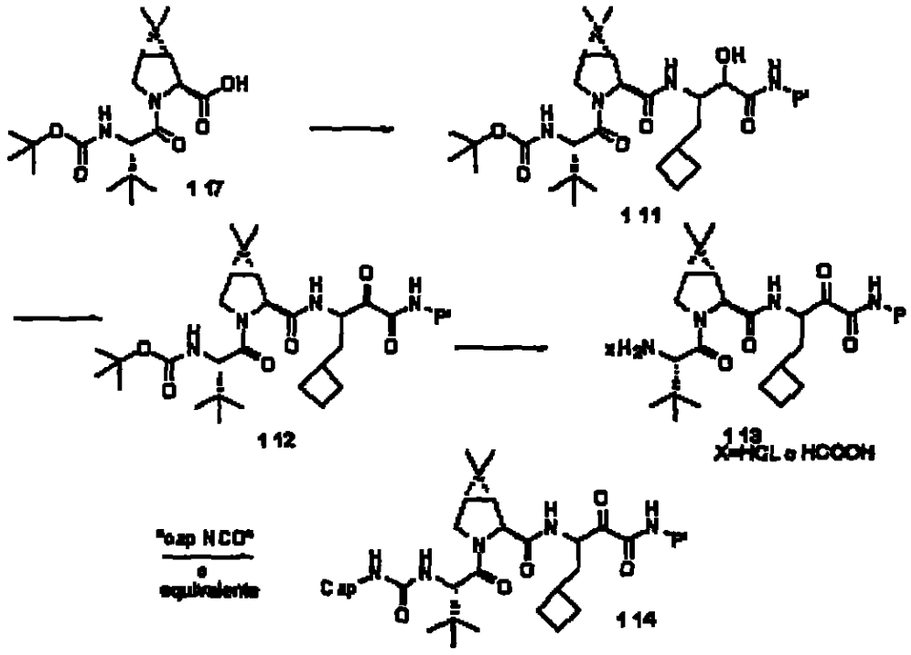


Método B

El acoplamiento peptídico del ácido 1 06 con la porción amida secundaria P_1-P' apropiada dio la hidroxilamida 1 09 La oxidación (Moffatt o Dess-Martin's) dio como resultado el compuesto objetivo 1 10

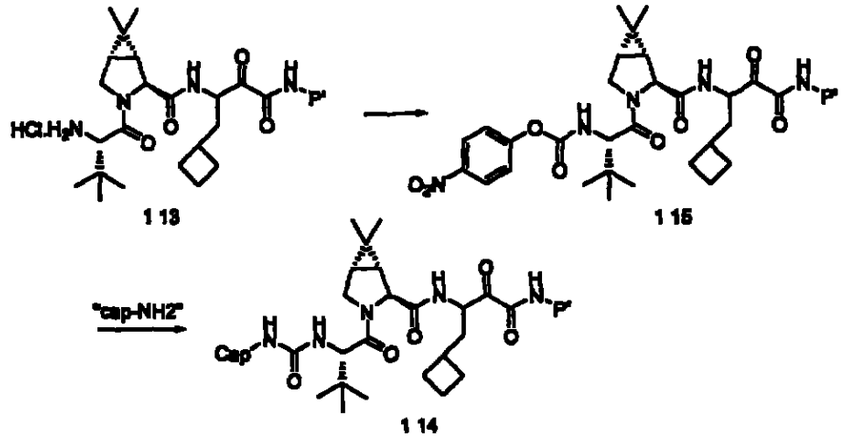
Método C

En otra variación, el acoplamiento peptídico del N-Boc-P_2-P_3-ácido 1 17 con la porción amida P_1-P' apropiada dio la hidroxilamida 1 11 La oxidación (Moffatt o Dess-Martin's) dio como resultado la cetoamida 1 12 La desprotección del N-Boc dio utilizando ácido fórmico o HCl 4 M en dioxano dio el formato o sal clorhidrato 1 13 El tratamiento con un isocianato adecuado (o equivalente de isocianato) dio como resultado el compuesto objetivo 1 14



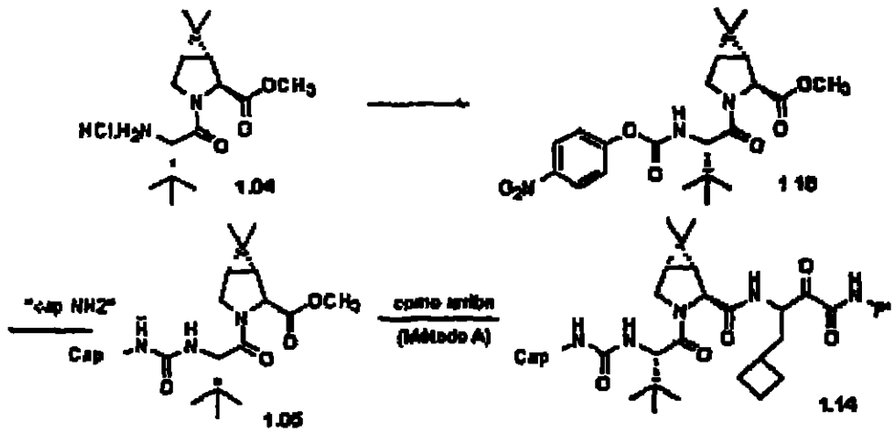
Método D

En aun otra variación, la sal clorhidrato 1 13 fue convertida en el carbamato de 4-nitrofenilo 1 15 mediante reacción con el cloroformato de 4-nitrofenilo El tratamiento posterior con una amina (o sal clorhidrato de amina) de elección proporcionó el compuesto objetivo 1 14



Método E

En aun otra variación, la sal clorhidrato dipeptídico 1 03 fue convertida en el carbamato de 4-nitrofenilo según lo descrito anteriormente El tratamiento con una amina (o sal clorhidrato de amina) de elección proporción el derivado de urea 1 05 La hidrólisis y posterior elaboración según lo descrito en los Métodos A/B proporcionaron los compuestos objetivos 1 14

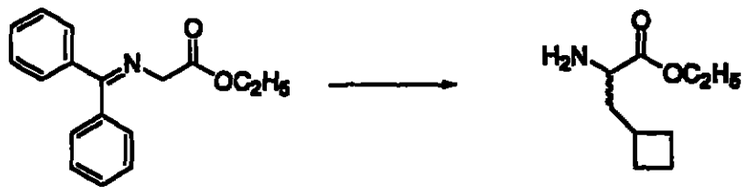


Preparación de los Intermediarios

Preparación de porciones P1-P'

Preparación de los Intermediarios 10 11 y 10 12

Paso 1.

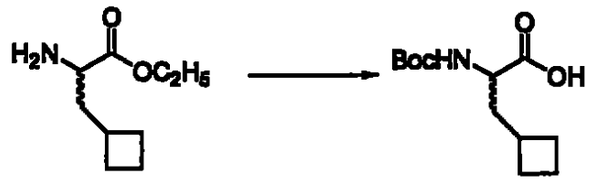


10 01 10.02

Una solución agitada de cetimina 10 01 (50 g, 187,1 mmol) bajo N_2 en THF seco (400 mL) se enfrió hasta –78 ^{0}C y se trató con solución 1 M de K-^{t}BuO (220 mL, 1,15 equiv) en THF LA mezcla de reacción se calentó hasta 0 ^{0}C y se agitó durante 1 h y se trató con bromometilciclobutano (28 mL, 249 mmol) La mezcla de reacción

se agitó a temperatura ambiente durante 48 h y se concentró *in vacuo* El residuo se disolvió en Et_2O (300 mL) y se trató con HCl ac. (2 M, 300 mL) La solución resultante se agitó a temperatura ambiente durante 5 h y se extrajo con Et_2O (1 L) La capa acuosa se basificó hasta pH ~12-14 con NaOH (50 % ac) y se extrajo con CH_2Cl_2 (3x300 mL) Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron para dar la amina pura (10 02, 18 g) en forma de un aceite incoloro

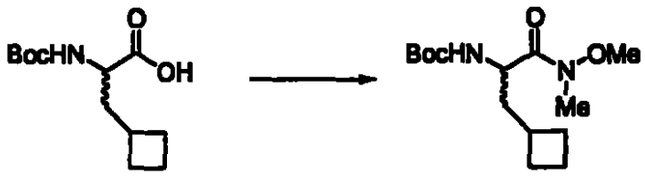
Paso 2



10 02 10 03

Una solución de la amina 10 02 (18 g, 105,2 mmol) a 0 ^{0}C en CH_2Cl_2 (350 mL) se trató con di-*ter*-butildicarbonato (23 g, 105,4 mmol) y se agitó a ta durante 12 h Después de completarse la reacción (TLC), la mezcla de reacción se concentró in *vacuo* y el residuo se disolvió en THF/H_2O (200 ml, 1 1) y se trató con $LiOH{\bullet}H_2O$ (6,5 g, 158,5 mmol) y se agitó a temperatura ambiente durante 3 h La mezcla de reacción se concentró y la capa acuosa básica se extrajo con Et_2O La capa acuosa se acidificó con HCl conc. hasta pH~1-2 y se extrajo con CH_2Cl_2 Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, y concentraron *In vacuo* para dar 10 03 en forma de un aceite incoloro viscoso el cual se utilizó para el siguiente paso sin más purificación

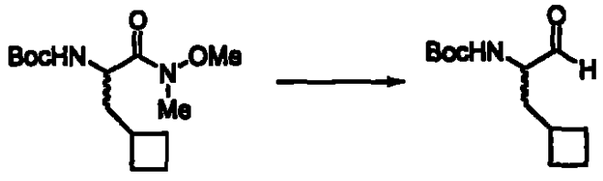
Paso 3



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-metilmorfolina (27 mL), clorhidrato de N,O-dimetilhidroxilamina (9,07 g, 93 mmol) y se agitó durante la noche a ta La mezcla de reacción se diluyó con HCl ac 1 N (250 mL), y las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (3x300 ml) Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, EtOAc/Hex 2 3) para dar la amida 10 04 (15,0 g) en forma de un sólido incoloro

Paso 4



10 04 10.05

Una solución de la amida 10 04 (15 g, 52,1 mmol) en THF seco (200 mL) se trató por goteo con una solución de $LiAlH_4$ (1M, 93 mL, 93 mmol) a 0 °C La mezcla de reacción se agitó a temperatura ambiente durante 1 h y se templó 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 ac (1 M, 150 mL) y se extrajo con CH_2Cl_2 (3x200 mL) Las capas orgánicas combinadas se lavaron con HCl ac (1 M), $NaHCO_3$

235
235

saturado, salmuera y se secaron ($MgSO_4$) La mezcla se filtró y concentró *In vacuo* para proporcionar 10 05 en forma de un aceite incoloro viscoso (14 g)

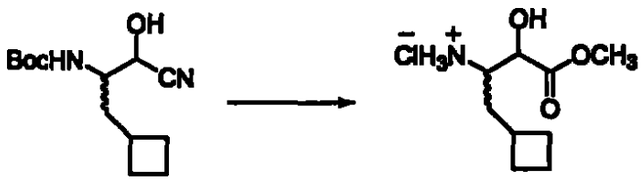
Paso 5



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 cianohidrina de acetona (10,86 g, 127,57 mmol) y se agitó a temperatura ambiente durante 24 hrs La mezcla de reacción se concentró *In vacuo* y se diluyó con HCl ac (1 M, 200 mL) y se extrajo en CH_2Cl_2 (3x200 mL) Las capas orgánicas combinadas se lavaron con H_2O, salmuera, se secaron ($MgSO_4$), filtraron, concentraron *In vacuo* y se purificaron mediante cromatografía (SiO_2, EtOAc/Hex 1 4) para proporcionar 10 06 (10,3 g) como un líquido incoloro

Paso 6



10.06 10 07

Se trató metanol saturado con HCl*, preparado mediante burbujeo de gas de HCl a través de CH_3OH (700 ml) a 0 °C, con la cianohidrina 10 06 y se calentó hasta reflujo durante 24 h La reacción se concentró *In vacuo* para proporcionar 10 07, el cual se utilizó en el siguiente paso sin purificación

* Alternativamente también puede utilizarse HCl 6M preparado mediante la adición de AcCl al metanol seco

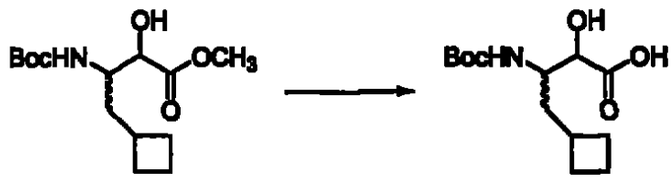
Paso 7



10 07 10 08

Una solución del clorhidrato de amina 10 07 en CH_2Cl_2 (200 mL) se trató con Et_3N (45,0 mL, 315 mmol) y Boc_2O (45,7g, 209 mmol) a –78 °C Luego, la mezcla de reacción se agitó a temperatura ambiente durante la noche y se diluyó con HCl (2 M, 200 mL) y se extrajo en CH_2Cl_2. Las capas orgánicas combinadas se secaron ($MgSO_4$) se filtraron y concentraron *in vacuo* y se purificaron mediante cromatografía (EtOAc/Hex 1 4) para proporcionar el hidroxiéster 10 08

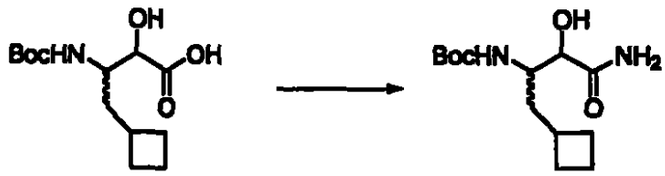
Paso 8.



10 08 10.09

Una solución del éster metílico 10 08 (3g, 10,5 mmol) en THF/H_2O (1 1) se trató con $LiOH \cdot H_2O$ (645 mg, 15,75 mmol) y se agitó a ta durante 2 h La mezcla de reacción se acidificó con HCl ac (1 M, 15 mL) y se concentró *in vacuo* El residuo se secó al vacío para dar 10 09 con rendimiento cuantitativo

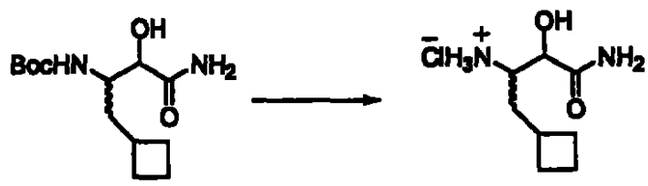
Paso 9



10 09 10 10

Una solución del ácido 10 09 (de lo que antecede) en CH_2Cl_2 (50 mL) y DMF (25 mL) se trató con NH_4Cl (2,94 g, 55,5 mmol), EDCI (3,15 g, 16,5 mmol), HOOBt (2,69 g, 16,5 mmol), y NMM (4,4 g, 44 mmol) La mezcla de reacción se agitó a temperatura ambiente durante 3 d Los solventes se eliminaron bajo vacío y el residuo se diluyó con HCl ac (250 mL) y se extrajo con CH_2Cl_2 Las capas orgánicas combinadas se lavaron con $NaHCO_3$ ac sat , se secaron ($MgSO_4$) se filtraron y se concentraron in vacuo para obtener 10 10, el cual se utilizó como estaba en los siguientes pasos (Alternativamente 10 10 también puede obtenerse directamente mediante la reacción de 10 06 (4,5 g, 17,7 mmol) con H_2O_2 ac (10 mL), $LiOH{\bullet}H_2O$ (820 mg, 20,8 mmol) a 0 °C en 50 mL de CH_3OH durante 0,5 h)

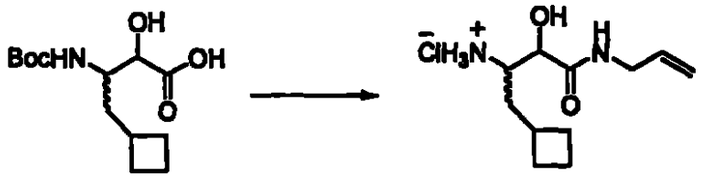
Paso 10



10 10 10 11

Una solución de 10 10 obtenido en el paso previo se disolvió en HCl 4 N en dioxano y se agitó a ta durante 2 h La mezcla de reacción se concentró in *vacuo* para dar el intermediario 10 11 como un sólido, el cual se utilizó sin más purificación

Paso 11

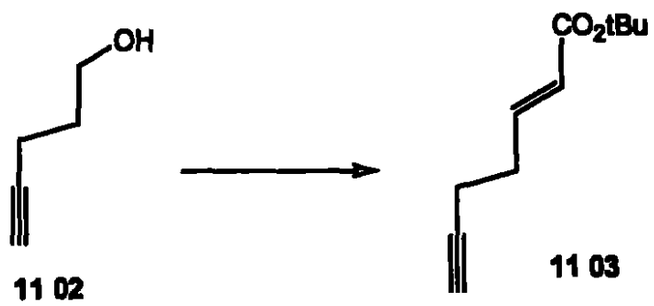


10 09 10 12

El intermediario requerido 10 12 fue obtenido a partir del compuesto 10.09 utilizando esencialmente los procedimientos antes descritos en los Pasos 9, 10 utilizando 2,0 equivalentes de alilamina en lugar de cloruro de amonio

Preparación del Intermediario 11 01

Paso 1

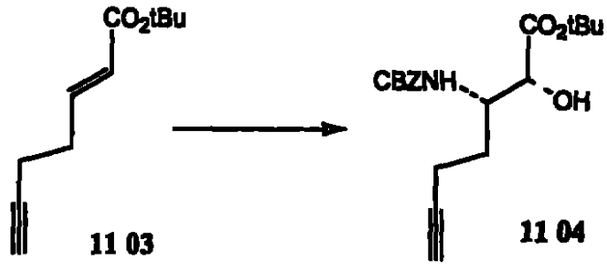


11 02 11 03

A una solución de 4-pentin-1-ol, 11 02 (4,15 g, Aldrich) se agregó Peryodinano de Dess-Martin (30,25g, Aldrich) y la mezcla resultante se agitó durante 45 min antes de la adición de (ter-Butoxicarbonilmetilen)trifenilfosforano (26,75g, Aldrich) La reacción oscura resultante se agitó durante la noche, se diluyó con EtOAc), se lavó con sulfito de sodio ac , NaHCO3 ac sat , agua, salmuera y se secó Los volátiles fueron eliminados bajo presión reducida y el residuo se purificó mediante cromatografía en columna sobre gel de sílice utilizando 1% EtOAc en hexanos como eluyente para dar el compuesto deseado, 11 03 (3,92g) Algunas fracciones impuras también fueron obtenidas aunque dejadas de lado en este momento

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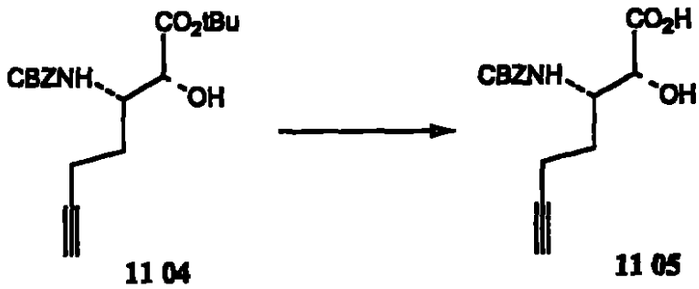
Paso 2



11 03 11 04

Utilizando el alqueno 11 03 (1,9 g) en n-propanol (20 ml, Aldrich)), bencilcarbamato (4,95 g, Aldnch) 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 osmato de potasio deshidrato (0,1544 g, Aldrich) y el procedimiento expuesto en *Angew Chem Int Ed Engl* (1998), 35, (23/24), pp 2813-7 dio un producto crudo el cual se purificó mediante cromatografía en columna sobre gel de sílice utilizando EtOAc Hexanos (1 5) para dar el aminoalcohol deseado 11 04 (1,37g, 37%) en forma de un sólido blanco

Paso 3

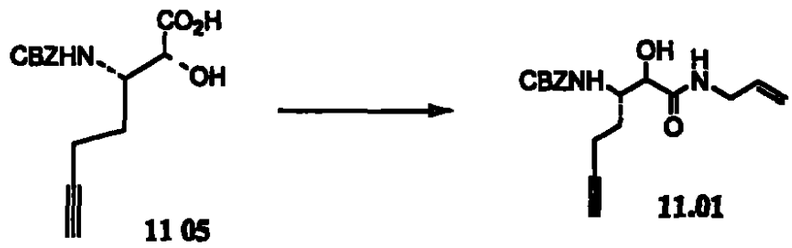


11 04 11 05

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 durante la noche Los volátiles fueron eliminados bajo presión reducida para dar el ácido 11 05 (0,621 g) en forma de un sólido blanco

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Paso 4

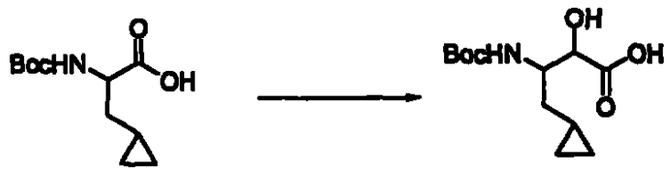


11 05 11.01

El reactivo BOP (3,65 g, Sigma) seguido por trietilamina (3,45 ml) fueron agregados hasta una solución de diclorometano (20 ml) del ácido carboxílico 11 05 (2,00 g) y alilamina (0,616 ml) a temperatura ambiente y la mezcla resultante se agitó durante la noche La mezcla de reacción se repartió entre EtOAc y 10% HCl ac La fase orgánica se separó, se lavó con bicarbonato de sodio ac sat., agua, se secó (sulfato de magnesio) El producto de reacción crudo se purificó mediante cromatografía en columna sobre gel de sílice utilizando (EtOAc.Hexanos, 70 30) como eluyente para proporcionar la amida deseada 11 01 (1,73 g) en forma de un aceite amarillo viscoso

Preparación de los intermediarios 12 03 y 12.04

Paso 1



12.01 12.02

El compuesto 12 01 (el Compuesto 12 01 fue obtenido comercialmente o puede ser sintetizado utilizando química similar a la descrita para la síntesis de 10 11 utilizando ciclopropano de bromometilo en lugar de bromometilciclobutano) fue

convertido en el material requerido 12 02 utilizando esencialmente los procedimientos descritos para el Intermediario 10 11, Pasos 3-8

Paso 2



12.02 12.03

El compuesto 12.02 fue convertido en el Intermediario requerido 12 03 utilizando esencialmente los procedimientos descritos para el Intermediario 10 11, Pasos 9, 10

Paso 3

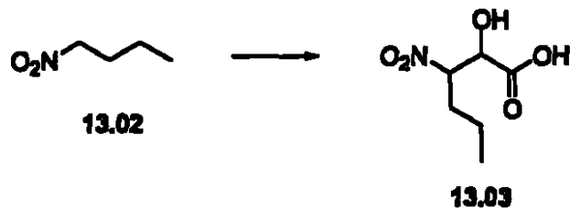


12.02 12 04

El compuesto 12 02 fue convertido en el Intermediario requerido 12 03 utilizando esencialmente los procedimientos descritos para el Intermediario 10 12, Paso 11

Preparación del Intermediario 13 01

Paso 1

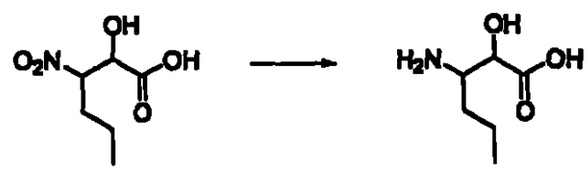


13.02 13.03

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A una solución agitada de 1-nitrobutano, 13 02 (16,5 g, 0,16 mol) y ácido glioxílico en H_2O (28,1 g, 0,305 mol) y MeOH (122 mL) a 0°C-5°C, se agregó por goteo trietilamina (93 mL, 0,667 mol) durante 2 hrs La solución se calentó hasta temperatura ambiente, se agitó durante la noche y se concentró hasta sequedad para dar un aceite Luego, el aceite se disolvió en H_2O y se acidificó hasta pH =1 con 10% HCl, seguido por 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, rendimiento 99%)

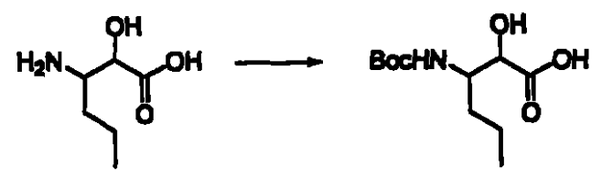
Paso 2



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 10% Pd/C (37 g) La solución resultante se hidrogenó a 401,2 kPa (59 psi) durante 3 hrs y luego a 408 kPa (60 psi) durante la noche Luego, el ácido acético se evaporó y se azeotropizó 3 veces con tolueno, luego se trituró con MeOH y éter La solución luego se filtró y se azeotropizó dos veces con tolueno para dar 13 04 en forma de un sólido blancuzco (131 g, 0,891 mol, 66%)

Paso 3

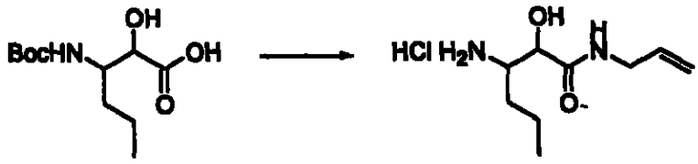


13 04 13.05

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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 NaOH 1 N (4,3 mL, 14,0 mmol) La solución resultante se agitó durante 10 minutos, seguido por adición de di-*t*-butildicarbonato (0,110 g, 14,0 mmol) y se agitó a 0°C durante 15 minutos Luego, la solución se calentó hasta temperatura ambiente, se agitó durante 45 minutos y se mantuvo en el refrigerador durante la noche y se concentró hasta sequedad para dar un material crudo A la solución de este material crudo en EtOAc (100 mL) y hielo, se agregó $KHSO_4$ (3,38 g) y H_2O (32 mL) y se agitó durante 4-6 minutos Luego, la capa orgánica se separó y la capa acuosa se extrajo dos veces con EtOAc y la capa orgánica combinada se lavó con agua, salmuera, se secó sobre Na_2SO_4, se filtró y concentró hasta sequedad para dar el producto 13 05 en forma de una goma clara (3,0 g, rendimiento 89%)

Paso 4



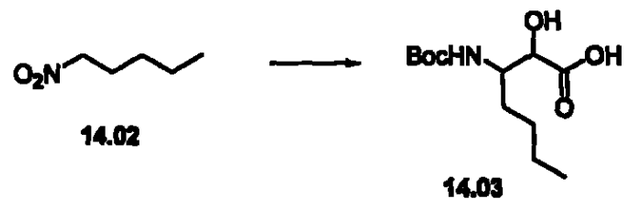
13.05 13 01

El compuesto 13 05 fue convertido en el intermediario requerido 13 01 utilizando esencialmente los procedimientos descritos para el intermediario 10 12, Paso 11

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244

Preparación del Intermediario 14.01

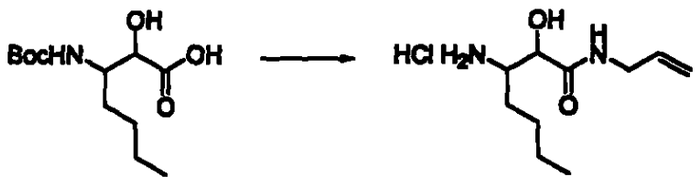
Paso 1



14.02 14.03

El compuesto 14 02 fue convertido en el material requerido 14.03 utilizando esencialmente los procedimientos descritos para el Intermediario 13 01, Pasos 1-3

Paso 2



14.03 14.01

El compuesto 14 03 fue convertido en el Intermediario requerido 14 01 utilizando esencialmente los procedimientos descritos para el Intermediario 10 12, Paso 11

Preparación del Intermediario 15.01

Paso 1

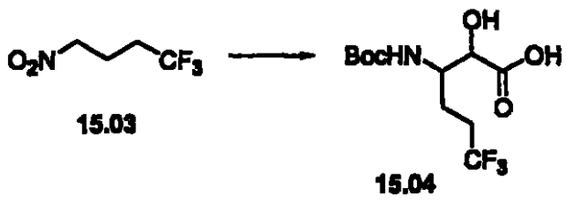


15.02 15.03

A una suspensión de nitrito de plata (9 g, 58,5 mmol) en éter dietílico (25 mL) a 0°C se agregó una solución de 4-yodo-1,1,1-trifluorbutano, 15 02 (10 g, 42,0 mmol) en éter dietílico (25 mL) lentamente a través de un embudo de adición (aprox 15 min) La mezcla resultante se agitó vigorosamente a 0°C y se calentó hasta temperatura ambiente Después de 50 h, el material sólido se separó por

filtración a través de una almohadilla de célite La solución de éter dietílico resultante se concentró *in vacuo* para dar 15 03 como un aceite incoloro, el cual se utilizó sin más purificación

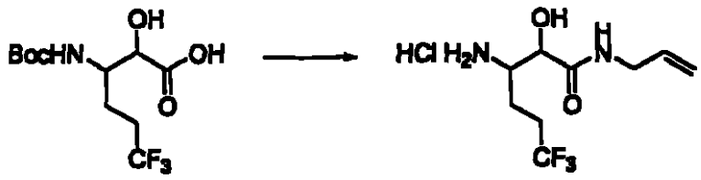
Paso 2



15.03 15.04

El compuesto 15 03 fue convertido en el material requerido 15 04 utilizando esencialmente los procedimientos descritos para el Intermediario 13 01, Pasos 1-3

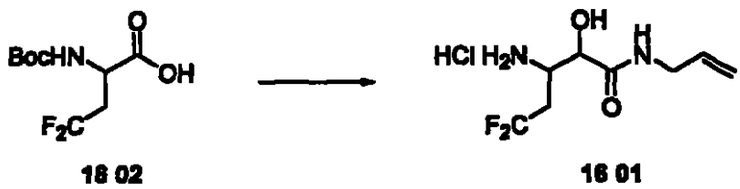
Paso 3



15 04 15.01

El compuesto 15 04 fue convertido al Intermediario requerido 15.01 utilizando esencialmente los procedimientos descritos para el Intermediario 10 12, Paso 11

Preparación de Intermediario 16 01

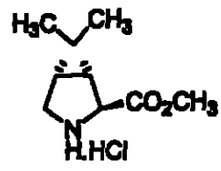


16 02 16 01

El ácido 16 02 (Winkler, D , Burger, K , *Synthesis*, 1996, 1419) es procesado según lo antes descrito (Preparación de Intermediario 16.12) para dar el Intermediario esperado 16 01

PREPARACIÓN DE PORCIONES P2 / P3-P2

Preparación de Intermediario 20 01



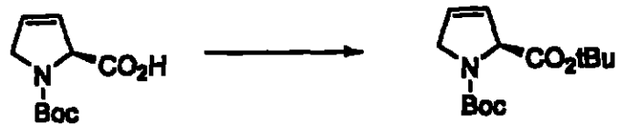
20.01

El aminoéster 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 fue disociado mediante la reacción del aminoácido Boc-protegido con HCl metanólico

(Nota En una variación de la síntesis reportada, el iluro de sulfonio utilizado para la construcción del anillo de 3,4-dimetilciclopropilo fue reemplazado con el iluro de fosfonio correspondiente)

Preparación de Intermediario 21 01

Paso 1



21 02 21 03

A una solución agitada de *N*-Boc-3,4-deshidroprolina 21 02 (5,0 g, 23,5 mmol), dicarbonato de di-*ter*-butilo (7,5 g, 34,4 mmol), y 4-*N*,*N*-dimetilaminopiridina (0,40 g,

3,33 mmol) en acetonitrilo (100 mL) a temperatura ambiente se agregó trietilamina (5,0 mL, 35,6 mmol) La solución resultante se agitó a esta temperatura durante 18 h antes de concentrarla *in vacuo* El residuo marrón oscuro se purificó mediante cromatografía en columna flash eluyendo con 10-25% EtOAc/hexano para dar el producto 21 03 en forma de un aceite amarillo pálido (5,29 g, 84%)

Paso 2



21.03 21.04

A una solución agitada del derivado de deshidroprolina 21 03 (10,1 g, 37,4 mmol), cloruro de bencitrietilamonio (1,60 g, 7,02 mmol) en cloroformo (120 mL) a temperatura ambiente se agregó hidróxido de sodio acuoso 50% (120 g) Después de agitar vigorosamente a esta temperatura durante 24 h, la mezcla oscura se diluyó con CH_2Cl_2 (200 mL) y éter dietílico (600 mL) Después de que las capas se separaron, la solución acuosa se extrajo con CH_2Cl_2/Et_2O (1 2, 3x600 mL) La solución orgánica se secó ($MgSO_4$) y se concentró El residuo se purificó mediante cromatografía en columna flash utilizando 5-20% EtOAc/hexano para dar 9,34 g (71%) de 21 04 en forma de un sólido blancuzco

Paso 3

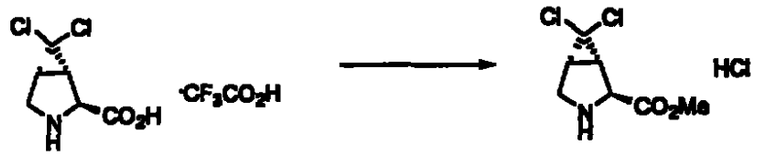


21 04 21 05

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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 horas antes de su concentración *in vacuo* para dar un residuo marrón, 21 05 el cual se utilizó en el Paso 4 sin más purificación

Paso 4

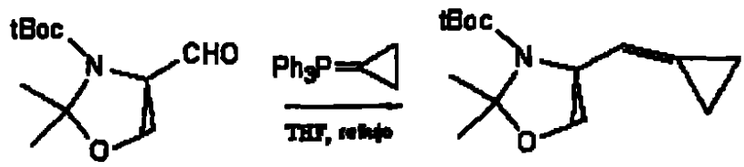


21.05 21.01

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 calentó hasta 65°C en un baño de aceite Después de 18 h, la mezcla se concentró *in vacuo* para dar un aceite marrón 21 01, el cual se utilizó sin más purificación

Preparación del Intermediario 22.01

Paso 1



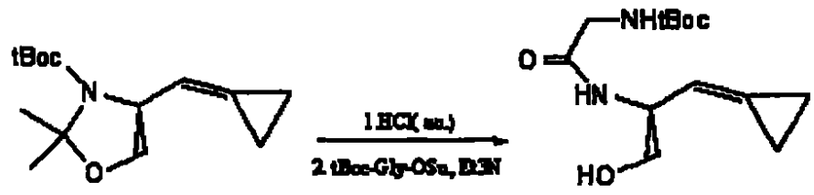
22.02 22.03

Se agregó bis(trimetilsilil)amida de potasio (158 ml de una solución 0,5M en tolueno, 79 mmol) a una suspensión agitada de bromuro de ciclopropiltrifenil-fosfonio (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 de la adición del aldehído 22 02 (9,68 g, 42,2 mmol) en THF (8 ml) Luego, la reacción se refluió bajo una atmósfera de nitrógeno durante un

2619
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período de 2 h Después de enfriamiento, se agregaron metanol, éter dietílico y sal Rochelles La fase orgánica se separó, se lavó con salmuera, se secó y concentró bajo presión reducida El producto de reacción crudo se purificó mediante cromatografía en columna sobre gel de sílice utilizando EtOAc-hexano (1 99) a EtOAc-hexano (5 95) para proporcionar el alqueno 22 03 (8,47g) en forma de un aceite amarillo

Paso 2



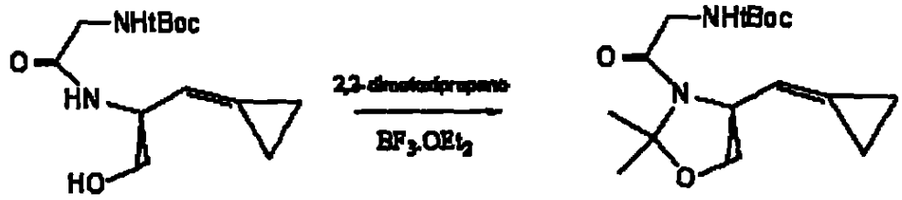
22.03 22.04

Una solución de HCl 1M en MeOH/MeOAc se preparó agregando 14,2 ml de cloruro de acetilo por goteo 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 1 M en MeOH/MeOAc (150 ml) mientras se enfriaba en un baño de hielo La mezcla resultante se mantuvo a esta temperatura durante 1 h, luego el baño de hielo se eliminó y la agitación continuó durante la noche a temperatura ambiente Los volátiles fueron eliminados bajo presión reducida para proporcionar un aceite amarillo el cual se utilizó en el siguiente paso 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 era de pH=9-10 Después de colocación en un baño de hielo, la mezcla se trató con N-Boc-Gly-OSu (11,22g, 41 mmol) El baño de hielo se retiró y la reacción se agitó a temp ambiente durante 1 h Los volátiles se eliminaron bajo presión reducida y el residuo se purificó

mediante cromatografía en columna sobre gel de sílice utilizando metanol (1-3%) en diclorometano proporcionando la amida deseada 22 04 (9,09 g)

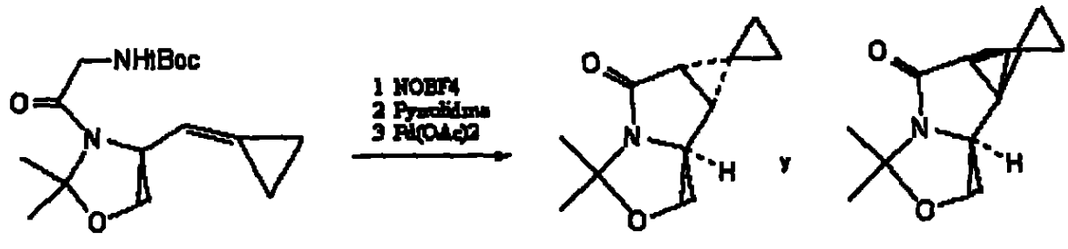
Paso 3



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 5,5 h La solución de reacción se trató con unas pocas gotas de trietilamina y los volátiles fueron eliminados bajo presión reducida El residuo se purificó mediante cromatografía en columna sobre gel de sílice utilizando 5-25% EtOAc en hexanos para proporcionar el N,O-acetal 22 05 (8,85 g)

Paso 4

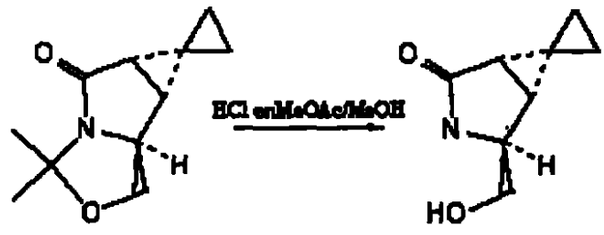


22.05 22.06 22.07

El carbamato 22 05 (8,81 g, 28,4 mmol) se disolvió en acetonitrilo (45 ml) y la solución se enfrió hasta –40°C bajo una atmósfera de nitrógeno Se agregaron

pirdina (6,9 ml, 85,3 mmol) seguido por tetrafluorborato 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 había más material de partida (aprox 2,25 h) Se agregó pirrolidina (20 ml, 240 mmol) y el baño de enfriamiento se retiró y se continuó la agitación a temperatura ambiente durante 1h y luego los volátiles se eliminaron bajo presión reducida El residuo se pasó rápidamente a través de una almohadilla de gel de sílice para proporcionar 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 Después de enfriamiento, los volátiles fueron eliminados bajo presión reducida y el residuo oscuro se purificó mediante cromatografía en columna sobre gel de sílice utilizando EtOAc-hexano (1 4) para proporcionar el i) la trans-pirrolidinona 22 06 (1,94g) seguido por ii) la cis-pirrolidinona 22 07 (1,97 g)

Paso 5

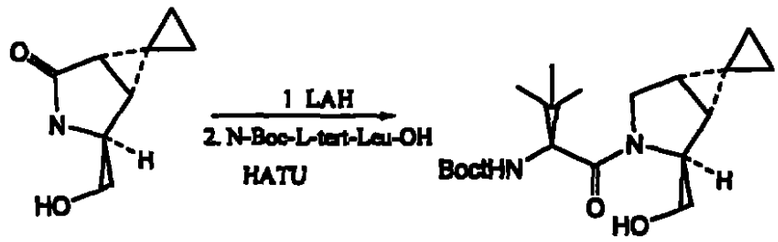


22.06 22.08

El HCl 1 M recientemente preparado en MeOAc/MeOH (10 ml, según lo descrito anteriormente) fue agregado al N,O-acetal 22 06 y se agitó a temperatura ambiente durante 1h El solvente se eliminó bajo presión reducida y el residuo se purificó mediante cromatografía en columna sobre gel de sílice utilizando 0-4%MeOH en diclorometano como eluyente para proporcionar el alcohol deseado 22 08 (1,42 g), un aceite amarillo

252

Paso 6

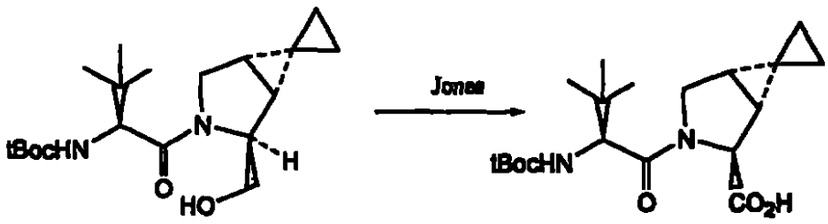


22.08 22.09

A una solución de la lactama 22 08 (1,29 g, 8,44 mmol) en tetrahidrofurano anhidro (55 ml) se agregó hidruro de litio y aluminio (2,40 g, 63,2 mmol) y la mezcla resultante se refluJó durante 8 h Después de enfriamiento, se agregó agua, seguido por NaOH ac 15% y la mezcla resultante se filtró a través de célite y el sólido se lavó completamente con THF y MeOH El solvente se eliminó bajo presión reducida y el residuo se redisolvió en diclorometano, se secó y concentró bajo presión reducida para proporcionar la pirrolidina, utilizada sin purificación Se agregó la base Hunigs (4,5 ml, 25,8 mmol) a una mezcla de N-Boc-L-ter-Leu-OH (1,76 g, 7,6 mmol) La pirrolidina cruda 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 a temperatura ambiente lentamente, durante la noche Se agregó EtOAc y la solución amarilla se lavó con HCl ac dil , bicarbonato de sodio ac sat , agua y salmuera La capa orgánica se secó y se concentró bajo presión reducida El residuo se purificó mediante cromatografía en columna sobre gel de sílice utilizando EtOAc hexanos (1 3) para dar la amida deseada 22 09 (2,00 g)

383
253

Paso 7

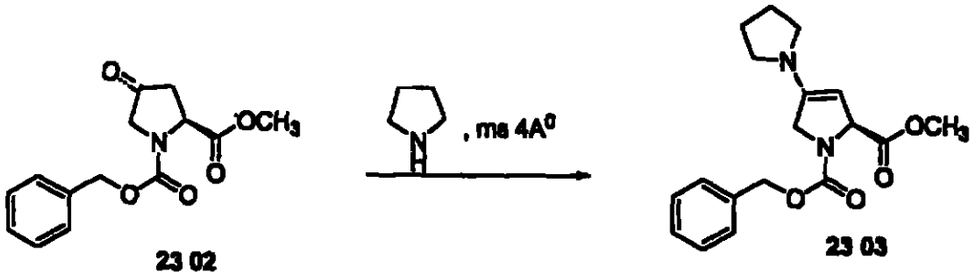


22.09 22 01

El alcohol 22 09 (2,00 g, 5,67mmol) se disolvió en acetona (116 ml) y se enfrió en un baño de hielo durante 10 min esta solución fue luego agregada a un reactivo Jones enfriado (14,2ml, aprox 2 mmol/ml) y la mezcla resultante se agitó a 5°C durante 0,5 h y el baño de enfriamiento fue retirado La reacción se agitó durante 2 horas adicionales, a temp ambiente, antes del agregado a sulfato de sodio (28,54 g), célite (15g) en EtOAc (100ml) Se agregó isopropanol (15 ml) después de 1 min y luego se agitó durante 10 min más y se filtró El filtrado se concentró bajo presión reducida, proporcionando un aceite marrón el cual se disolvió en EtOAc Esta solución se lavó con agua, ácido cítrico ac al 3%, salmuera, se secó y concentró para proporcionar el ácido carboxílico deseado 22 01 (1,64 g) en forma de un sólido blanco

Preparación de Intermediario 23 01

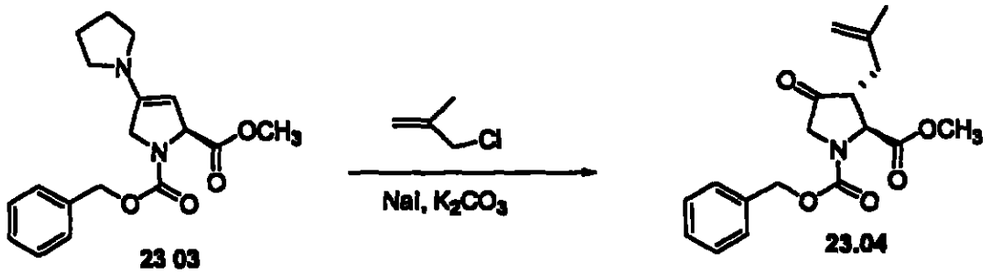
Paso 1



23 02 23 03

A la mezcla del éster 23 02 (6,0 g) y tamiz molecular (5,2 g) en cloruro de metileno anhidro (35 mL) se agregó pirrolidina (5,7 mL, 66,36 mmoL) La suspensión marrón resultante se agitó a temperatura ambiente bajo N_2 durante 24 h, se filtró y se lavó con CH_3CN anhidro El filtrado combinado se concentró para proporcionar el producto deseado, 23 03

Paso 2



23 03 23.04

A una solución del producto 23 03 del paso precedente en CH_3CN (35 mL) se agregó K_2CO_3 anhidro, cloruro de metalilo (2,77 g, 30,5 mmoL), NaI (1,07 g, 6,7 mmoL) La suspensión resultante se agitó a temperatura ambiente bajo N_2 durante 24 h Se agregaron 50 mL de agua enfriada con hielo seguido por una solución $KHSO_4$ 2N hasta que el pH fue de 1 Se agregó EtOAc (100 mL) y la mezcla se agitó durante 0,75 h La capa orgánica combinada se recogió y se lavó con salmuera, se secó sobre $MgSO_4$, y se evaporó para proporcionar el producto deseado, 23 04

Paso 3



23.04 23.05

El producto 23 04 del paso precedente (2,7 g, 8,16 mmoL) se disolvió en dioxano (20 mL) y se trató con LiOH 1N recientemente preparado (9 mL) La mezcla de reacción se agitó a temperatura ambiente bajo N_2 durante 20 h La mezcla de reacción se absorbió en EtOAc y se lavó con H_2O La fase acuosa combinada se enfrió hasta 0^0C y se acidificó hasta pH 1,65 utilizando HCl 1N La mezcla turbia se extrajo con EtOAc (2 x 100 mL) La capa orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$, y se concentró para dar el ácido deseado, 23 05 (3,40 g)

Paso 4

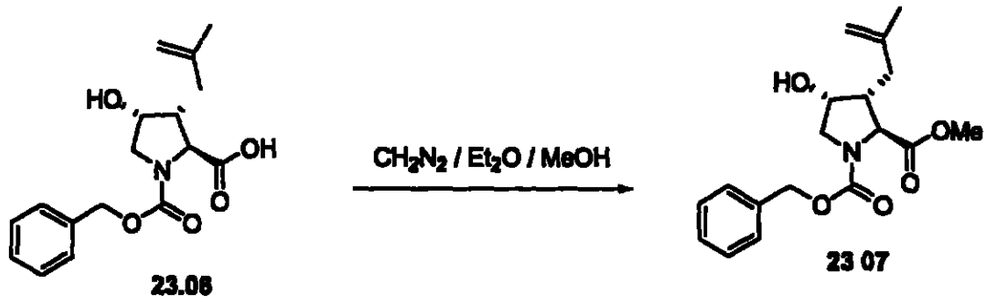


23.05 23.06

A una suspensión de $NaBH(OAc)_3$ (3,93g, 18,5 mmoL) en CH_2Cl_2 (55 mL) se agregó una solución del producto 23 05 del paso precedente 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 capa orgánica se separó, se filtró, se secó y se evaporó para proporcionar el producto deseado, 23 06

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256

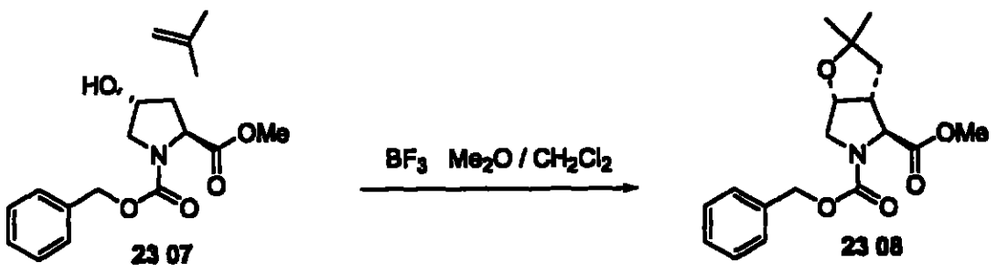
Paso 5



23.06 23 07

A una solución del producto 23 06 del paso precedente (1,9 g) en MeOH (40 mL) se trató con exceso de solución de CH_2N_2 / Et_2O y se agitó durante la noche La mezcla de reacción se concentró hasta sequedad para proporcionar un residuo crudo El residuo se cromatografió sobre gel de sílice, eluyendo con un gradiente de EtOAc / hexano para dar 1,07 g del producto deseado puro, 23 07

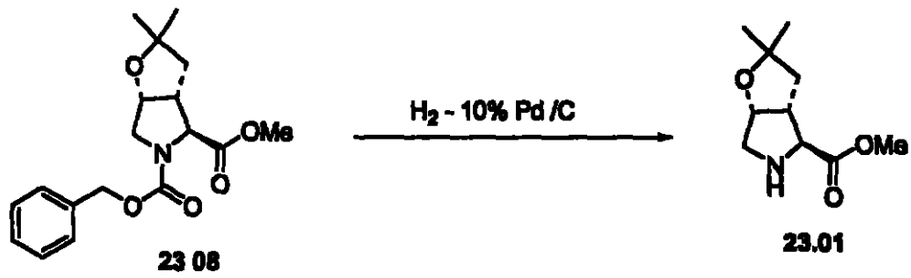
Paso 6



23 07 23 08

A una solución del product 23 07 del paso precedente (1,36 g) en CH_2Cl_2 anhidro (40 mL) se trató con BF_3. Me_2O (0,7 mL) La mezcla de reacción se agitó a temperatura ambiente durante 20 h y se templó con $NaHCO_3$ sat. (30 mL) y se agitó durante 1/2 hr La capa orgánica se separó y la capa orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$, se concentró para dar el residuo crudo El residuo se cromatografió sobre gel de sílice eluyendo con un gradiente de EtOAc / hexano para dar 0,88 g del compuesto deseado, 23 08

Paso 7



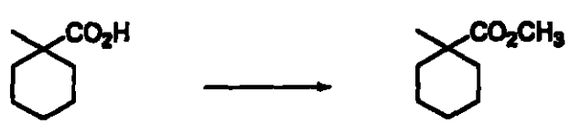
23 08 23.01

A una solución del producto 23 08 (0,92 g) del paso precedente en MeOH (30 mL) se agregó Pd/C al 10 % (0,16 g) a temperatura ambiente y se hidrogenó a temperatura ambiente bajo presión de 1 atm La mezcla de reacción se agitó durante 4 h y se concentró hasta sequedad para proporcionar el compuesto deseado, 23 01

PREPARACIÓN DE PORCIONES P3

Preparación del Intermediario 50.01

Paso 1

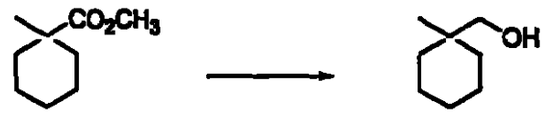


50.02 50 03

A una solución de 50 02 (15 g) en MeOH (150 mL) se agregó HCl conc (3-4 mL) y la mezcla se refluió durante 16 h La mezcla de reacción se enfrió hasta temperatura ambiente y se concentró El residuo se absorbió en éter dietílico (250 mL) y se lavó con solución de bicarbonato de sodio saturado frío y salmuera La capa orgánica se secó (Na_2SO_4) y se concentró para dar el éster metílico 50.03 (12,98 g) el cual se utilizó más adelante sin más purificación

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258

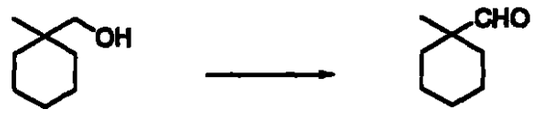
Paso 2



50 03 50.04

El éster metílico 50 03 de lo que antecede se disolvió en cloruro de metileno (100 mL) y se enfnó hasta -78°C, bajo atmósfera de nitrógeno Se agregó por goteo DIBAL (solución 1,0 M en cloruro de metileno, 200 mL) durante un período de 2 h La mezcla de reacción se calentó hasta temperatura ambiente durante 16 h La mezcla de reacción se enfrió hasta 0°C y se agregó por goteo MeOH (5-8 mL) Una solución de tartarato de potasio sódico al 10% acuoso (200 mL) se agregó lentamente con agitación Se diluyó con cloruro de metileno (100 mL) y la capa orgánica se separó (junto con algo de precipitado blanco) La capa orgánica se lavó con HCl 1 N (250 mL), salmuera (200 mL), se secó (Na_2SO_4) y se concentró para proporcionar el alcohol 50 04 (11,00 g) en forma de un aceite claro

Paso 3

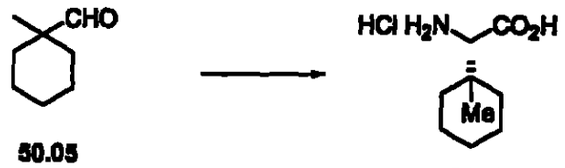


50 04 50 05

El alcohol 50 04 de lo que antecede 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 calentó lentamente hasta temperatura ambiente durante 16 h La mezcla de reacción se diluyó con éter dietílico (500 mL) y se filtró a través de una almohadilla de célite El filtrado se concentró y el residuo se absorbió en éter dietílico (500 mL) Esto se hizo pasar a través de una almohadilla de gel de sílice y el filtrado se concentró para proporcionar el aldehído 50 05 el cual se utilizó más adelante sin más purificación

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Paso 4

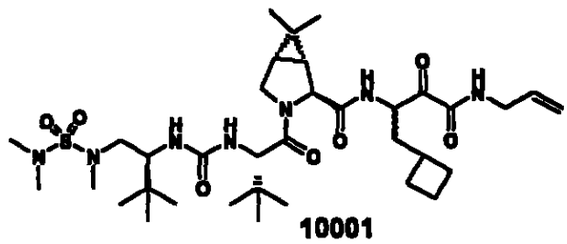


50.05 50 01

El aldehído 50 05 de lo que antecede fue convertido en el material deseado 50 01 utilizando esencialmente el método de Chakraborty *et al* (Tetrahedron, 1995, 51(33), 9179-90)

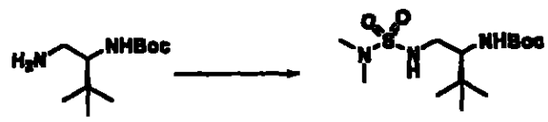
PREPARACIÓN DE EJEMPLOS ESPECÍFICOS

Ejemplo 1 Síntesis de compuesto de Fórmula 10001



10001

Paso A



10001a 10001b

La amina, 10001a, (C A Busacca *et al, Tetrahedron Asymmetry*; (2000) 9 1907) (1,5 g, 6,9 mmol, 1 equiv) se disolvió en diclorometano seco 20 ml) y se enfrió hasta -78 °C Se agregaron 3 ml (3 equiv) de Et_3N seguido por la lenta adición de cloruro de dimetilsulfamilo (1,5 eq , Sigma-Aldrich) disuelto en DCM La temperatura se mantuvo a -78 °C hasta completarse la adición y luego se agitó durante la noche permitiéndole subir hasta temperatura ambiente Se diluyó con cloruro de metileno y se lavó con agua, HCl ac 1N y finalmente con salmuera Las capas orgánicas se

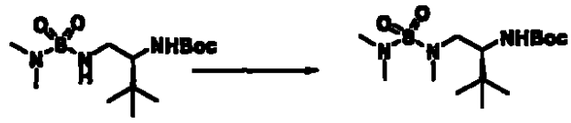
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secaron sobre sulfato de sodio anhidro, se filtraron y concentraron in *vacuo* El producto crudo aislado fue purificado mediante columna flash (10→30 % EtOAc-Hexano) para proporcionar 1,27g (58%) de **10001b**

^{1}H RMN (CDCl$_3$, 300 MHz) δ, 4,6 (d, 1 H), 3,45 (m, 1 H,), 3,25 (d, 1 H), 2,89 (s, 6 H), 1,89 (bs, NH), 1,22 (s, 9H), 0,98 (s, 9 H)

EM (ESI), m/z, Intensidad relativa 324 [(M+1) 85], 268 (100), 224 (50)

Paso B



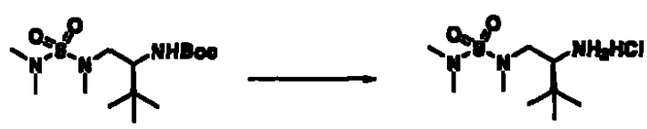
10001b **10001c**

A la sulfonilurea protegida con Boc **10001b** (440 mg,1,25 mmol, 1 equiv) en DMF(10 mL) a 0° C se agregó Cs_2CO_3 (613 mg, 1,5 equiv, 1,88 mmol) y MeI (6,36 mmol, 5 equiv , 0,601 mL) bajo atmósfera inerte La mezcla de reacción se agitó a temperatura ambiente durante 90 min y se templó con agua Las capas acuosas fueron extraídas con EtOAc, lavadas 4 veces con agua y salmuera Las capas orgánicas se secaron sobre sulfato de sodio anhidro, se filtraron y el solvente se separó por evaporación para proporcionar 420 mg (91%) de **10001c** el cual se utilizó en la siguiente reacción sin más purificación

^{1}H RMN (CDCl$_3$, 300 MHz) δ, 4,59 (d, 1 H), 3,62-3,58 (m, 1 H,), 3,29-3,22 (m, 1 H), 2,80 (s, 3 H), 2,79 (s, 6H), 1,89 (bs, NH), 1,22 (s, 9 H), 0,98 (s, 9 H)

EM (ESI), m/z, Intensidad relativa 338 [(M+1) 60], 282 (100), 238 (90)

Paso C



10001c **10001d**

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A la sulfonilurea protegida con Boc 10001c (890 mg, 1 equiv) se agregó solución 4M de HCl en dioxano (25 mL) a temp ambiente y se agitó durante 1 hr Después de la desaparición del material de partida (TLC), la mezcla de reacción se concentró y se azeotropizó con hexanos y éter El residuo se trituró con éter y el sólido separado se filtró y se secó al vacío para dar un sólido amarillo pálido (720 mg, ~100%) Se utilizó en una reacción adicional sin purificación

paso D

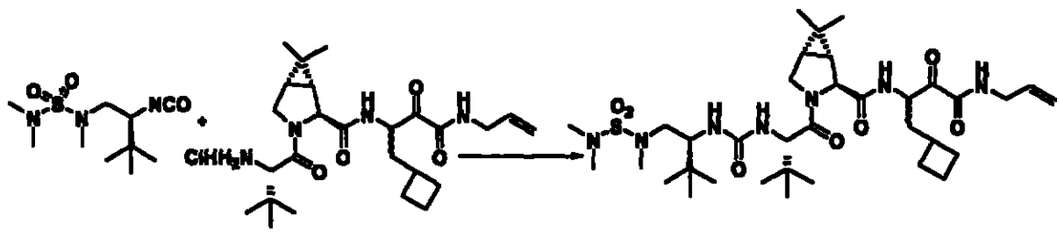


10001d **10001e**

A la sal clorhidrato de amina 10001d (720 mg, 2,63 mmol) en diclorometano (1 5 ml) se agregaron 15 ml de $NaHCO_3$ saturado ac y se agitó vigorosamente a 0°C durante 5 min Se extrajo con jeringa una solución de fosgeno (2 equiv 20% en tolueno) a la capa inferior y se continuó la agitación vigorosa inmediatamente Se controló la TLC algunas veces y después de 2 horas, mostró un completo consumo de material de partida La capa de cloruro de metileno se separó y la capa acuosa se extrajo con diclorometano (30 ml) Las capas orgánicas combinadas se secaron sobre sulfato de sodio anhidro, se filtraron y concentraron utilizando un evaporador rotativo bajo presión reducida a temperatura ambiente hasta la mitad del volumen y luego se introdujo N_2 durante 15 minutos Se diluyó la solución hasta 130 mL con diclorometano y se utilizó como una solución 0,02 M en otras reacciones

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Paso E

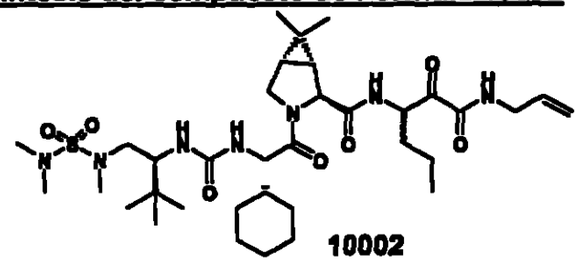


10001e **10001f** **10001**

A la sal clorhidrato de amina, **10001f** (sintetizada mediante acoplamiento del intermediario 10 12 y 1 17 utilizando HATU seguido por oxidación Dess-Martin y desprotección Boc siguiendo el método C o el procedimiento descrito para la síntesis de 13001h) (130 mg, 0,261mmol, 1 equiv) en diclorometano (5 ml) se agregó DIPEA (6 equiv) a 0°C Una solución de isocianato **10001e** (1 equiv, 13 ml de solución 0,02M) bajo atmósfera de N_2 y se agitó durante 30 min a temperatura del hielo y 90 min a temperatura ambiente La mezcla de reacción se templó con ácido cítrico y se extrajo con EtOAc La capa orgánica se lavó con salmuera, se secó sobre sulfato de sodio anhidro, se filtró y concentró in *vacuo* El producto crudo se purificó utilizando cromatografía en columna flash (SiO_2, 10-40% acetona-hexano) para proporcionar 110 mg (59%) de **10001** en forma de un sólido incoloro

EM (ESI), m/z, intensidad relativa 724[(M+1) 45], 377 (100)

Ejemplo 2 Síntesis del compuesto de Fórmula 10002

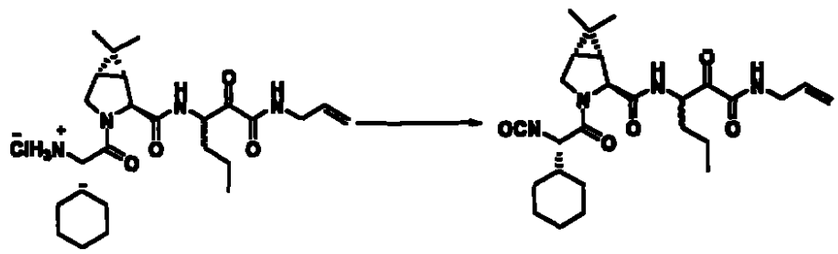


10002

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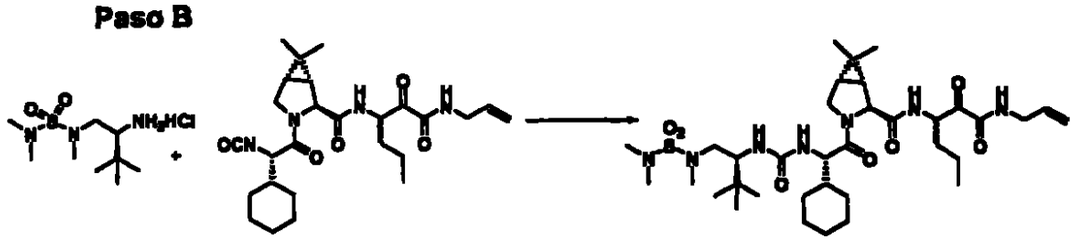
Paso A



10002a **10002b**

A una solución de la sal clorhidrato de amina **10002a** (500 mg, 1,00 mmol, 1 equiv) en diclorometano (15 ml) se agregó una solución de $NaHCO_3$ ac sat (15 mL) La mezcla de reacción se agitó vigorosamente a temperatura del hielo durante 5 min Se separó por jeringa una solución de fosgeno (2 equiv 20 % en tolueno) a la capa inferior y se continuó la agitación vigorosa inmediatamente Se controló la TLC algunas veces y después de 2 horas mostró un completo consumo de material de partida y luego se separaron las capas Se lavó la capa de agua una vez más con DCM (3 ml) y se secó sobre sulfato de sodio Se filtró y evaporó a alto vacío hasta la mitad del volumen y luego se purgó N_2 durante 15 minutos Se utilizó 10002b como solución base de 0,02M diluyendo con 50 mL de diclorometano

Paso B



10001d **10002b** **10002**

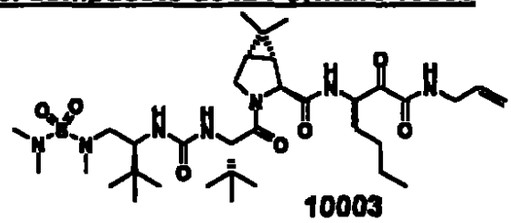
A la sal de amonio **10001d**, (80 mg, 0,293 mmol, 1 equiv) en diclorometano (10 ml) se agregó DIPEA (6 equiv) a temperatura del hielo Se agregó isocianato **10002b** (1 equiv, 14,6 ml de solución 0,02M) bajo atm de N_2, y se agitó durante 30 min a temperatura del hielo y 90 min a temperatura ambiente Se templó con ácido

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cítrico y se extrajo con EtOAc y se lavó con salmuera Se secó sobre sulfato de sodio anhidro y se filtró y separó por evaporación el solvente El producto crudo se purificó utilizando cromatografía flash sobre gel de sílice (10-40% acetona-hexano) para proporcionar 120 mg (57 %) de 10002 en forma de un sólido incoloro

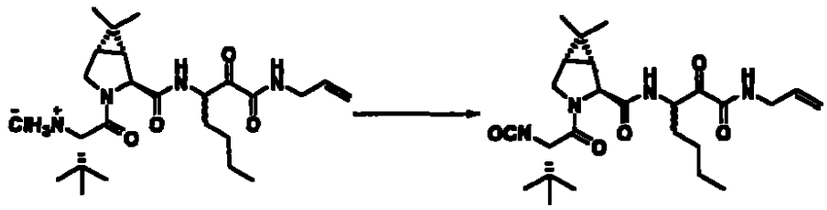
EM (ESI), m/z, intensidad relativa 724 [(M+1) 100], 461 (45), 403 (80)

Ejemplo 3 Síntesis del compuesto de la Fórmula 10003



10003

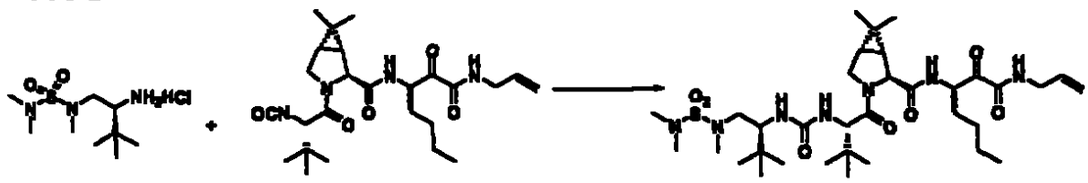
Paso A



10003a 10003b

Al clorhidrato de amina 10003a, preparado según lo descrito anteriormente, (500 mg, 1,03 mmol, 1 equiv) en DCM (15 ml) se agregaron 15 ml de $NaHCO_3$ sat Se agitó vigorosamente a la temperatura del hielo durante 5 min Se detuvo la agitación y se separó mediante jeringa el fosgeno(1,11 mL, 2 equiv , 20% en tolueno) a la capa inferior y se continuó la agitación vigorosa inmediatamente Se controló la TLC algunas veces y después de 2 horas mostró un completo consumo de material de partida y luego se separaron las capas Se lavó la capa acuosa una vez más con DCM (3 ml) y se secó sobre sulfato de sodio Se filtró y evaporó a alto vacío hasta la mitad del volumen y luego se purgó con N_2 durante 15 minutos Se utilizó como una solución base de 10003b (0,02M) diluyendo con 50 mL de diclorometano

Paso B

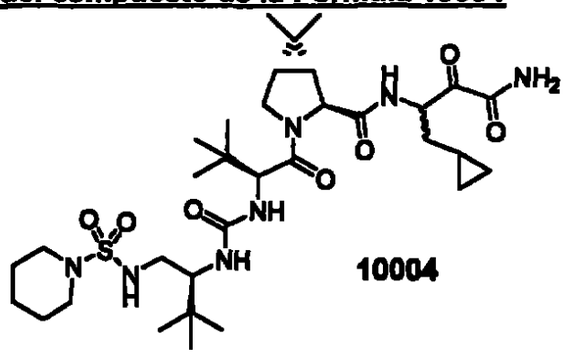


10001d **10003b** **10003**

A una solución de sal de amonio, **10001d**, (20 mg, 0,073mmol, 1 equiv) en DCM (5 ml) se agregó DIPEA (6 equiv) a temperatura del hielo, se agregó isocianato **10003b** (1 equiv, 0,073 mmol, 3,66 mL de solución 0,02M) bajo atm de N_2 y se agitó durante 30 min a la temperatura del hielo y 90 min a temperatura ambiente Se templó con ácido cítrico y se extrajo con EtOAc y se lavó con salmuera Se secó sobre sulfato de sodio anhidro, se filtró y se separó por evaporación el solvente El producto crudo se purificó mediante columna de sílice flash (10-40% acetona-hexano) para proporcionar 28 mg , 55 % de **10003**

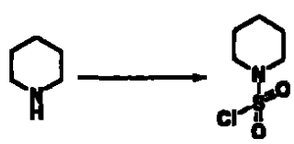
EM (ESI), m/z, intensidad relativa 724 [(M+1) 100], 461 (45), 403 (80)

Ejemplo 4 Síntesis del compuesto de la Fórmula 10004



10004

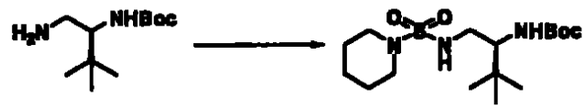
Paso A



10004a **10004b**

A 0,95mL (11,7mmol) de cloruro de sulfurilo en 20 mL de éter se agregó por goteo 2,3mL (23,4mmol) de piperidina a -78° C La reacción se agitó a temperatura ambiente durante 3 horas El sólido insoluble se retiró mediante filtración y el filtrado se lavó con HCl 1N, $NaHCO_3$ sat y salmuera La capa orgánica se secó sobre $MgSO_4$, se filtró y el filtrado se concentró hasta sequedad para proporcionar 1,00 g de **10004b** rendimiento 46%

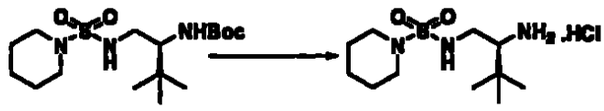
Paso B



10001a **10004c**

A 0,350g (1,62mmol) de **10001a** en 10mL CH_2Cl_2 se agregaron 0,23 mL (1,62mmol) de Et_3N, luego 0,446g (2,42mmol) de **10004b** en 5 mL CH_2Cl_2 por goteo a temperatura ambiente La mezcla de reacción se agitó a temperatura ambiente durante toda la noche La mezcla de reacción se diluyó con EtOAc, se lavó con una solución de NH_4Cl ac. y salmuera Las capas orgánicas se secaron sobre $MgSO_4$, se filtraron, se concentraron in *vacuo* y se purificaron mediante cromatografía con gel de sílice con 6→24% EtOAc en Hexano para proporcionar 0,353g de producto Rendimiento 60%

Paso C

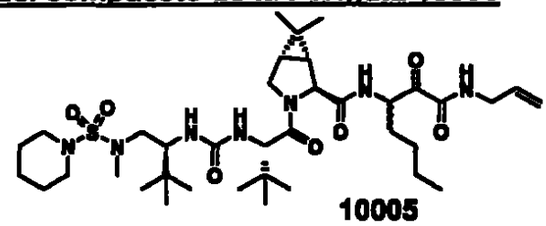


10004c **10004d**

A 15mg (0,041mmol) de **10004c** en un frasco se agregaron 2ml (8 mmol) de HCl 4M (en dioxano) y se agitó a TEMPERATURA AMBIENTE durante 50 min La mezcla de reacción se concentró hasta sequedad in *vacuo* para proporcionar 32 mg de **2004d** Rendimiento 100%

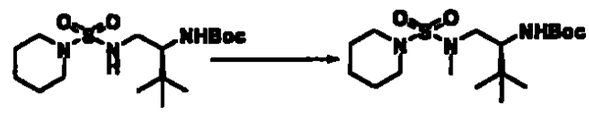
Nota La conversión de 10004d a 10004 fue idéntica al paso B en la Síntesis del Ejemplo 3 preparativa del compuesto de la Fórmula 10003

Ejemplo 5 Síntesis del compuesto de la Fórmula 10005



10005

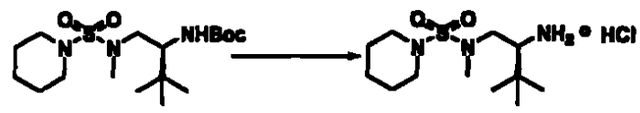
Paso A



10004c 10005a

A una solución de 0,275 g (0,76mmol) de 10004c en DMF se agregó 0,369g (1,13mmol) de Cs_2CO_3 y 0,085mL (1,37mmol) de MeI a 0°C La reacción se agitó a temperatura ambiente durante la noche La mezcla de reacción se diluyó con agua y se extrajo con EtOAc La capa orgánica se lavó con salmuera, se secó, se concentró in *vacuo* y el residuo se purificó mediante cromatografía (SiO_2 8-32% EtOAc en hexano) para proporcionar 0,256 g de producto 10005a Rendimiento 89%

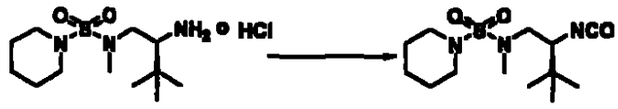
Paso B



10005a 10005b

A una solución de 0,291 g (0,77mmol) de 10005a en frasco se agregó 3mL (12 mmol) de HCl 4M (en dioxano) y se agitó a temperatura ambiente durante 50 min Después de completarse la reacción según lo indicado por TLC la mezcla de reacción se concentró in *vacuo* hasta sequedad para proporcionar 0,241g de 10005b

Paso C



10005b 10005c

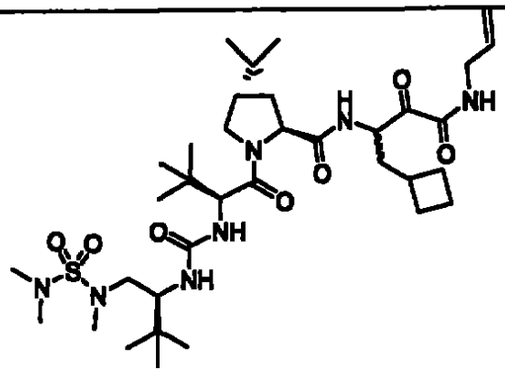
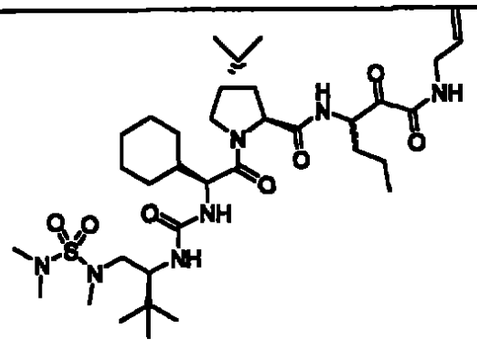
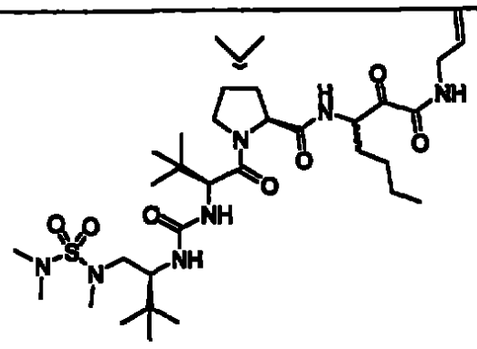
A 0,241g (0,77mol) de 10005c en CH_2Cl_2 a 0°C se agregó 0,81 mL (1,54 mmol) de solución 1,9 M de tolueno de fosgenina y 10 mL de solución de $NaHCO_3$ acuosa saturada La mezcla de reacción se agitó a temperatura ambiente durante 1,0 h La capa orgánica se separó y se secó sobre (Na_2SO_4), se filtró, se concentró hasta la mitad del volumen Se diluyó adicionalmente con CH_2Cl_2 para proporcionar una solución 0,07 M

Nota La conversión de 10005c a 10005 fue idéntica al paso B en la Síntesis del Ejemplo 3 preparativa de los compuestos 10003

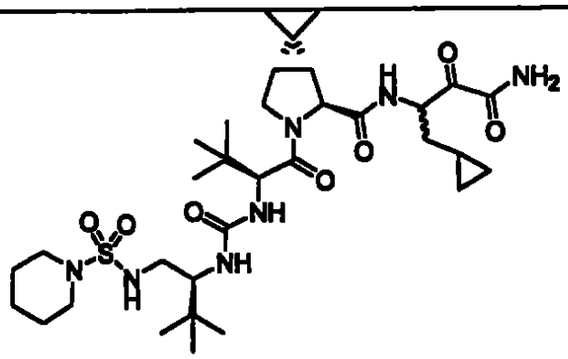
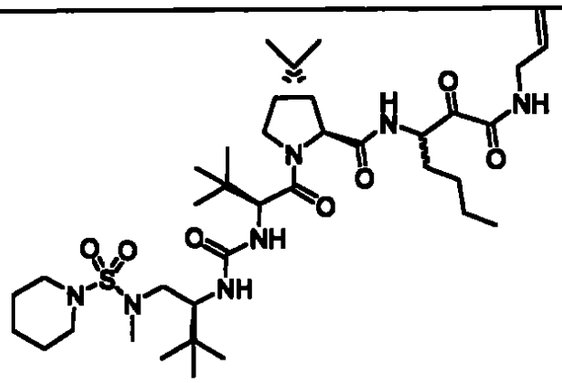
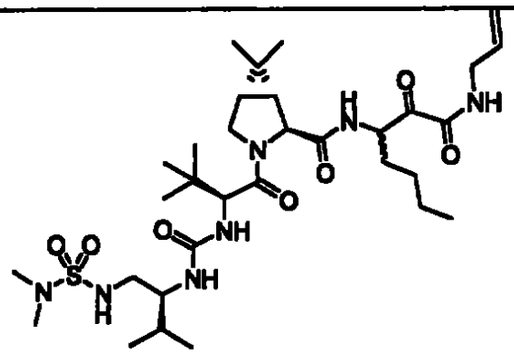
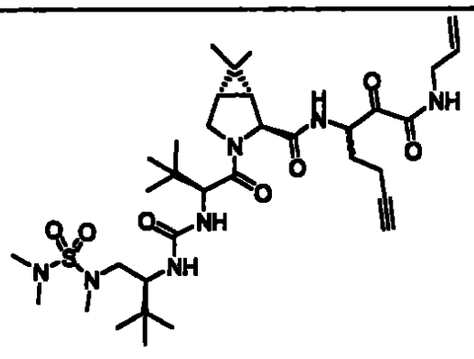
Los compuestos indicados en la siguiente Tabla 1 fueron sintetizados utilizando reacciones similares a las mostradas en los Ejemplos 1-5 Rango de KI* indicó A≤75 nM, 75<B ≤ 250 nM, C>250 nM

369
269

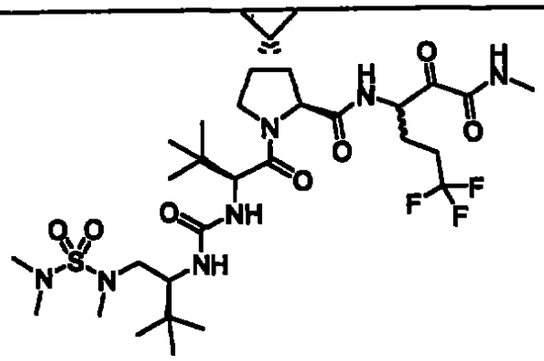
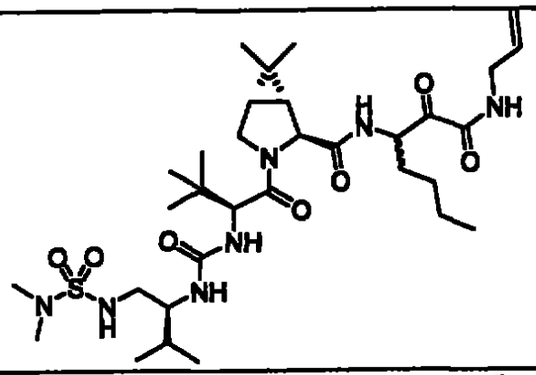
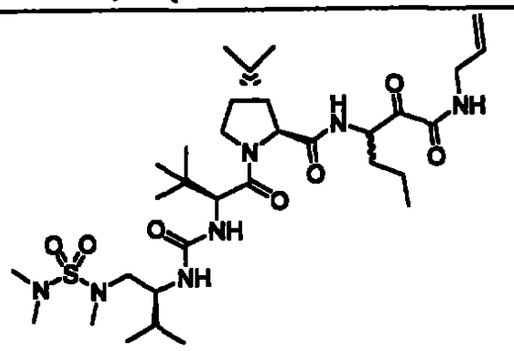
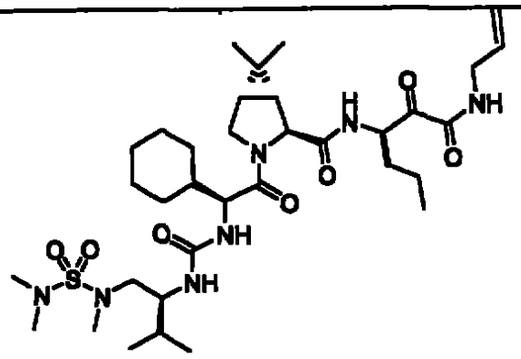
Tabla 1

Item	Estructura	K_i*
10001		A
10002		A
10003		A

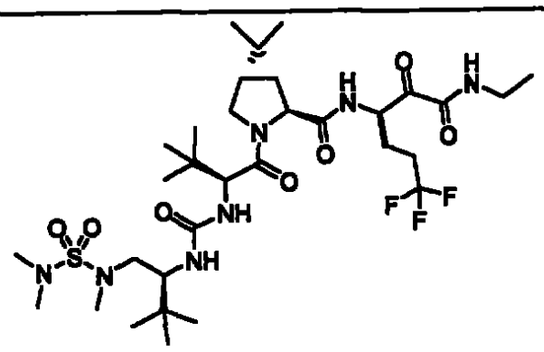
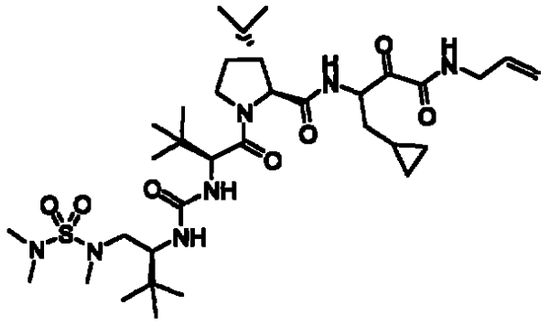
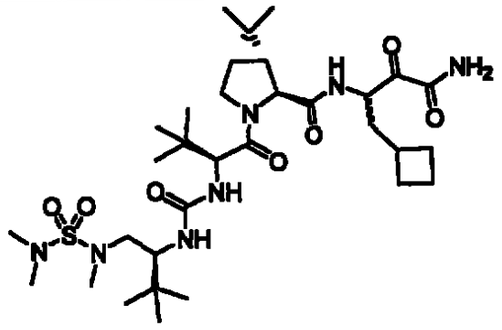
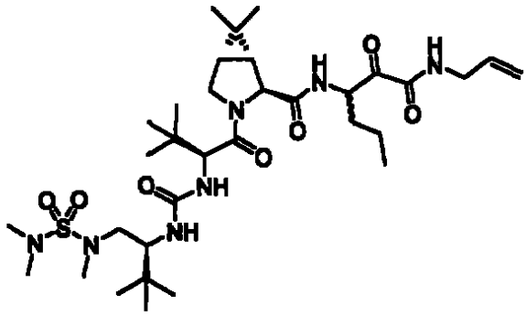
270 270

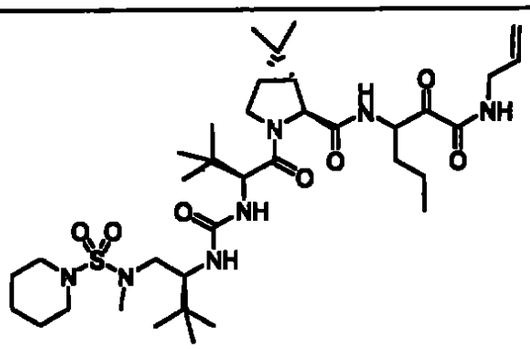
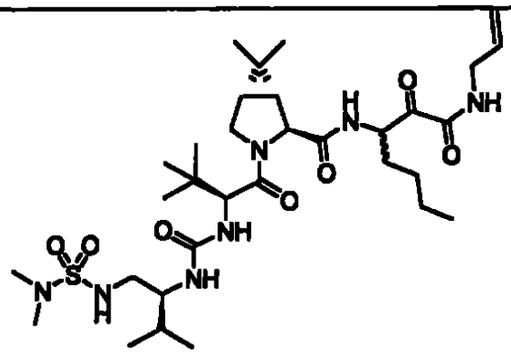
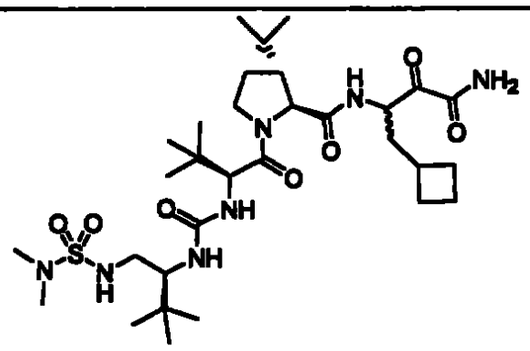
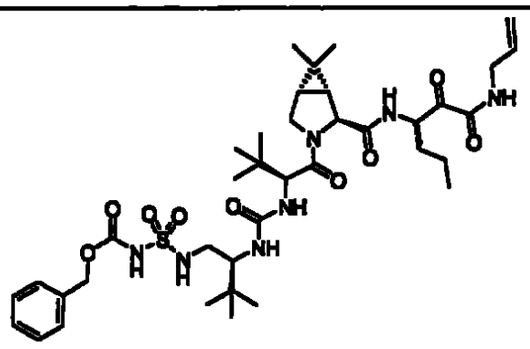
10004		A
10005		A
10006		B
10007		A

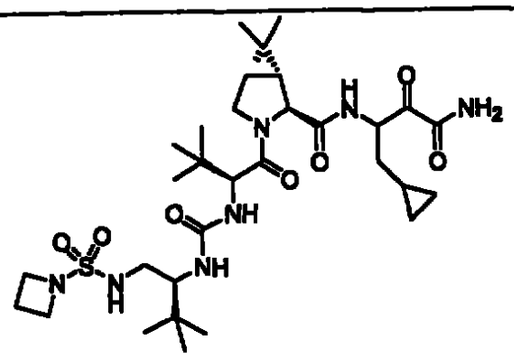
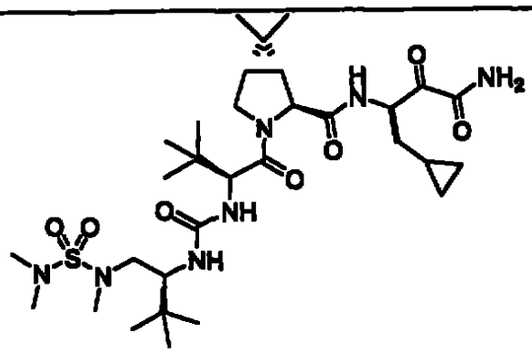
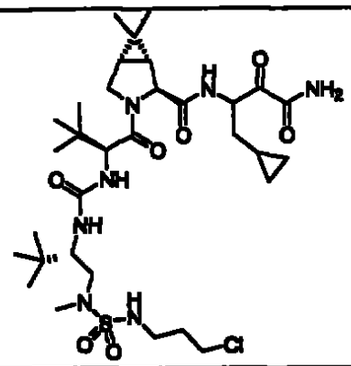
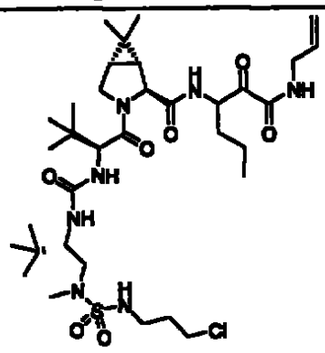
271

10008		A
10009		B
10010		A
10011		A

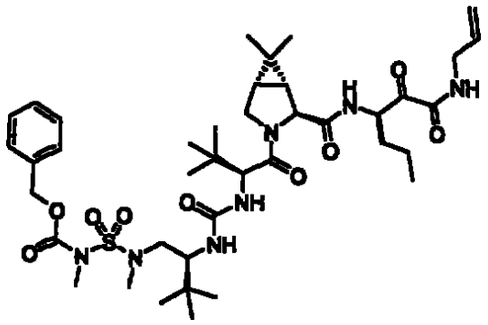
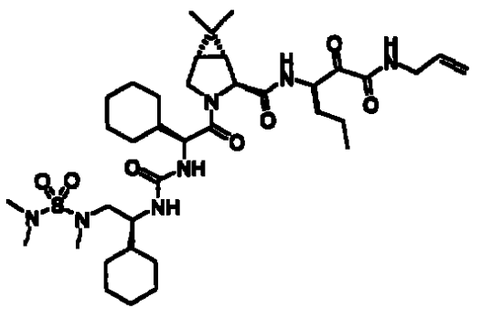
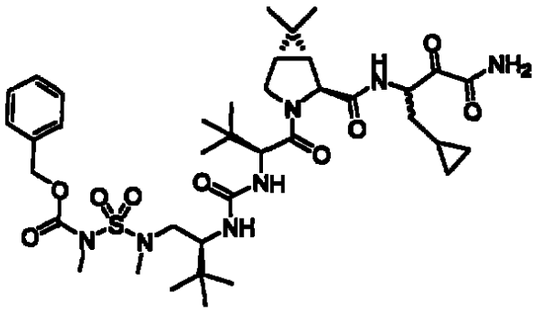
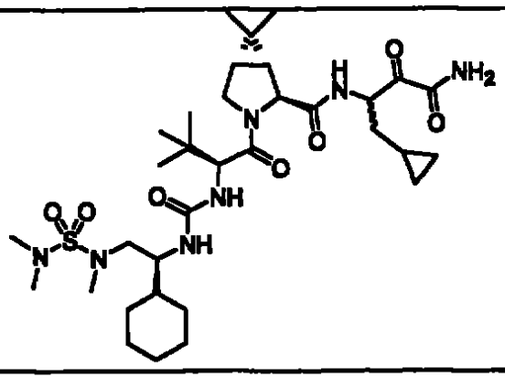
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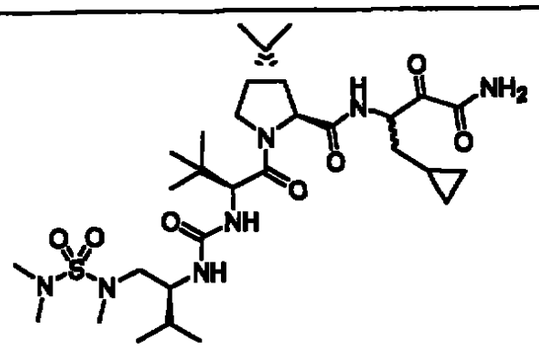
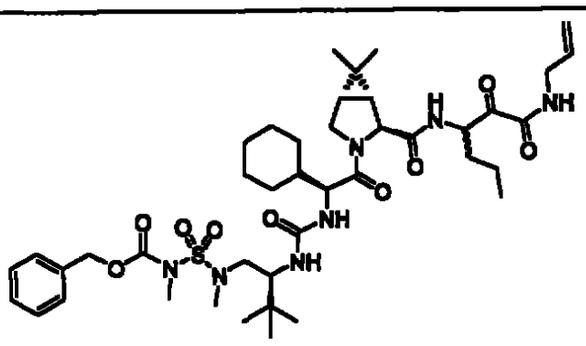
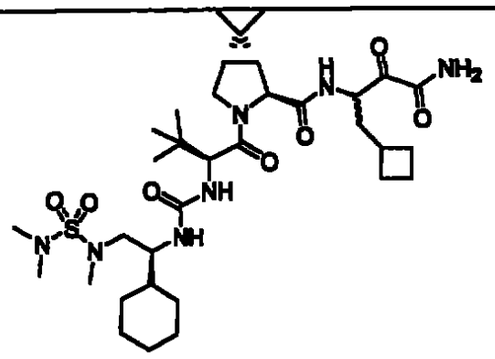
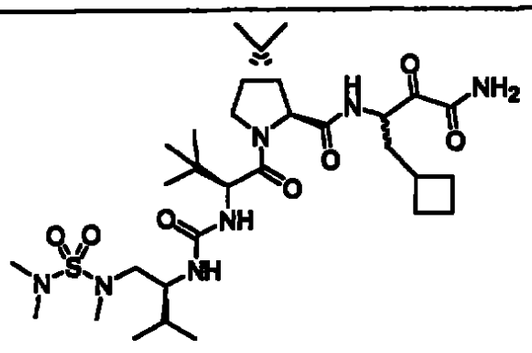
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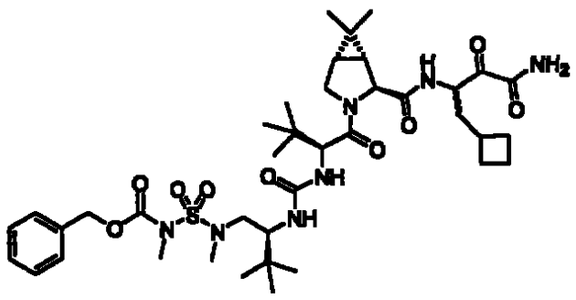
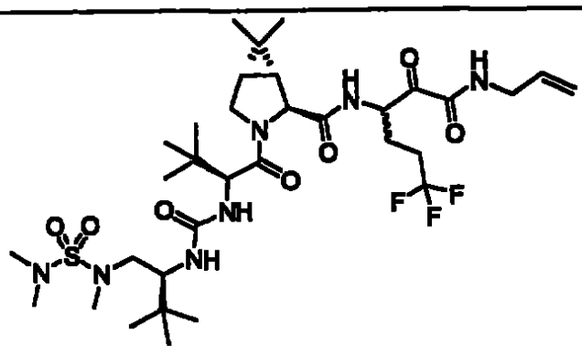
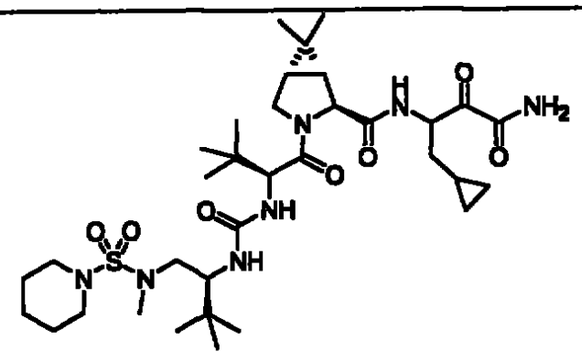
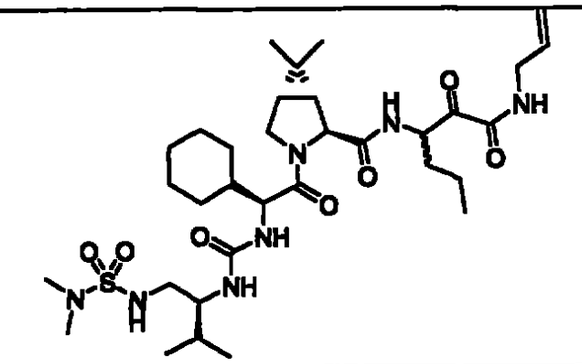
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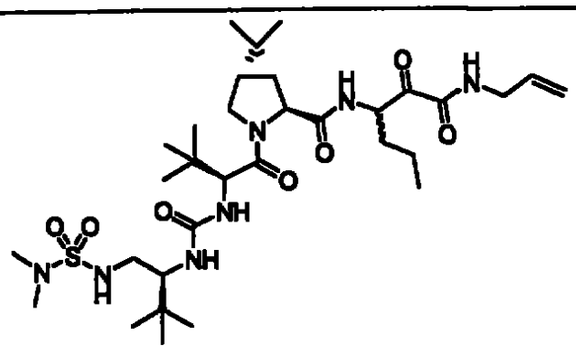
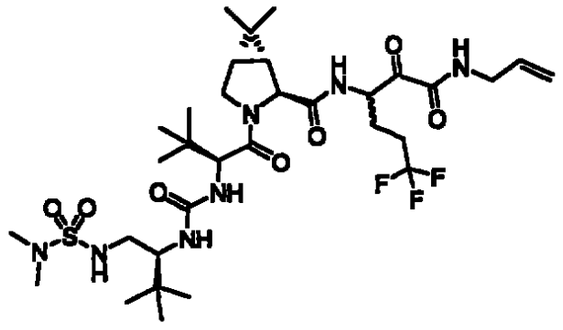
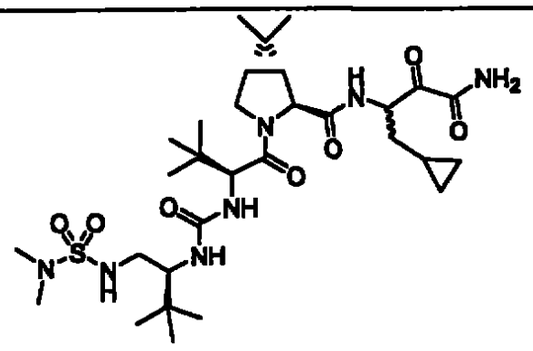
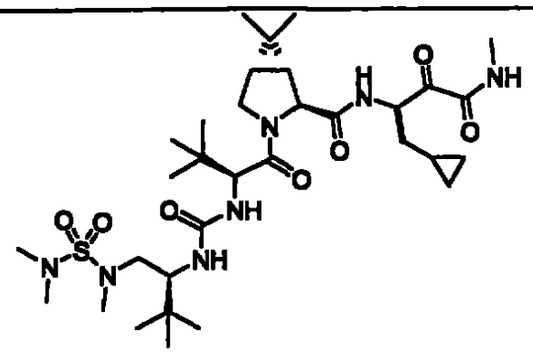
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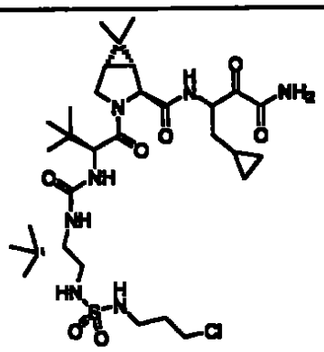
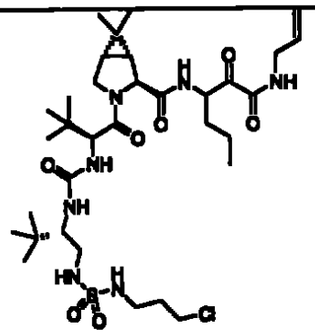
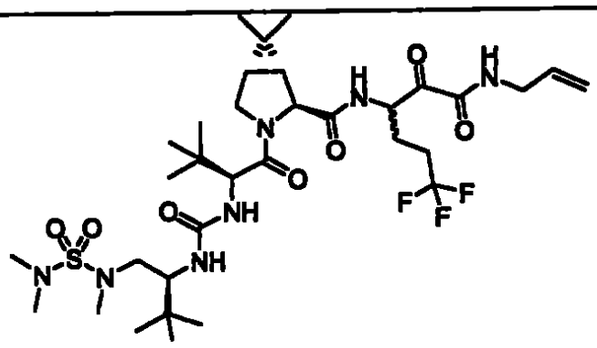
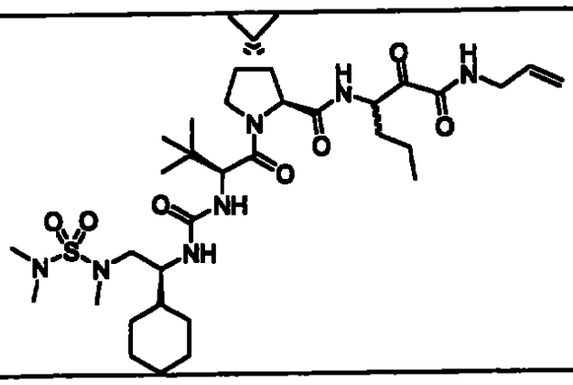
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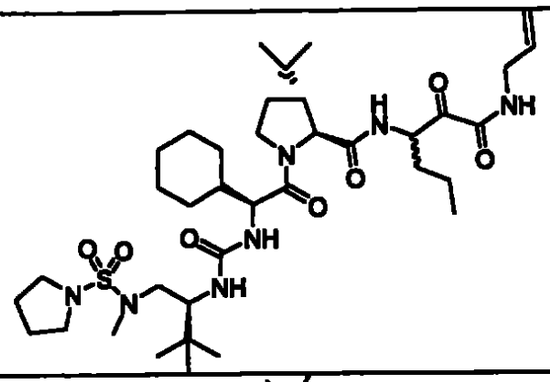
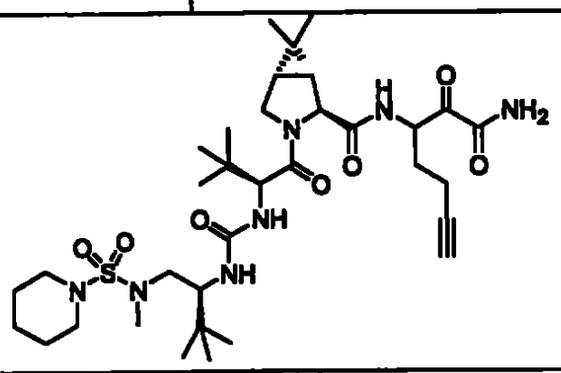
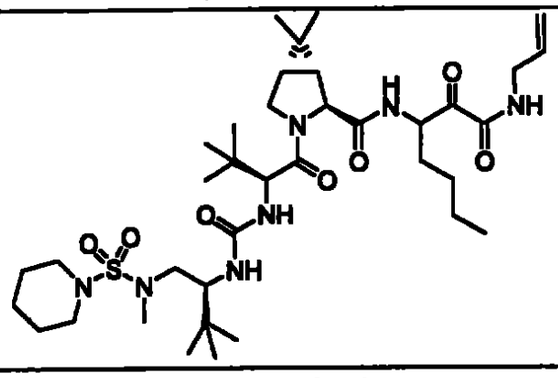
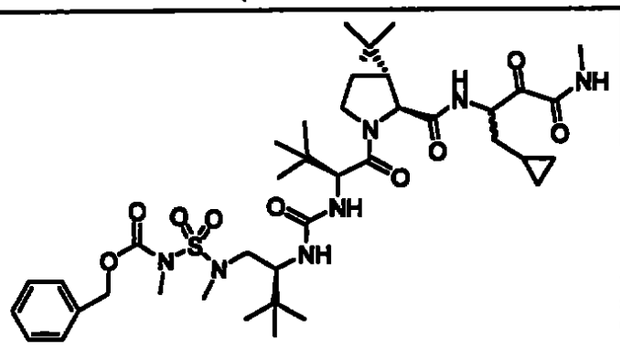
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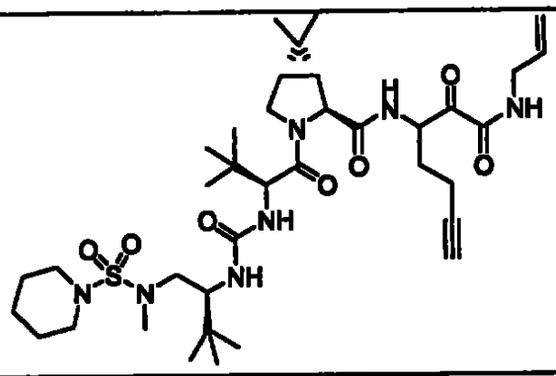
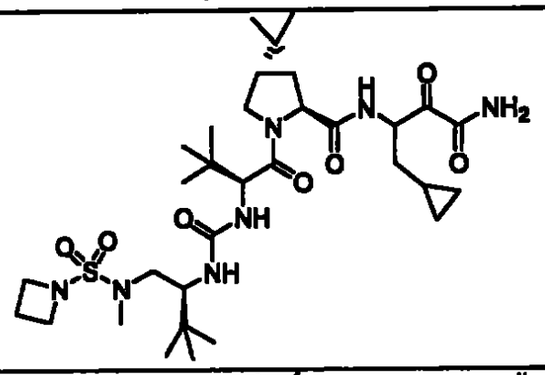
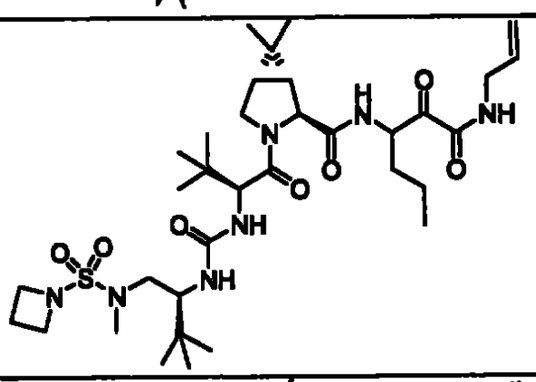
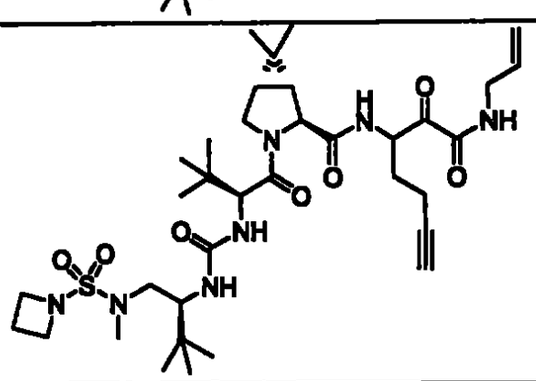
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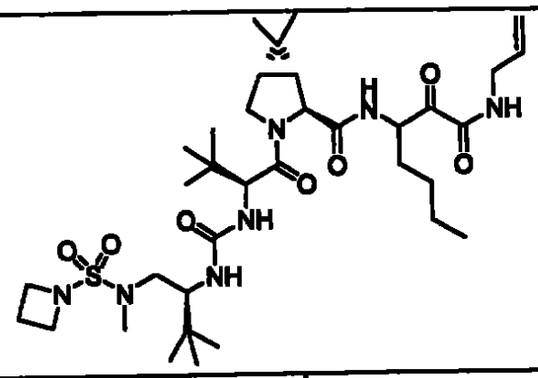
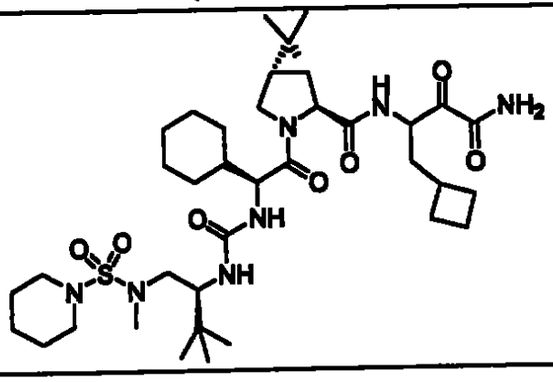
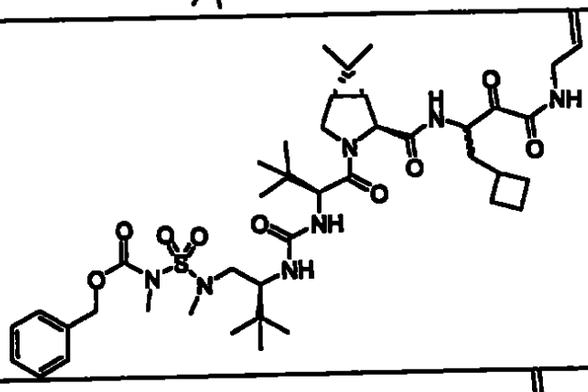
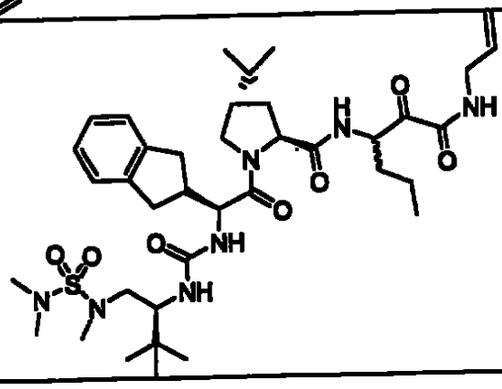
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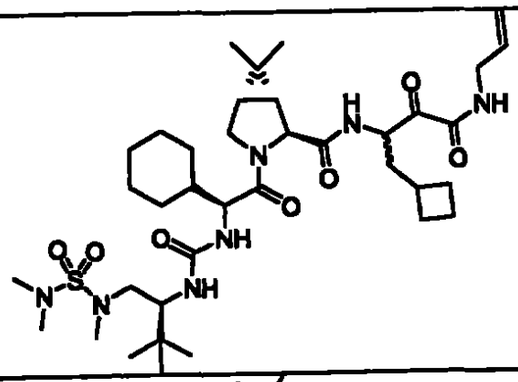
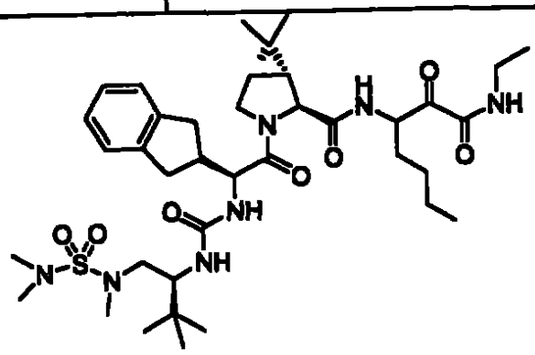
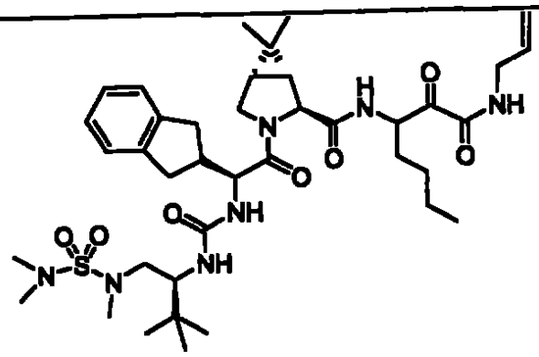
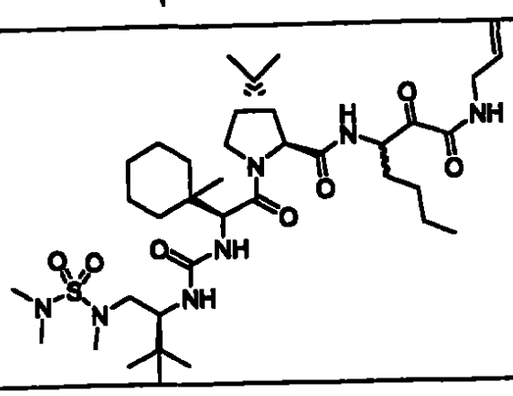
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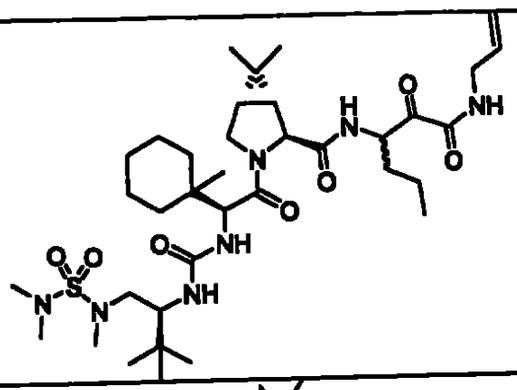
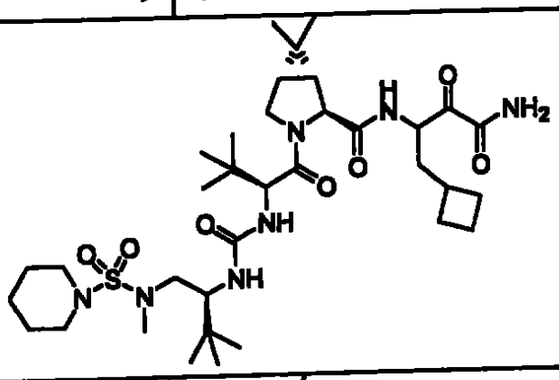
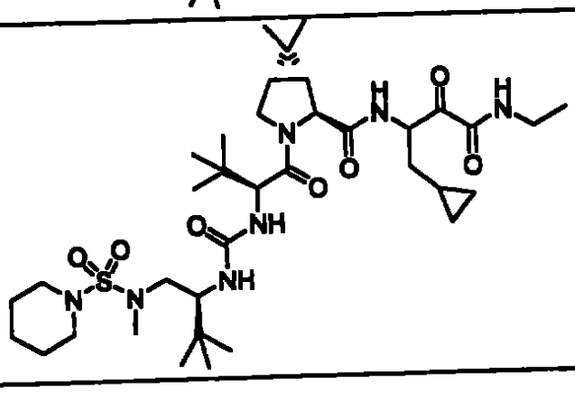
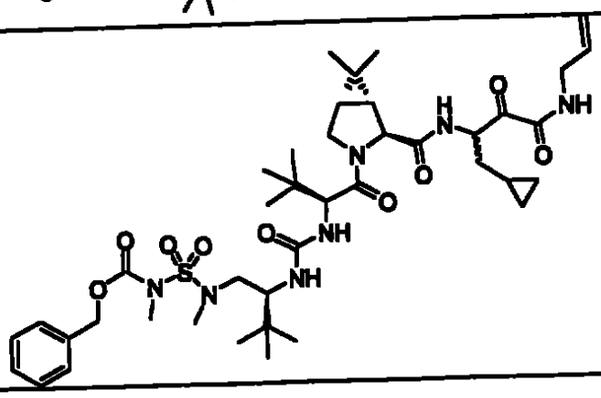
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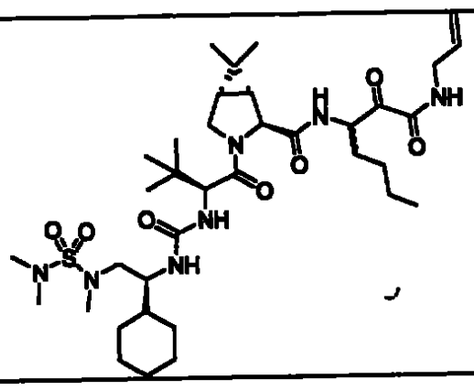
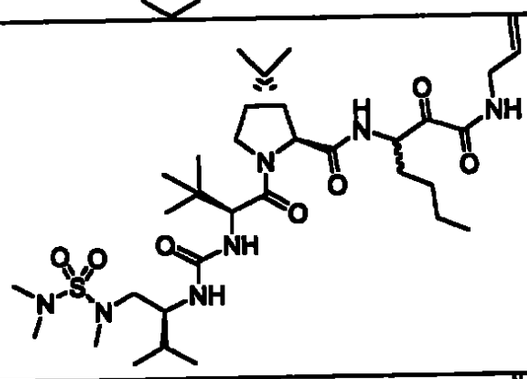
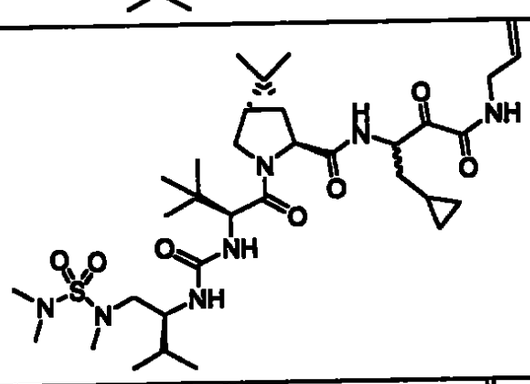
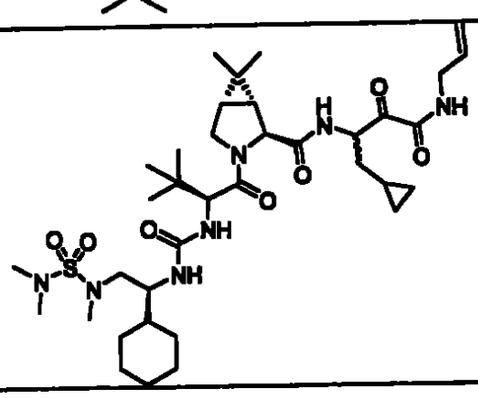
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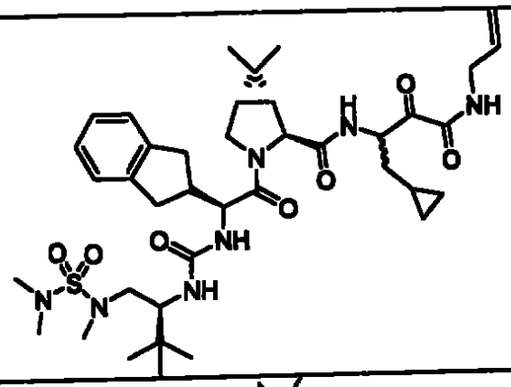
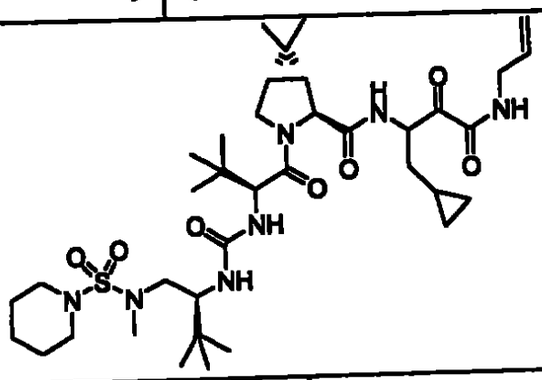
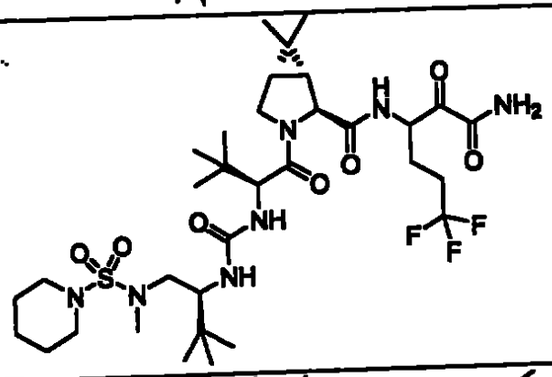
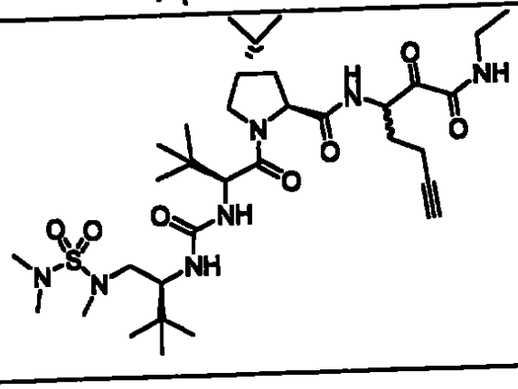
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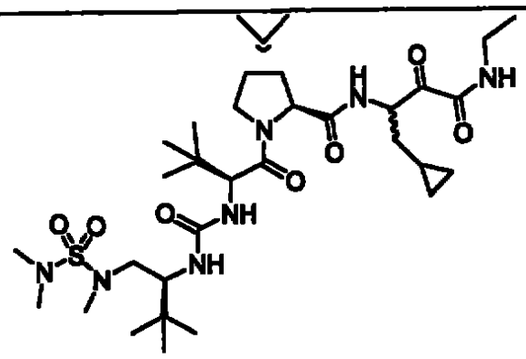
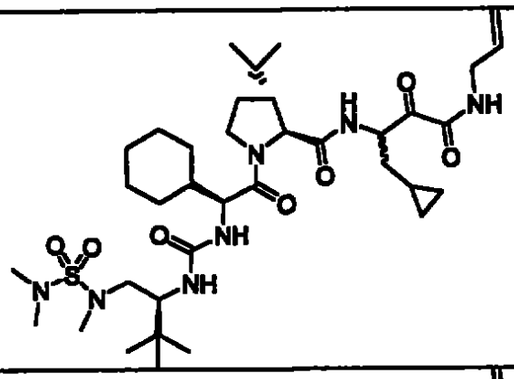
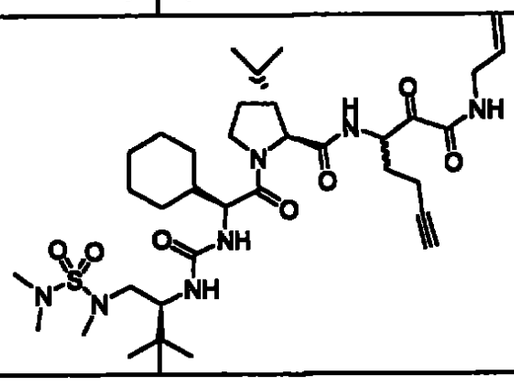
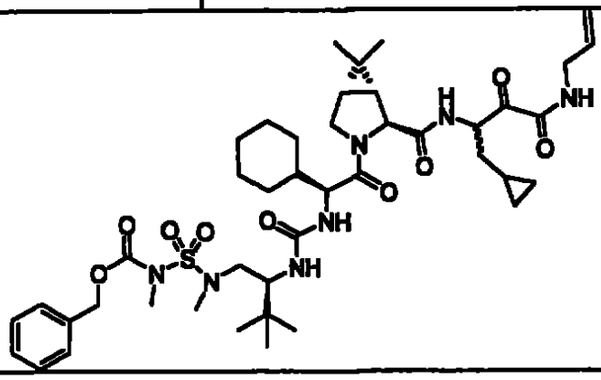
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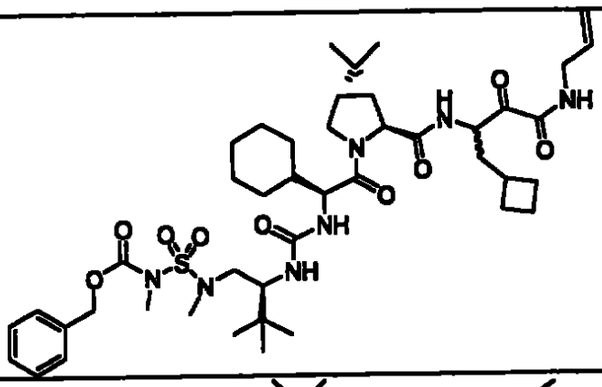
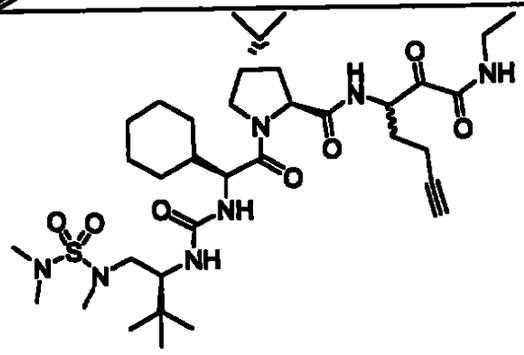
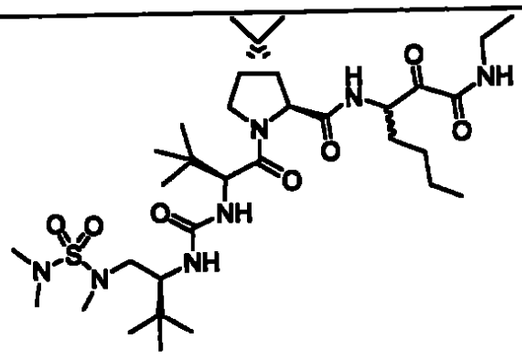
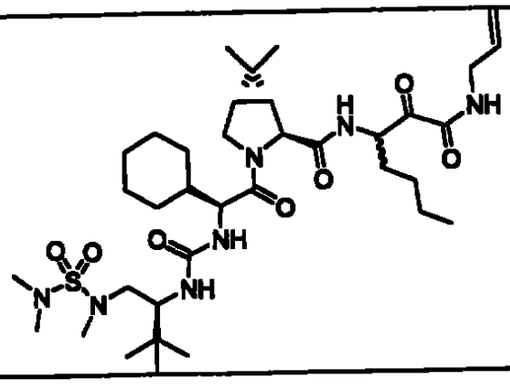
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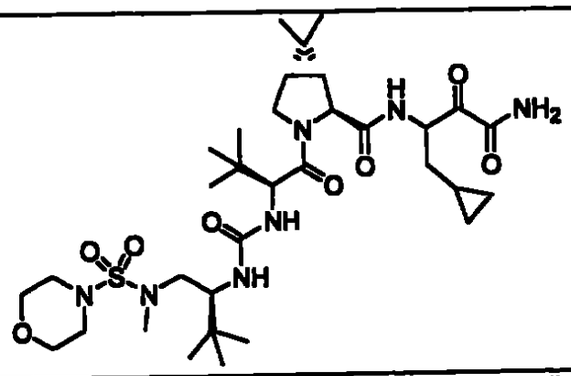
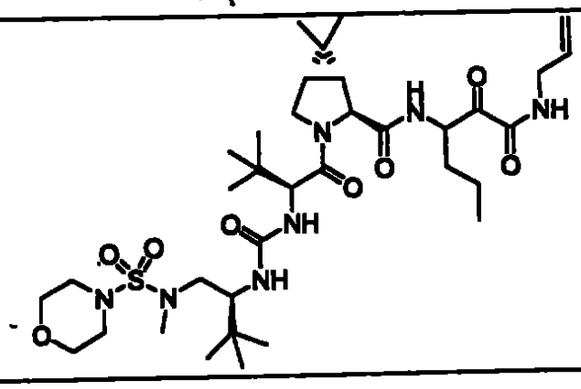
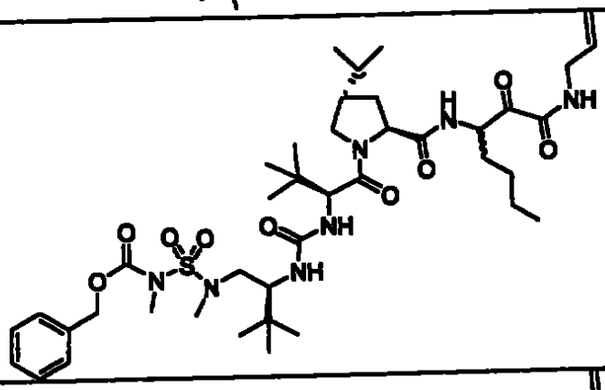
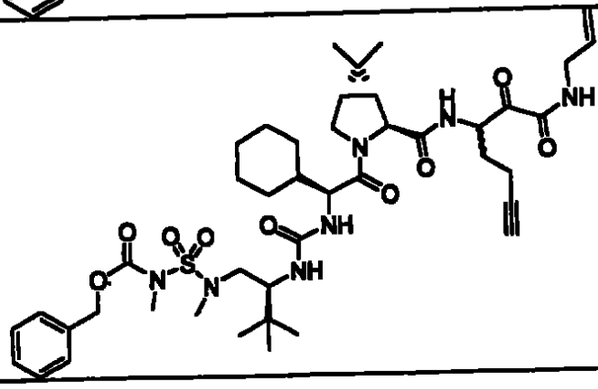
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287

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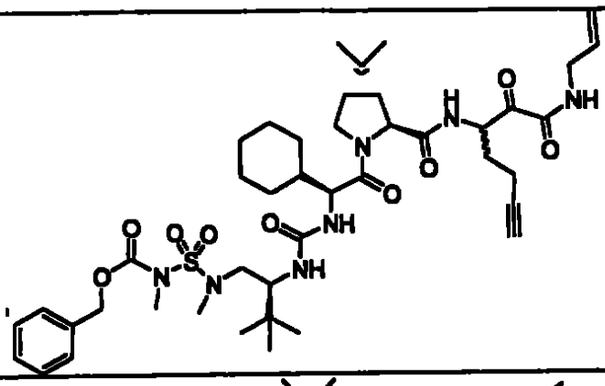
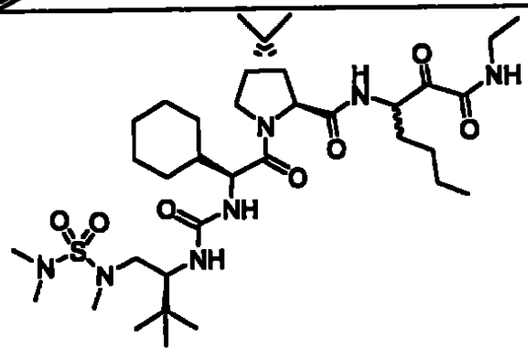
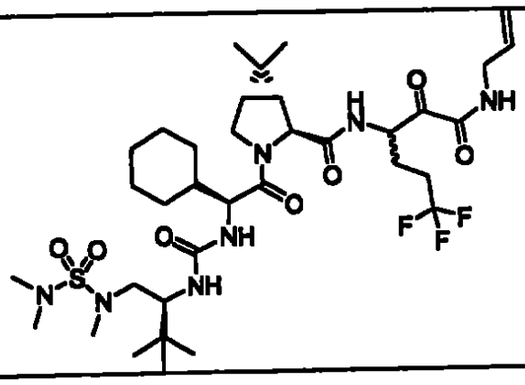
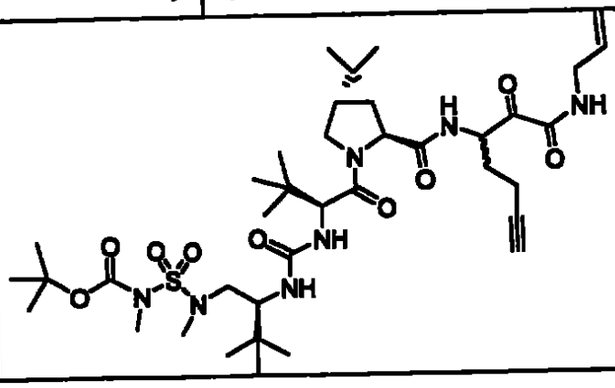
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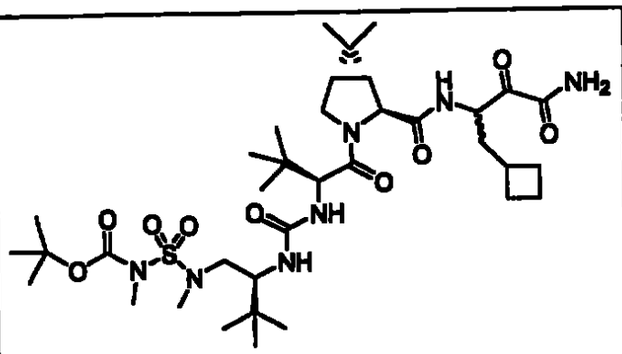
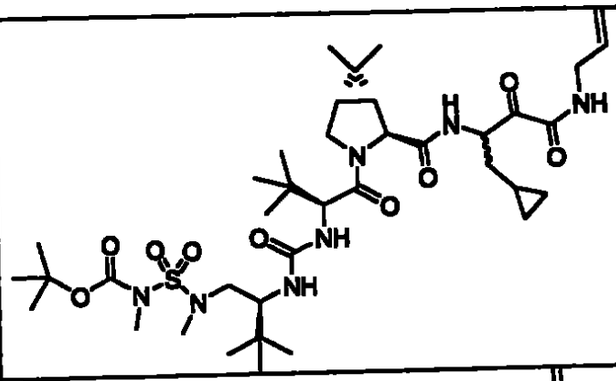
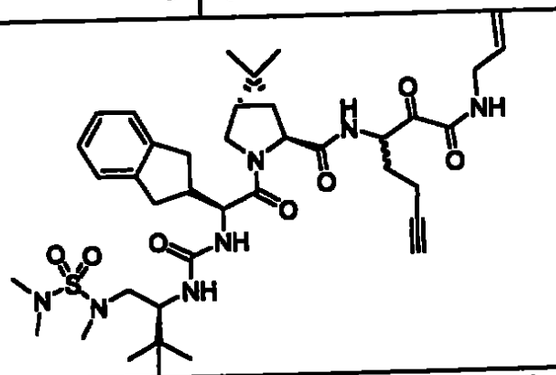
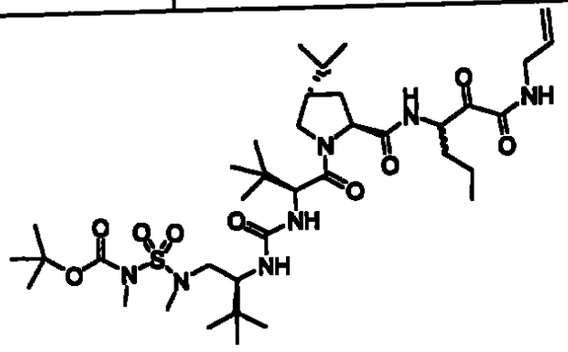
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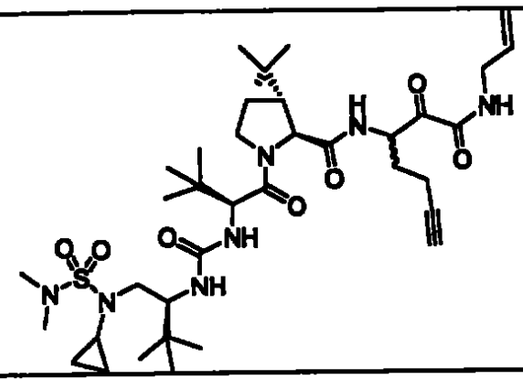
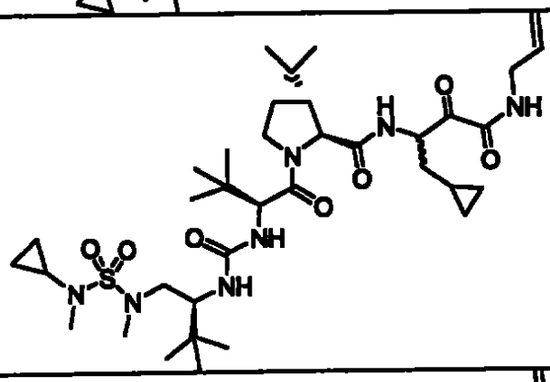
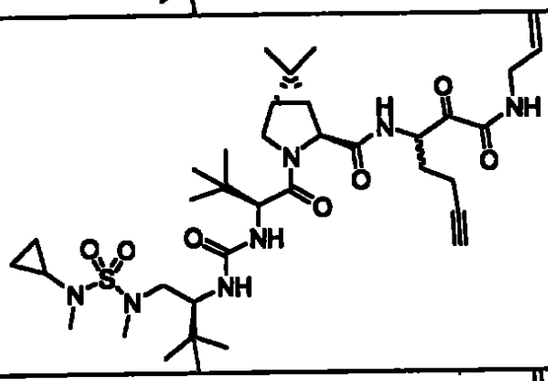
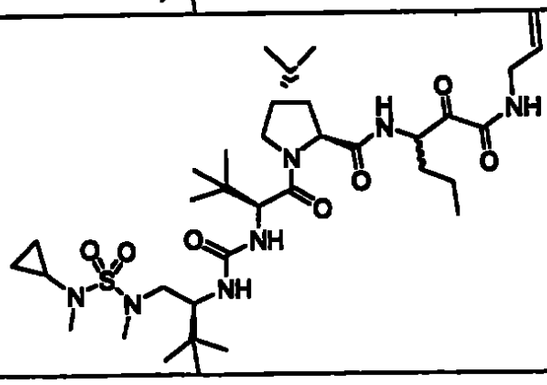
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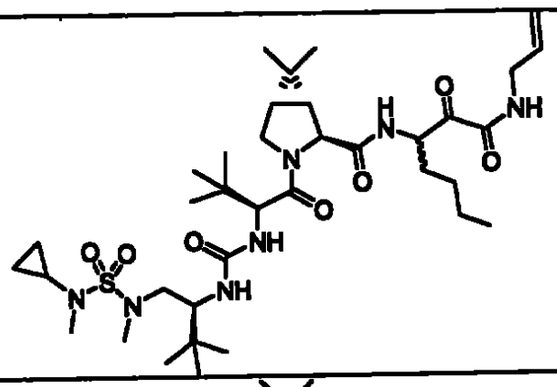
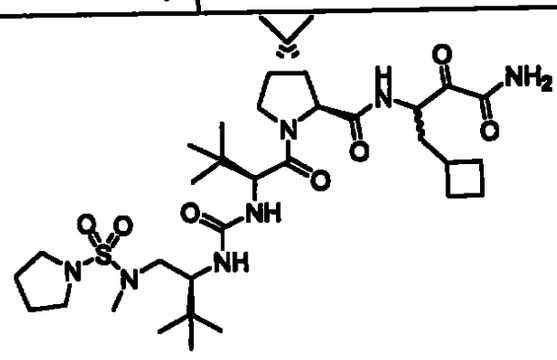
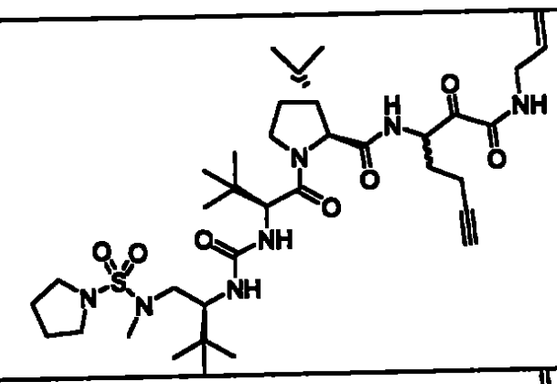
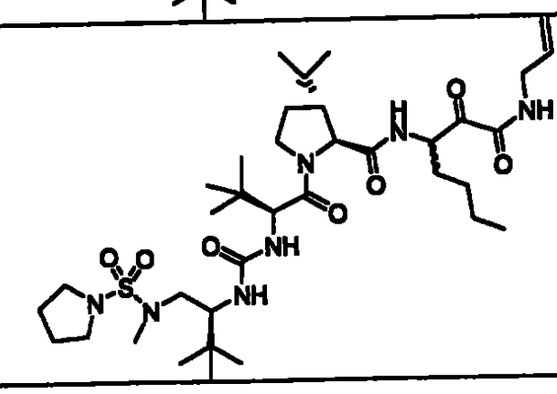
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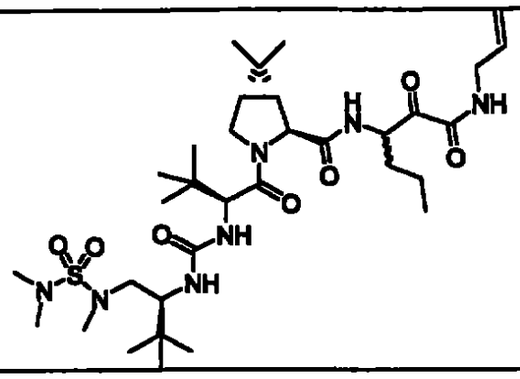
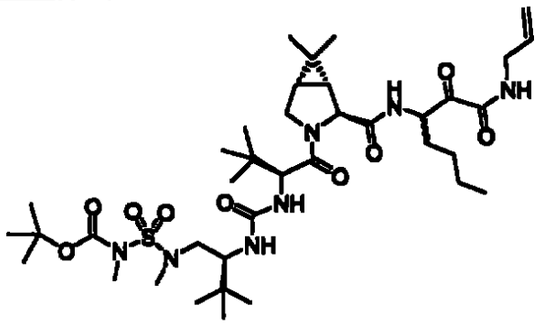
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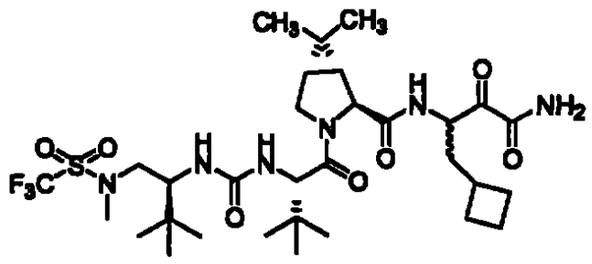
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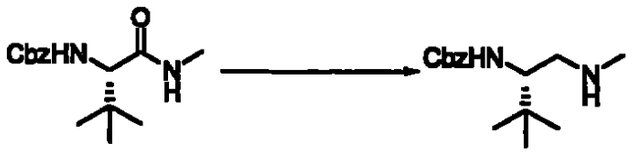
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10101		A

Ejemplo-6 Síntesis del compuesto de la Fórmula11001



11001

Paso A



11001a **11001b**

Una solución de amida **11001a** (Obtenida mediante protección con Cbz de *ter*-butilglicina –N-metilamida obtenida de fuente comercial TCI-Japón) 18 g, 64,67

mmol) en tolueno (200 mL) se trató con BH_3•DMS (solución 2 M en THF, 65 mL, 130 mmol) y se calentó a 80°C durante 3 h La mezcla de reacción se enfrió hasta temperatura ambiente y se trató cuidadosamente con NaOH ac (solución 2 M) y se extrajo en CH_2Cl_2 (3x200 mL) Las capas orgánicas combinadas fueron extraídas con $NaHCO_3$ (3x300 mL), salmuera (300 mL), secadas ($MgSO_4$) y purificadas por cromatografía (SiO_2, metanol amoniacal (7M)/CH_2Cl_2 1 20) para proporcionar **11001b** en forma de aceite incoloro

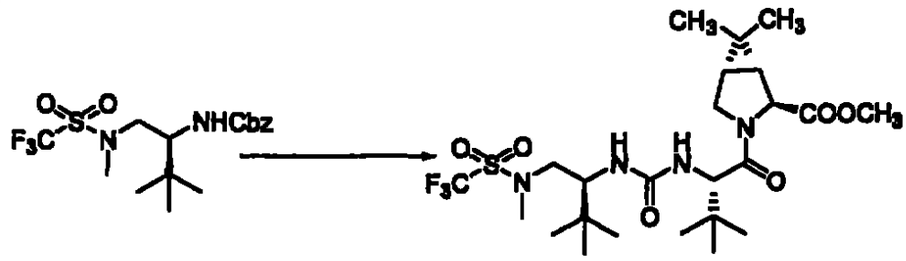
Paso B



11001b **11001c**

Una solución de amina **11001b** (900 mg, 3,40 mmol) en CH_2Cl_2 a 0°C se trató con NMM (511 mg, 5,10 mmol) y anhídrido trífilco (585 mg, 5,10 mmol) y se agitó a 0°C durante 12 h La mezcla de reacción se diluyó con CH_2Cl_2 (300 mL) y se lavó con HCl ac en exceso (1M, 500 mL) La capa orgánica se secó ($MgSO_4$) se filtró y se concentró in *vacuo* y se purificó mediante cromatografía (SiO_2, Hex/EtOAc 1 9-1 1) para proporcionar sulfonamida de trifluormetano ***11001c***

Paso C



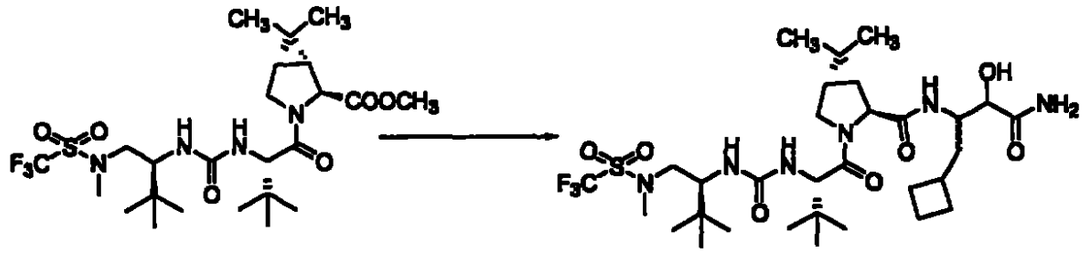
11001c **11001d**

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Una solución de 11001c (1,28 g, 3,22 mmol) en metanol (30 mL) se trató con hidróxido de paladio (200 mg, 10% p/C) y se hidrogenó a 408 kPa (60 psi) durante 3 h La mezcla de reacción se filtró a través de un tapón de celite® y el filtrado se concentró in *vacuo* El residuo se utilizó directamente en otra reacción sin purificación

Una solución de la amina desprotegida (200 mg, 0,763 mmol) en DMF (3 mL), CH_2Cl_2 (3 mL) se trató con 4-nitrofenilcarbamato 1.16 (409 mg, 0,915 mmol), NMM (308 mg, 3,05 mmol) a 0°C y se agitó a ta durante la noche La mezcla de reacción se concentró in *vacuo* y se diluyó con CH_2Cl_2 (150 mL) y se lavó con HCl ac (1M, 2x125 mL), $NaHCO_3$ saturado ac (2x125 mL), salmuera (100 mL), se secó ($MgSO_4$), se filtró y purificó mediante cromatografía (SiO_2, CH_2Cl_2/EtOAc 1 19) para proporcionar 11001d

Paso D



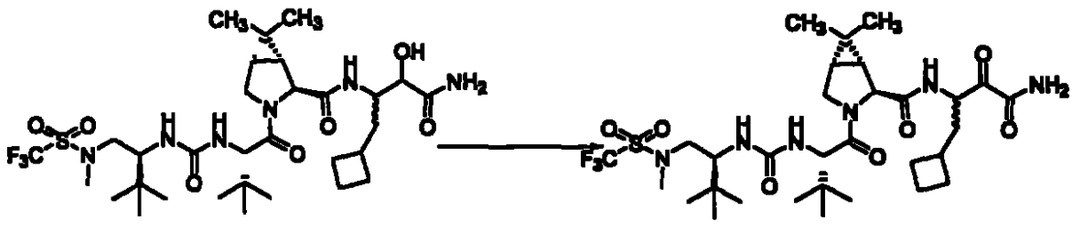
11001d 11001e

Una solución de éster metílico 11001d (210 mg, 0,368 mmol) en THF seco (3 mL) se trató con H_2O (3 mL), metanol (3 mL) y se trató con LiOH monohidrato (41,9 mg, 1 mmol) y se agitó durante 3 h a ta La mezcla de reacción se acidificó hasta pH~2 y se extrajo en CH_2Cl_2 (100 mL) La capa orgánica se lavó con H_2O (100 mL), salmuera (100mL) se secó ($MgSO_4$) se filtró y concentró in *vacuo* para proporcionar ácido que se utilizó como estaba en la siguiente reacción

397
297

Una solución del ácido (50 mg, 0,089 mmol) en CH_2Cl_2 seco (2 mL) y DMF (2 mL) se enfrió hasta 0°C y se trató con amina **10 11** (20 mg, 0,116 mmol) HATU (57,03 mg, 0,15 mmol) y NMM (40,4 mg, 0,40 mmol) La reacción se agitó a 0°C durante 36h y se concentró in *vacuo* El residuo se disolvió en CH_2Cl_2 (100 mL) y se lavó con HCl ac (1 M, 2x 100 mL), $NaHCO_3$ saturado ac (2x100mL) salmuera (100 mL), se secó ($MgSO_4$) se filtró, se concentró in *vacuo* para proporcionar **11001e** el cual se utilizó en la siguiente reacción sin más purificación

Paso E

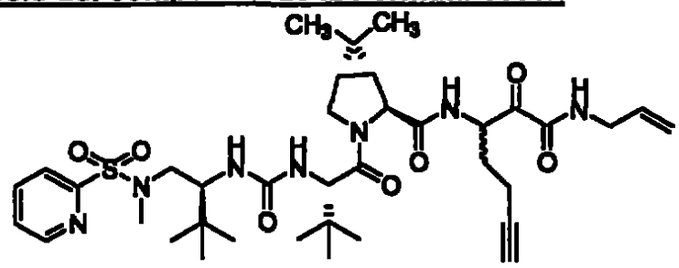


11001e **11001**

Una solución de **11001e** (50 mg, 0,075 mmol) en tolueno (3 mL) y DMSO (3 mL) se trató con EDCI (134 mg, 0,703 mmol), y ácido dicloroacético (45,3 mg, 0,351 mmol, 30 uL) y se agitó a temperatura ambiente durante 3 h La mezcla de reacción se diluyó con CH_2Cl_2 (60 mL) y se lavó con $NaHCO_3$ saturado ac (30 mL), HCl ac. (1 M, 30 mL), salmuera (30 mL), se secó ($MgSO_4$) se filtró, se concentró in *vacuo* y se purificó mediante cromatografía (SiO_2, acetona/Hexanos 20-50% gradiente lineal) para proporcionar **11001**

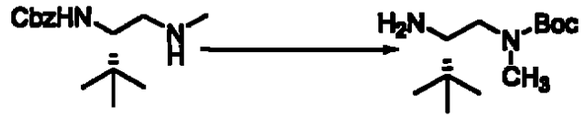
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Ejemplo 7 Síntesis del compuesto de la Fórmula 11002



11002

Paso A

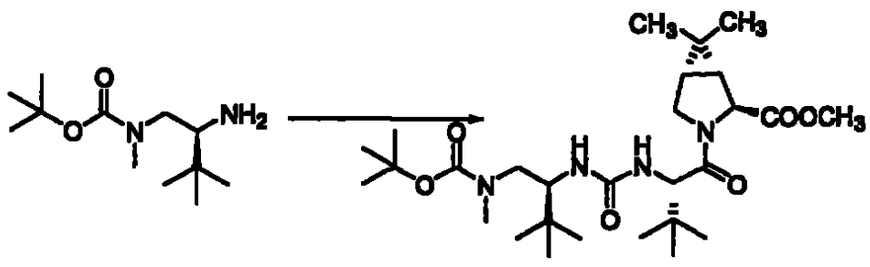


11001b **11002a**

Una solución de amina **11001b** (4,0 g, 15,14 mmol) en CH_2Cl_2 (100 mL) se trató con di-*ter*-butildicarbonato (4,13 g, 18,91 *mmol*) y se agitó a temperatura ambiente durante 12 h La mezcla de reacción se concentró in *vacuo* y se purificó mediante cromatografía (SiO_2, EtOAc/Hexanos 1 5) para proporcionar amina Boc protegida

Una solución del compuesto Boc protegido en metanol se trató con hidróxido de paladio y se hidrogenó a 408 kPa (60 psi) durante 12 h La mezcla de reacción se filtró a través de un tapón de celite® y el filtrado se concentró *in vacuo* El residuo **11002a** se utilizó en pasos subsiguientes sin más purificación

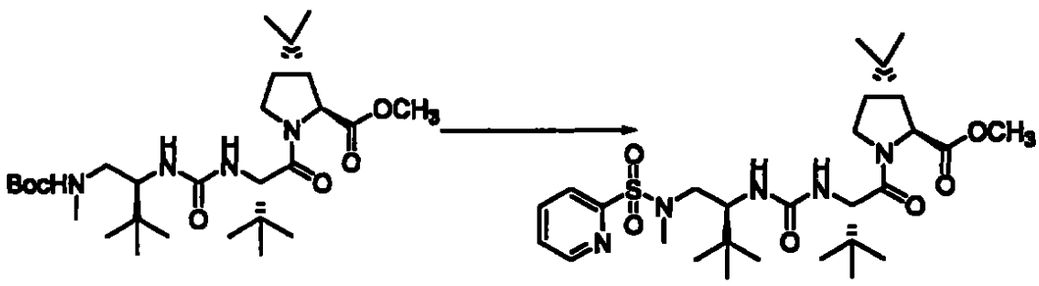
Paso B



11002a **11002b**

Una solución de la amina **11002a** (134 mg, 0,58 mmol) en acetonitrilo (20 mL) se trató con 4-nitrofenilcarbamato **1 16** (260 mg, 0,58 mmol), NMM (177 mg, 1,74 mmol) a 0°C y se agitó a temperatura ambiente durante la noche La mezcla de reacción se concentró in *vacuo*, se diluyó con CH_2Cl_2 (250 mL) y se lavó con HCl ac (1M, 2x125 mL), $NaHCO_3$ saturado ac (2x125 mL), salmuera (100 mL), se secó ($MgSO_4$) se filtró y se purificó mediante cromatografía (SiO_2, CH_2Cl_2/EtOAc 1 19) para proporcionar **11002b** (279 mg)

Paso C



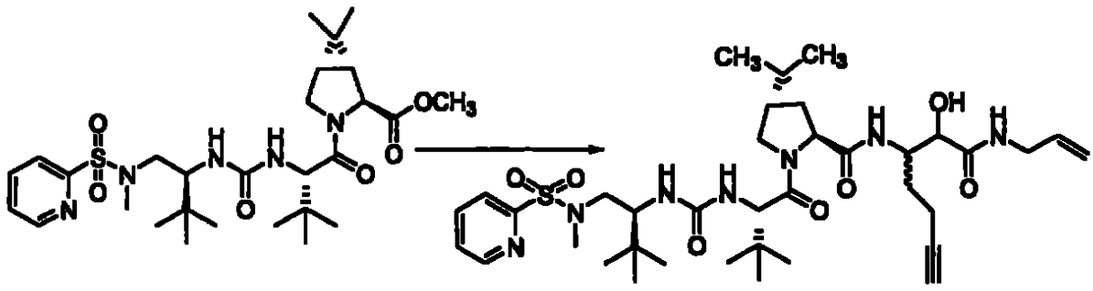
11002b **11002c**

Una solución de **11002b** (279 mg, 0,52 mmol) en HCl dioxano 4 M se agitó a temperatura ambiente durante 2 h y se concentró in *vacuo* El residuo se utilizó en otra reacción como estaba

La sal de amonio (274 mg, 0,58 mmol) se disolvió en CH_2Cl_2 DMF (1 1) y se enfrió hasta 0°C La mezcla de reacción se trató con 4 eq de Et_3N (233 mg, 2,33 mmol) y 2 eq de cloruro de 2-piridinsulfonilo (248 mg, 1,2 mmol) y se agitó a temperatura ambiente durante la noche La mezcla de reacción se lavó con $NaHCO_3$ saturado, y la capa orgánica se extrajo con CH_2Cl_2 La capa orgánica se secó con $MgSO_4$, se filtró, y se concentró in *vacuo* El producto crudo se purificó utilizando cromatografía de gel de sílice utilizando un sistema Horizon HPFC (30% – > 90% EtOAc/hexanos) para proporcionar 240 mg de **11002c**

300
300

Paso D

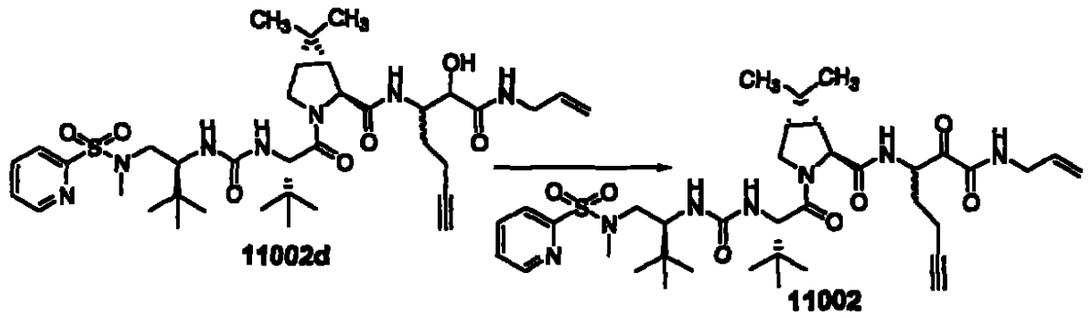


11002c 11002d

11002c (240 mg, 0,41 mmol) se disolvió en THF y H_2O (3 1) y se trató con 2,5 eq de $LiOH \cdot H_2O$ La mezcla de reacción se trató con MeOH hasta que la solución se homogeneizó La mezcla de reacción se agitó a temperatura ambiente durante aproximadamente 3 hr La mezcla de reacción se trató con HCl ac 1 M y se concentró in *vacuo* La capa acuosa se extrajo con CH_2Cl_2, se secó con $MgSO_4$, se filtró y se concentró in *vacuo* El crudo se utilizó en acoplamientos adicionales sin purificación alguna

El ácido (179 mg, 0,32 mmol) se disolvió en 1 1 CH_2Cl_2/DMF y se enfrió hasta 0°C La mezcla de reacción se trató con 1,3 eq de 11 01 desprotegido (11 01 fue desprotegido disolviendo (200 mg, 0,61 mmol) en 10 mL de TFA y 3 mL de Me_2S y reposo durante 3h La mezcla de reacción se concentró in *vacuo* y se utilizó como estaba en posteriores acoplamientos) (238 mg, 0,41 mmol) 3,5 eq de NMM (112 mg 1,1 mmol), y 1,5 eq de HATU (180 mg, 0,47 mmol), y se almacenó en el refrigerador (~ 0°C) durante la noche La mezcla de reacción se concentró bajo alto vacío, y el residuo se trató con $NaHCO_3$ saturado La capa acuosa se extrajo con CH_2Cl_2, se secó con $MgSO_4$, se filtró y se concentró in *vacuo*

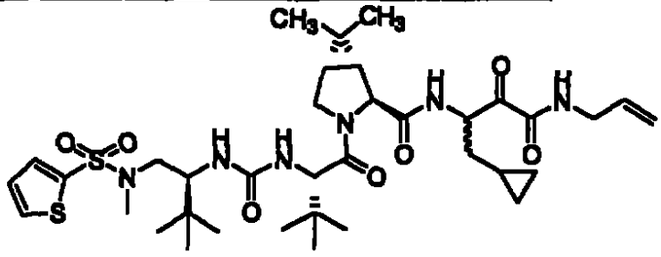
Paso E



11002d 11002

11002d (313 mg, 0,42 mmol) se disolvió en CH_2Cl_2 y se trató con 3 eq de peryodinano Dess-Martin (535 mg, 1,3 mmol) La mezcla de reacción se agitó a temperatura ambiente durante aproximadamente 2 horas La mezcla de reacción se diluyó con 2 1 1 M $NaHSO_3$/$NaHCO_3$ saturado, y la capa acuosa se extrajo con CH_2Cl_2 La capa orgánica se lavó con $NaHSO_3$ 1 M y $NaHCO_3$ saturado, se secó con $MgSO_4$, se filtró y se concentró in *vacuo* El producto crudo se purificó utilizando cromatografía de gel de sílice con un sistema de HPFC Horizon (20%-->60% acetona/hexanos) para proporcionar 11002

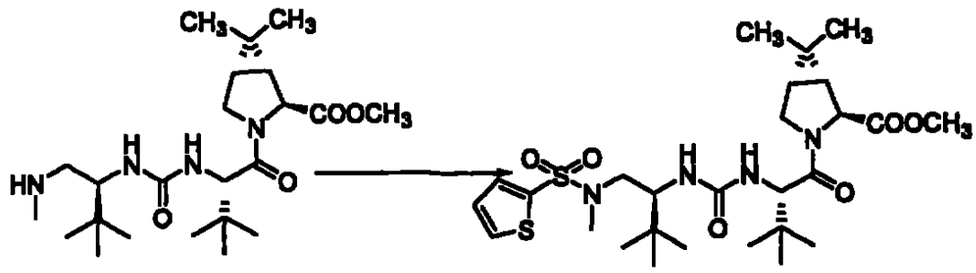
Ejemplo 8. Síntesis del compuesto de la Fórmula 11003



11003

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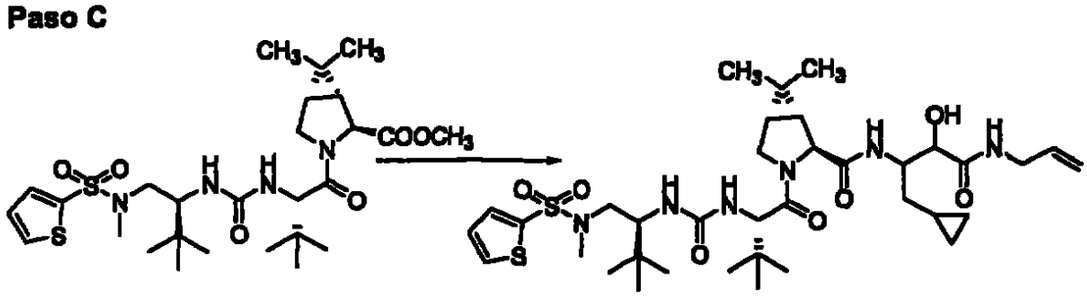
Paso A



11002c **11003a**

Una solución de la sal de amonio **11002c** (880 mg, 1,86 mmol) en cloruro de metileno seco se enfrió *hasta* 0°C y se trató con trietilamina (0,5 mL, 3,71 mmol) y cloruro de 2-tiofensulfonilo (678 mg, 3,71 mmol) y se agitó a 0°C durante 48 h La mezcla de reacción se absorbió en cloruro de metileno y la capa orgánica se lavó con HCl ac (solución 1 M), y salmuera Las capas orgánicas combinadas se secaron ($MgSO_4$) se filtraron y concentraron in *vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/Hexanos 1 4) para proporcionar 978 mg de **11003a** en forma de un sólido incoloro

Paso C

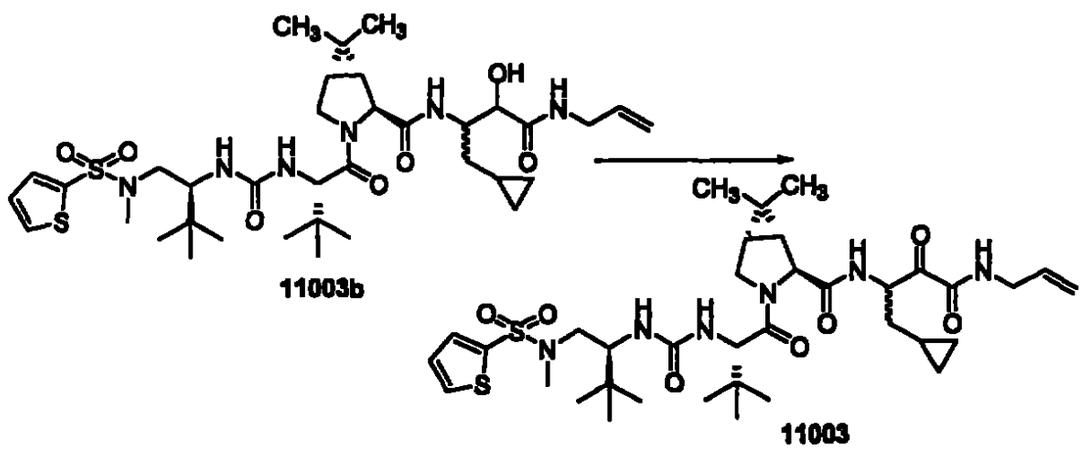


11003a **11003b**

Una solución de <u>11003a</u> (1,2 g, 2,22 mmol) en THF/H_2O se trató con LIOH•H_2O y se agitó a temperatura ambiente durante 3 h La mezcla de reacción se acidificó con HCl ac 1 M y se extrajo con CH_2Cl_2 Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron in *vacuo* y se utilizaron como estaban en el siguiente paso

Una solución de ácido (100 mg, 0,175 mmol) en CH_2Cl_2 seco (4 mL) y DMF (4 mL) se enfrió hasta 0°C y se trató con la amina **12 04** (100 mg, 0,263 mmol) HATU (100 mg, 0,263 mmol) y NMM (70,4 mg, 0,704 mmol) La reacción se agitó a 0°C durante 14 h y se concentró in *vacuo* El residuo se disolvió en CH_2Cl_2 (100 mL) y se lavó con HCl ac (1 M, 2x 100 mL), $NaHCO_3$ saturado ac (2x100mL) salmuera (100 mL), se secó ($MgSO_4$), se filtró, se concentró in *vacuo* para proporcionar **11003b** el cual se utilizó en la siguiente reacción sin más purificación

Paso D

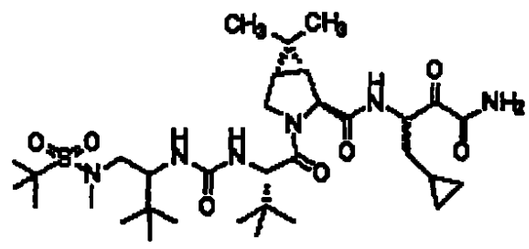


Una solución del alcohol **11003b** (100 mg, 0,133 mmol) en CH_2Cl_2 seco (4 mL) se trató con reactivo Dess-Martin (Dess, D B , Martin, J C *J Am Chem Soc* 1991, *113*, 7277) (150 mg, 0,345 mmol) y se agitó a temperatura ambiente durante 2 h La mezcla de reacción se diluyó con $Na_2S_2O_3$ ac (5%, 30 mL) y $NaHCO_3$ saturado ac (30 mL) y se agitó a temperatura ambiente durante 15 min La mezcla de reacción se extrajo con CH_2Cl_2 (100 mL) y las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, se concentraron in *vacuo* y se purificaron mediante

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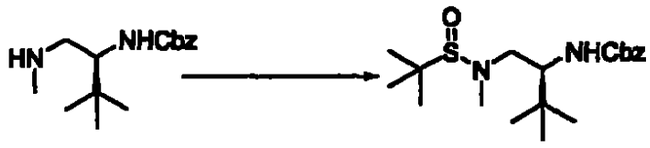
cromatografía (SiO_2, acetona/Hexanos 20%-55% gradiente lineal) para proporcionar 11003

Ejemplo 9 Síntesis del compuesto de la Fórmula 11004



11004

Paso A

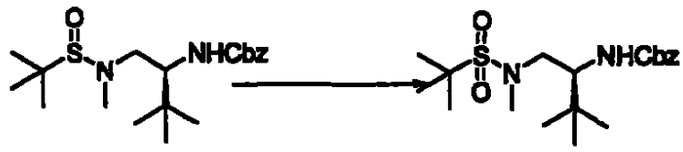


11001a 11004a

Una solución de la amina 11001a (150 mg, 0,567 mmol) en CH_2Cl_2 (5 mL) se enfrió hasta 0° C y se trató con NMM (100 mg, 100 mL) La reacción se trató con *ter*-butilsulfenilcloruro (Sun, P, Weinreb, S M , Shang, M *J Org Chem* 1997, *62*, 8604) (0,5 mL, solución 1,3 M en CH_2Cl_2) y se agitó a temperatura ambiente durante la noche La mezcla de reacción se diluyó con HCl ac (1M, 30 mL) y se extrajo con CH_2Cl_2 (3x30 mL) La capa orgánica combinada se extrajo con salmuera (30 mL) se secó ($MgSO_4$) se filtró y concentró in *vacuo* y se purificó mediante cromatografía (SiO_2, acetona/Hexanos) para proporcionar 11004a

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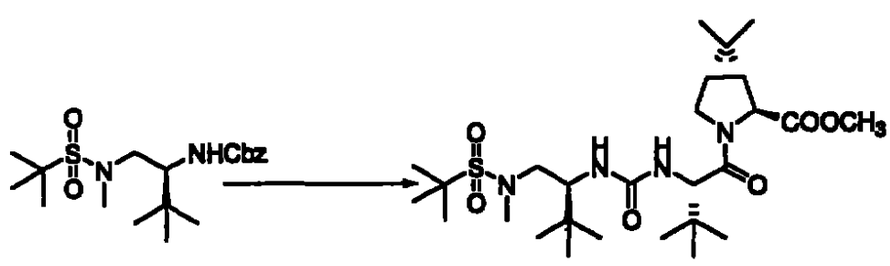
Paso B



11004a **11004b**

Una solución de sulfenamida ***11004a*** (2,00 g, 5,43 mmol) en CH_2Cl_2 (60 mL) se trató con MCPBA (2,34 g, 8,145 mmol, 60%) y se agitó a temperatura ambiente durante 1h La mezcla de reacción se diluyó con $Na_2S_2O_3$ ac (10%, 50 mL) y $NaHCO_3$ ac (saturado, 100 mL) y se agitó a temperatura ambiente durante 30 min La mezcla de reacción se extrajo con CH_2Cl_2 (150 mL) y las capas orgánicas combinadas se lavaron con agua, salmuera, se secaron ($MgSO_4$) se filtraron y concentraron in *vacuo* y se purificaron mediante cromatografía (SiO_2, EtOAc/Hex 1 9→1 1) para proporcionar ***11004b***.

Paso C



11004b **11004c**

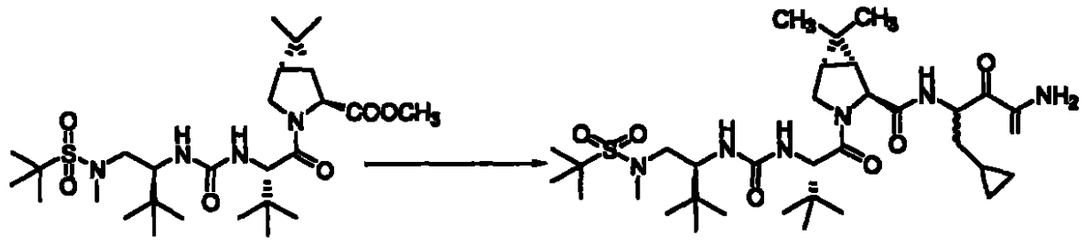
Una solución del compuesto Cbz-protegido ***11004b*** (1,5 g, 3,90 mmol) en metanol (25 mL) se trató con hidróxido de paladio (10% sobre C) y se hidrogenó a 408 kPa (60 psi) durante 1 h La mezcla de reacción se filtró a través de un tapón de célite y se concentró in *vacuo* Se utilizó para la siguiente reacción sin purificación alguna

Una solución de la amina desprotegida (1,00 g, 4,00 mmol) en acetonitrilo (20 mL) se trató con 4-nitrofenilcarbamato 1 16 (1,879 g, 4,20 mmol), NMM (1,062 g,

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10,5 mmol) y se agitó a temperatura ambiente durante la noche La mezcla de reacción se concentró in *vacuo* y se diluyó con CH_2Cl_2 (200 mL) y se lavó con HCl ac (1M, 2x125 mL), $NaHCO_3$ saturado ac (2x125 mL), salmuera (100 mL), se secó ($MgSO_4$), se filtró, and se purificó mediante cromatografía (SiO_2, CH_2Cl_2/EtOAc 1 19) para proporcionar 11004c.

Paso D



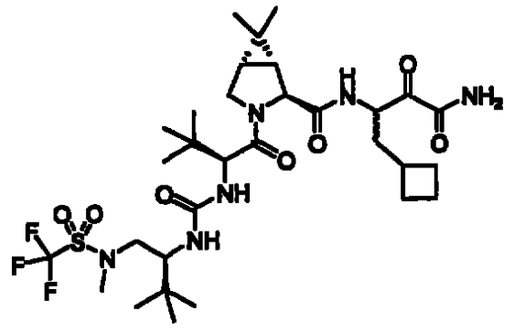
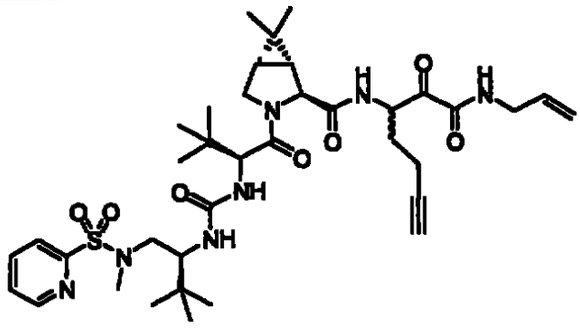
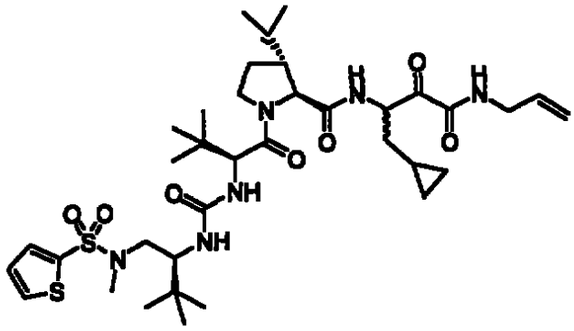
11004c **11004**

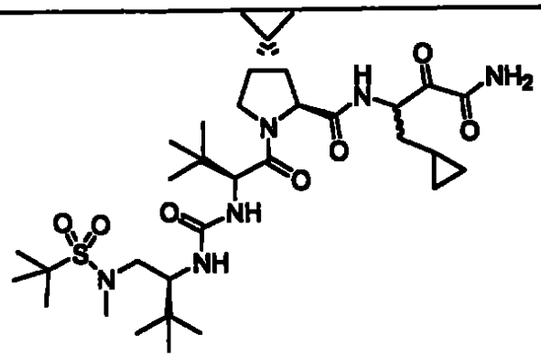
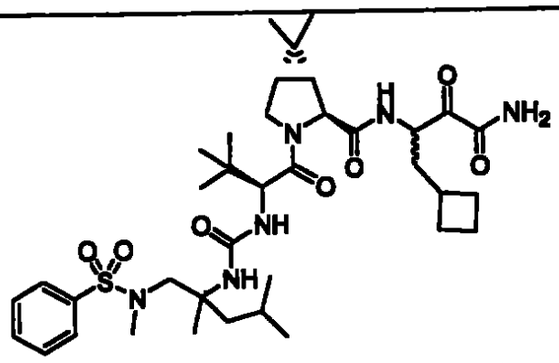
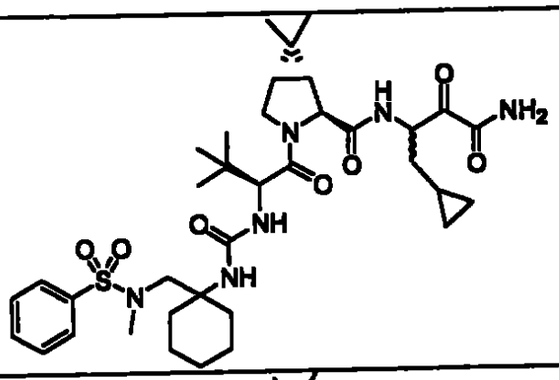
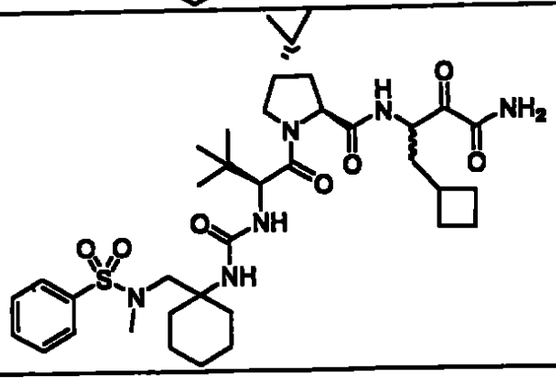
El intermediario **11004c** fue convertido en **11004** mediante acoplamiento al intermediario 12 03 seguido por oxidación Moffett idéntica a los procedimientos descritos en el Ejemplo 6 preparativo de la síntesis de 11001, Paso D y Paso E

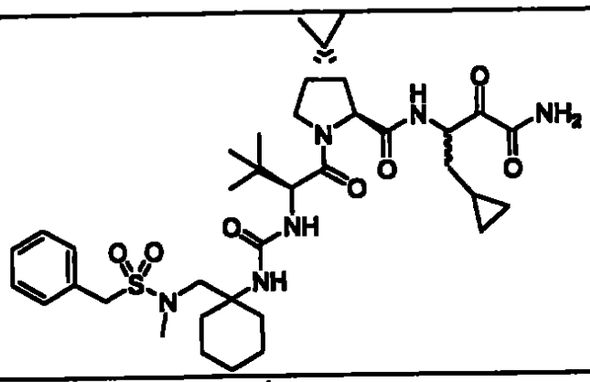
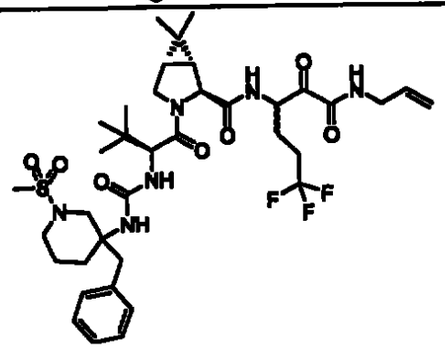
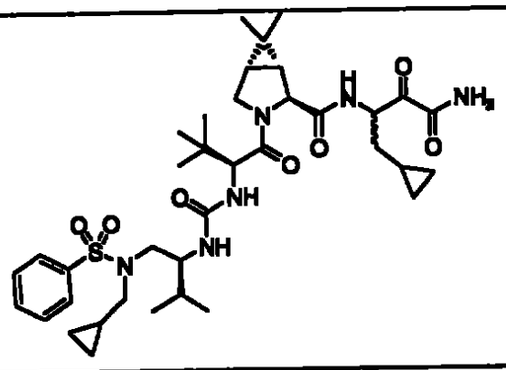
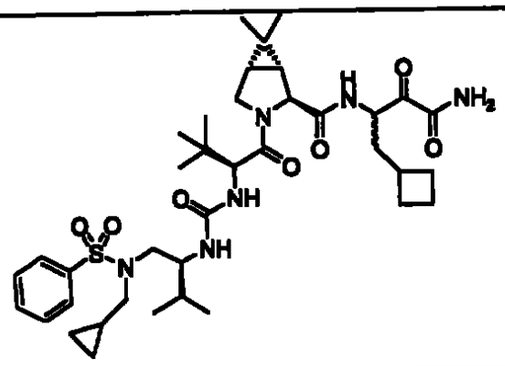
Los compuestos mostrados en la siguiente Tabla 2 fueron sintetizados utilizando reacciones similares a las mostradas en los Ejemplos anteriores El rango de KI* indicó A≤75 nM, 75<B≤250 nM, C>250 nM

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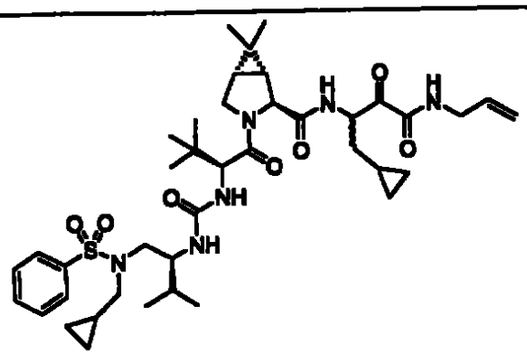
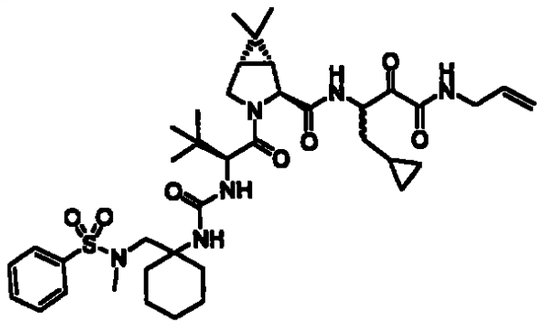
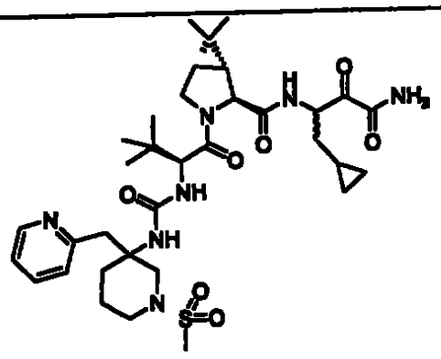
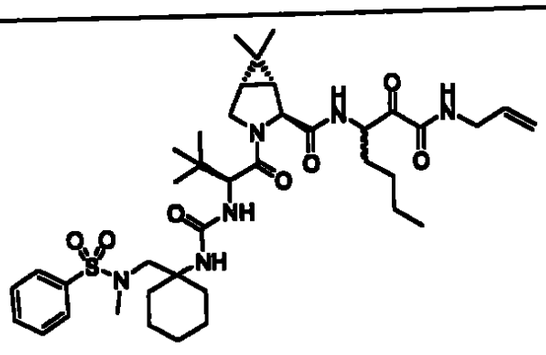
Tabla 2

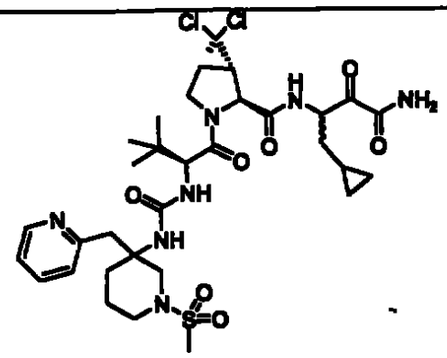
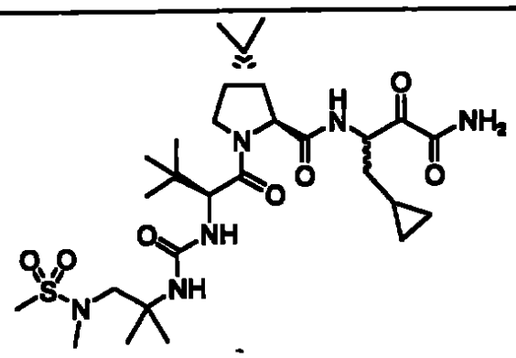
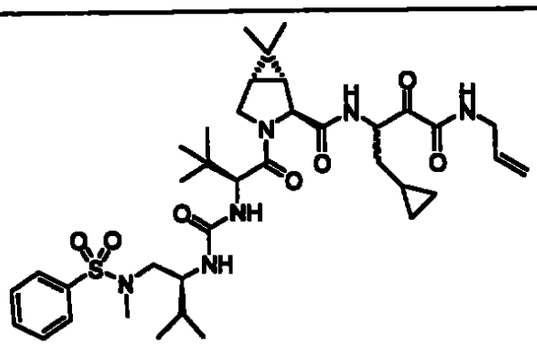
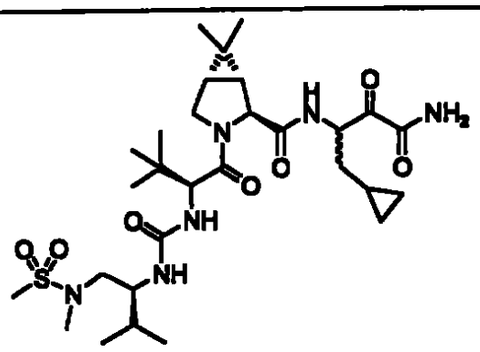
Item	Estructura	KI*
11001		A
11002		A
11003		A

11004		A
11005		B
11006		A
11007		A

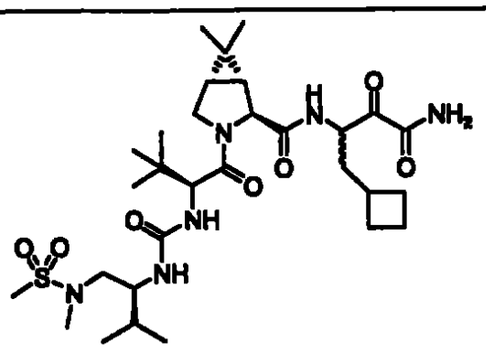
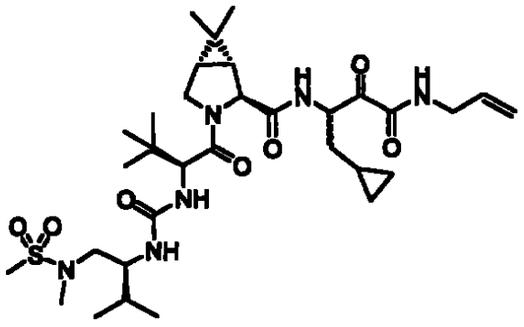
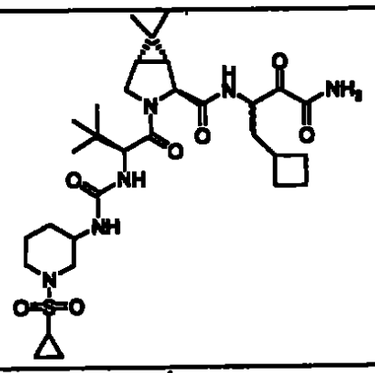
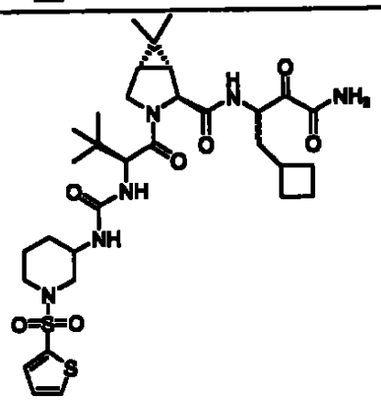
11008		A
11009		C
11010		A
11011		A

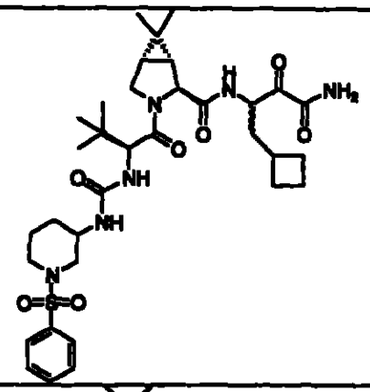
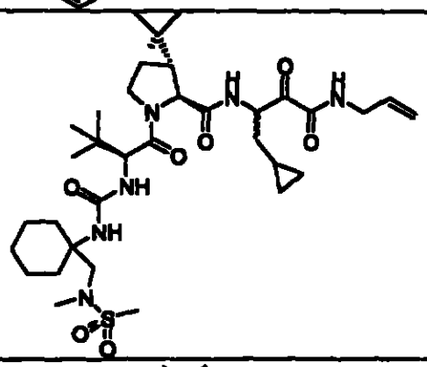
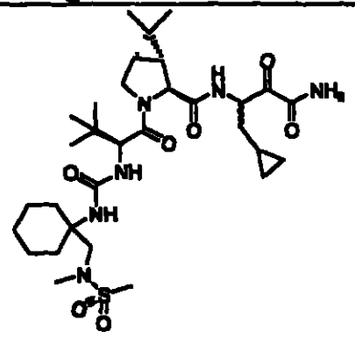
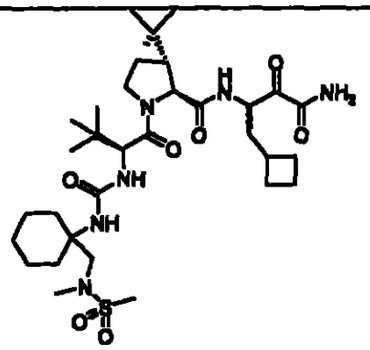
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11012		A
11013		A
11014		C
11015		A

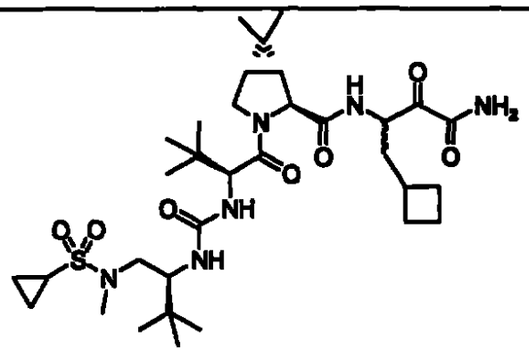
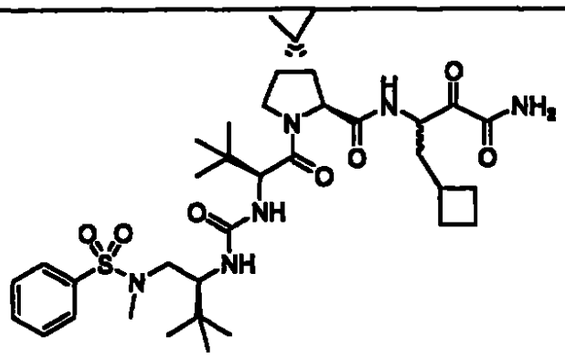
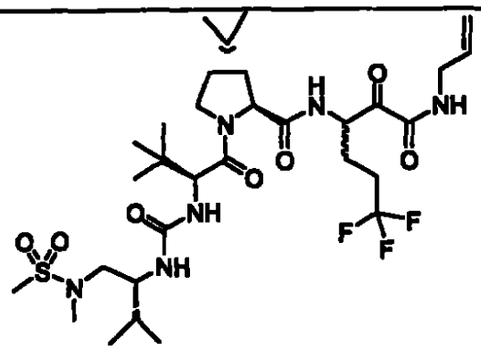
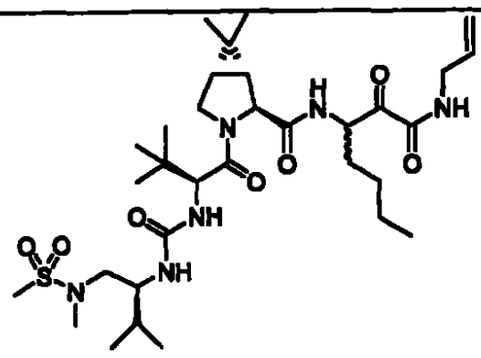
11016		C
11017		B
11018		A
11019		A

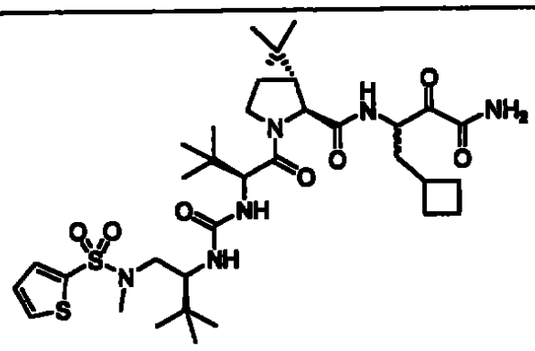
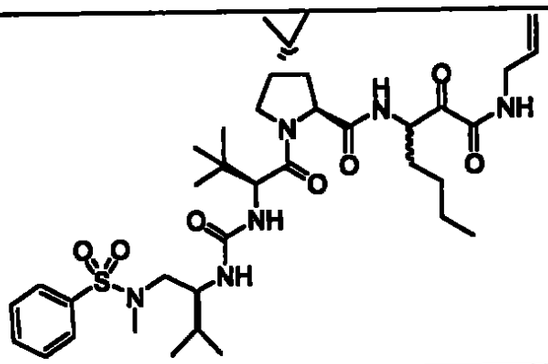
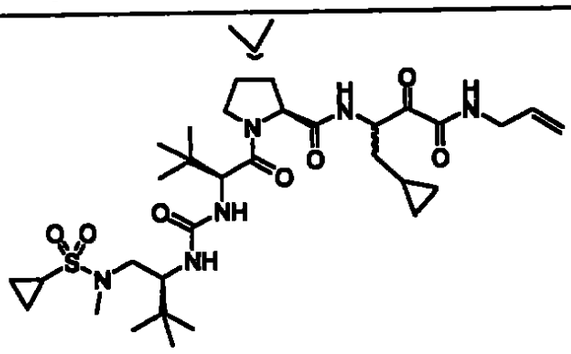
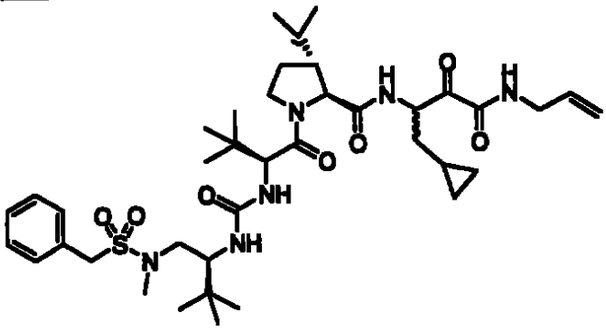
~~312~~
312

11020		A
11021		A
11022		B
11023		B

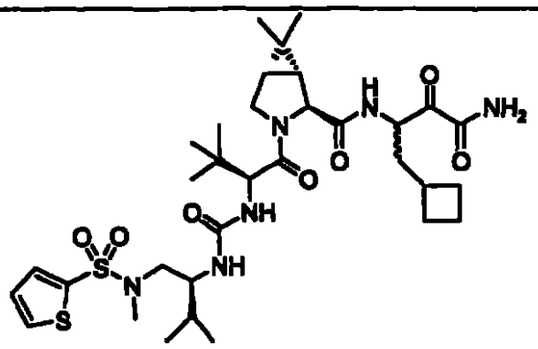
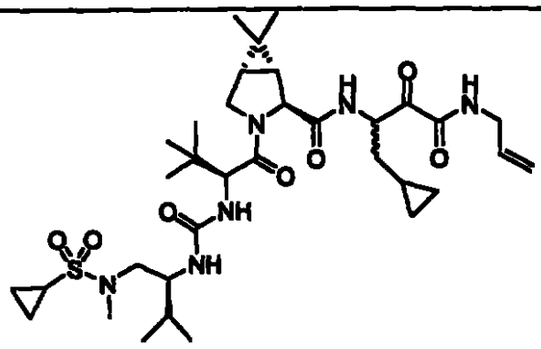
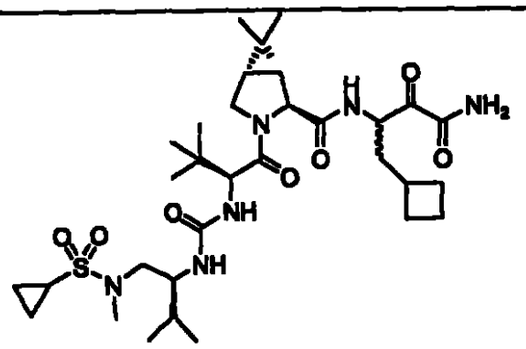
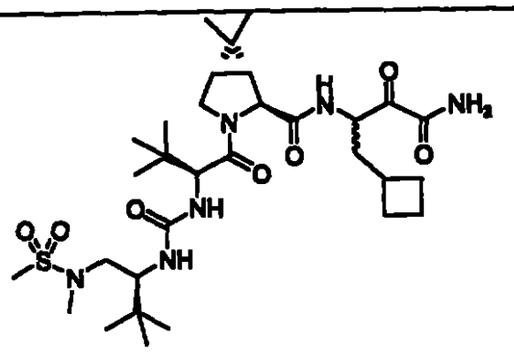
11024		B
11025		A
11026		A
11027		A

~~314~~
314

11028		A
11029		A
11030		A
11031		A

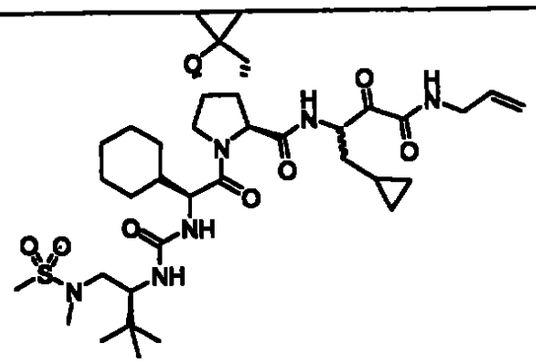
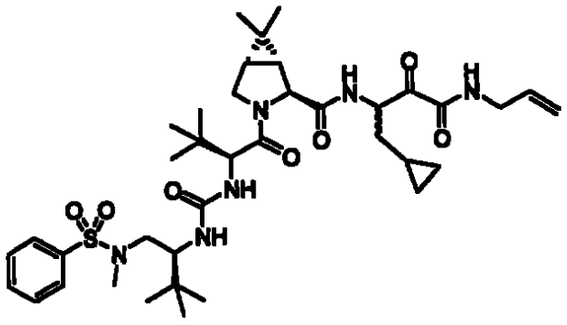
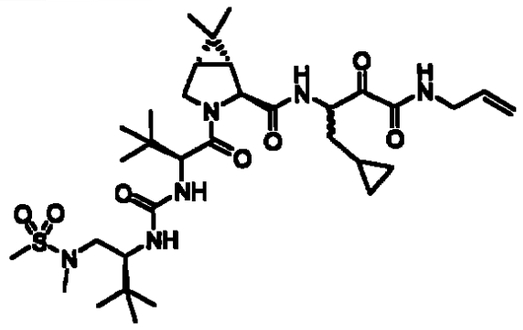
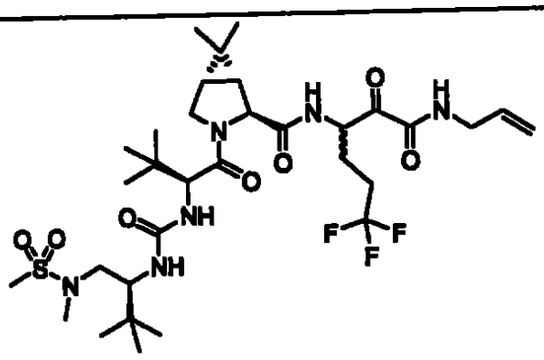
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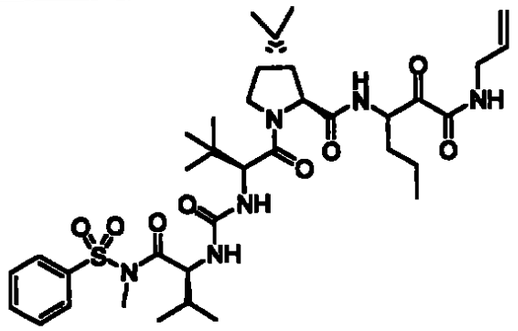
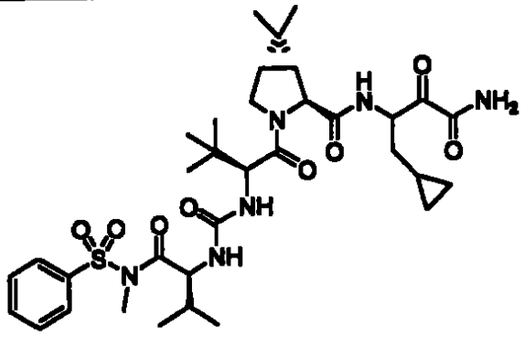
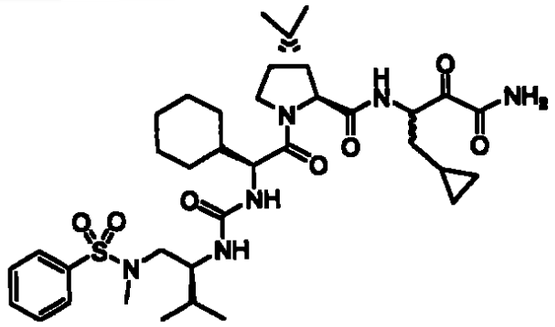
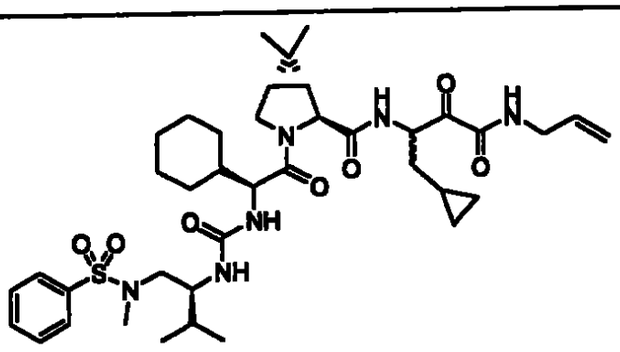
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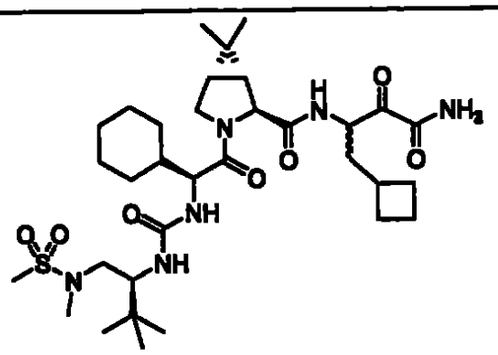
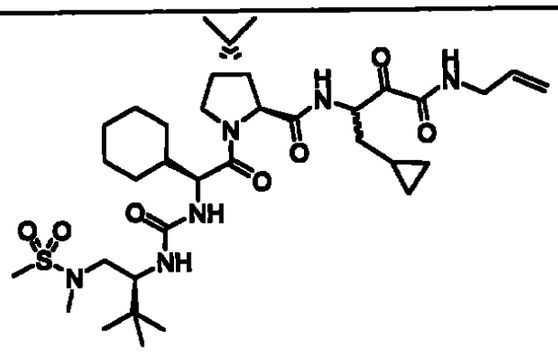
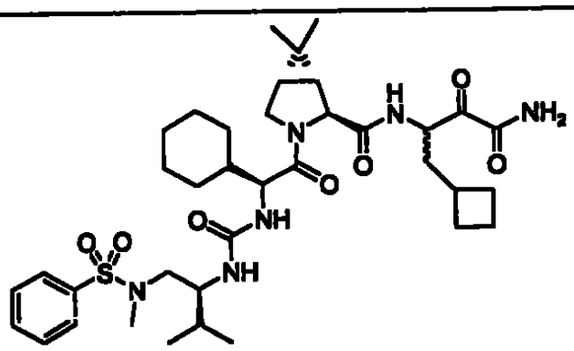
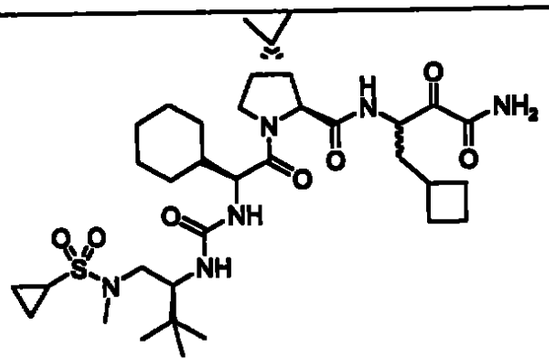
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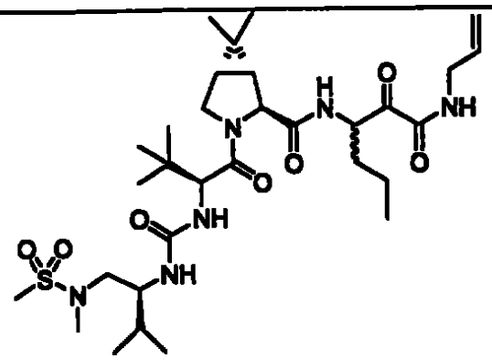
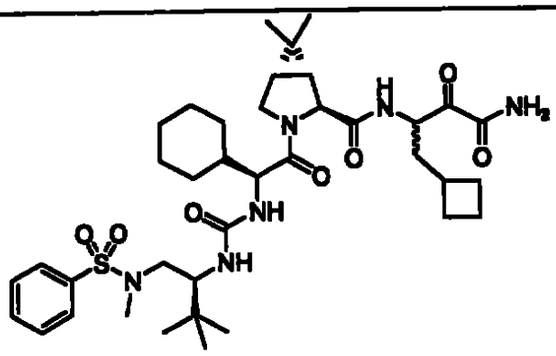
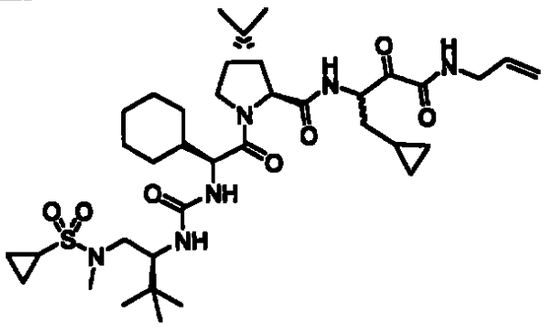
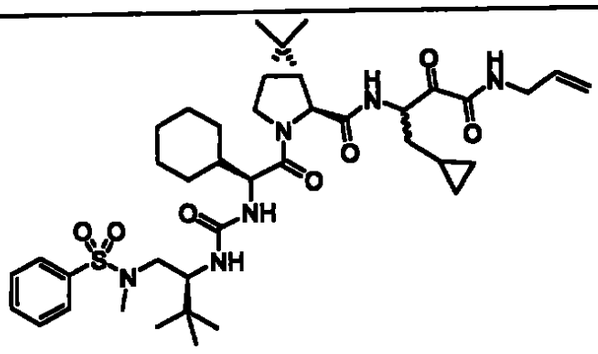
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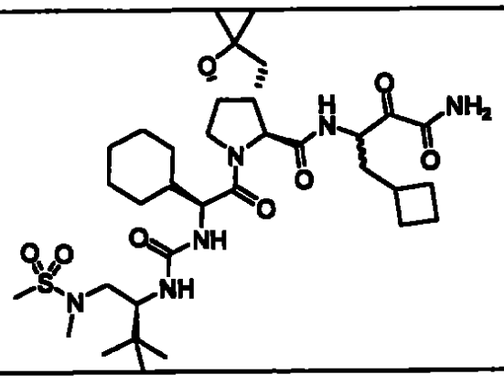
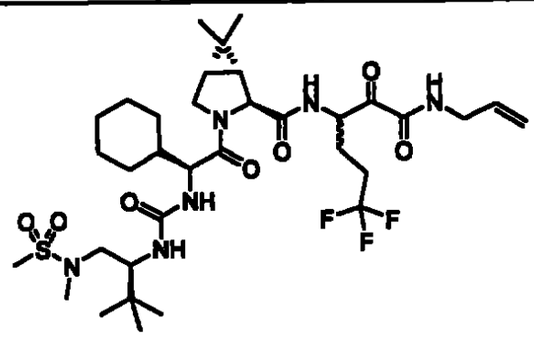
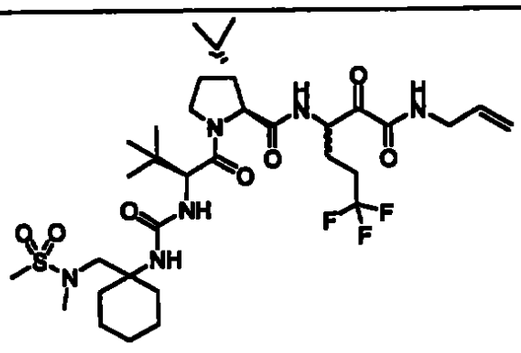
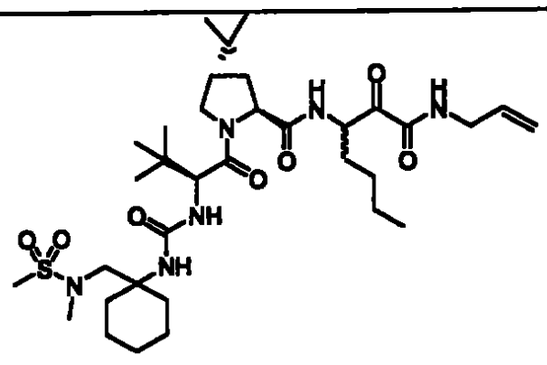
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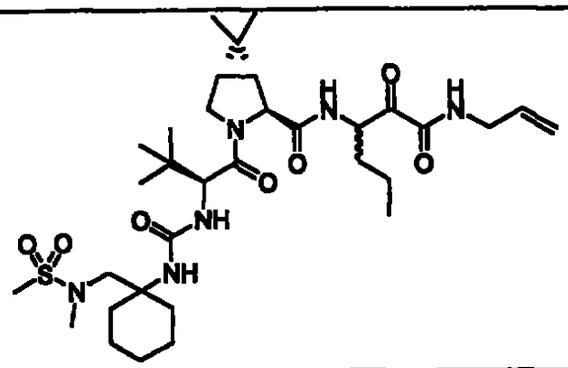
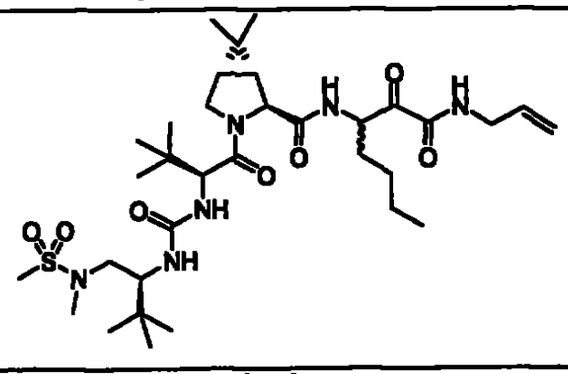
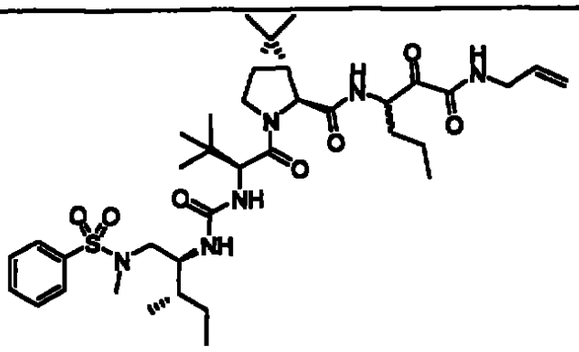
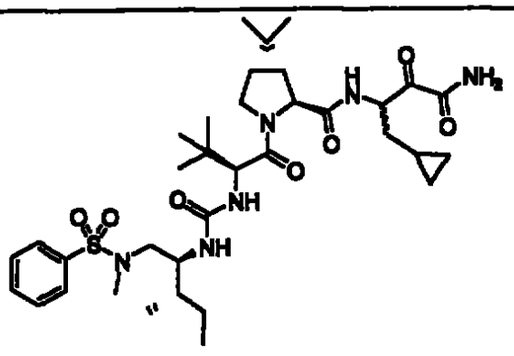
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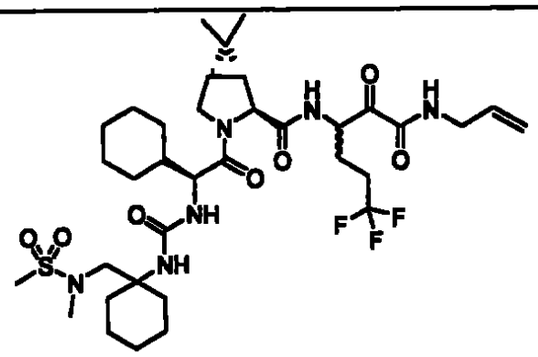
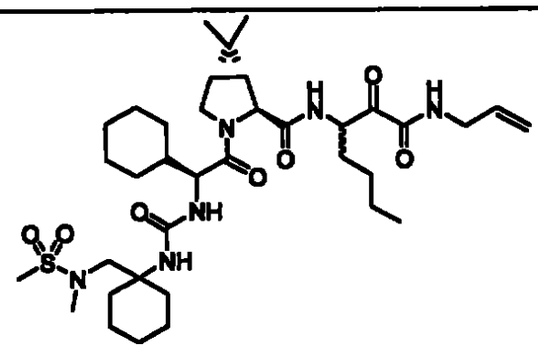
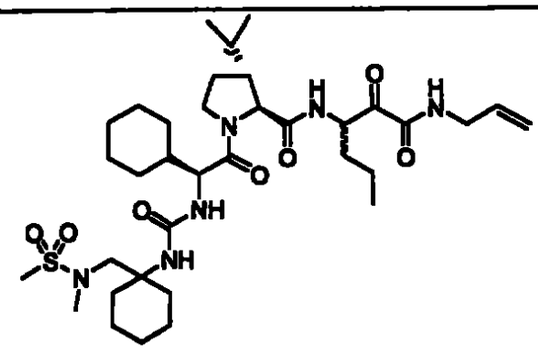
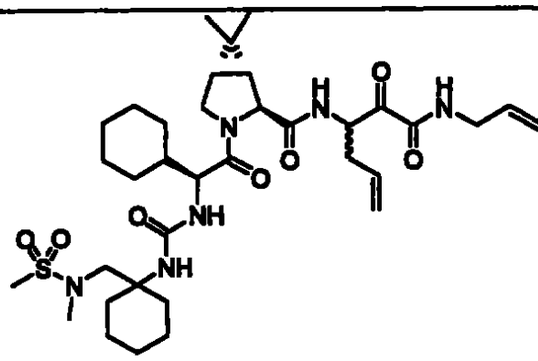
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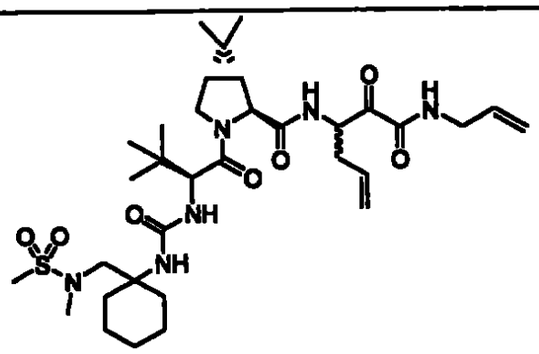
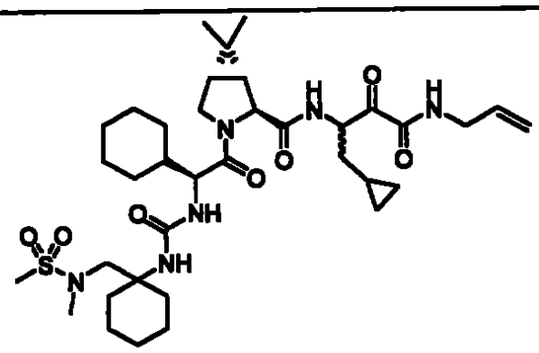
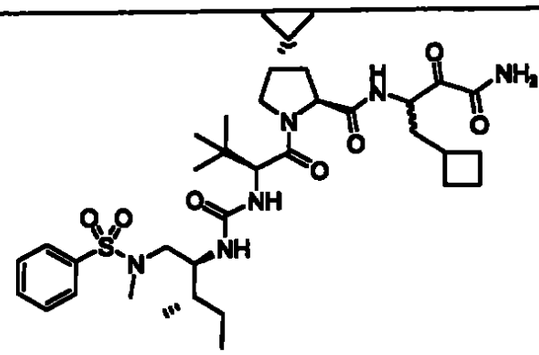
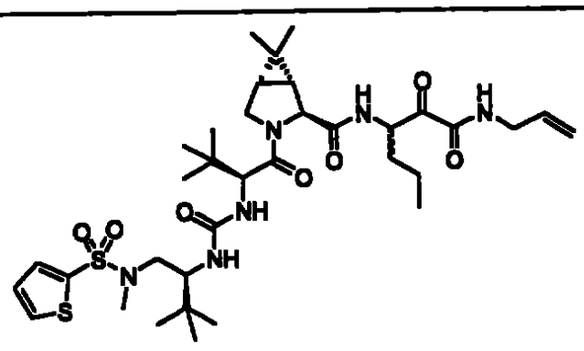
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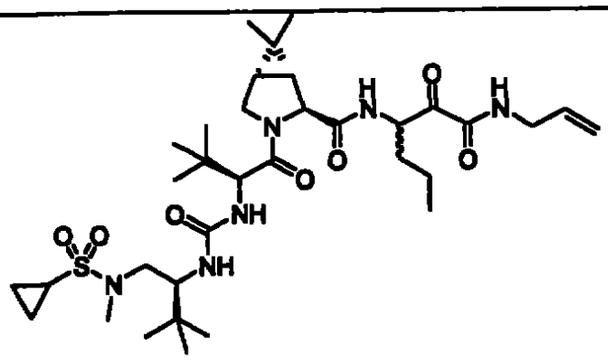
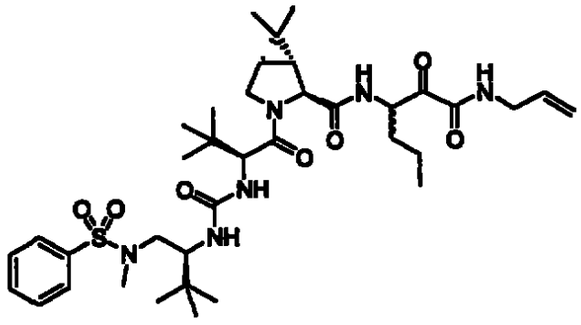
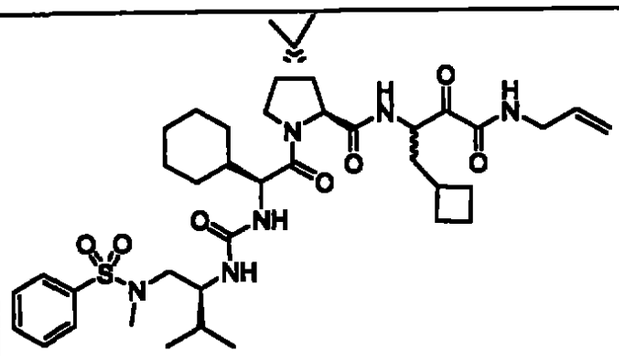
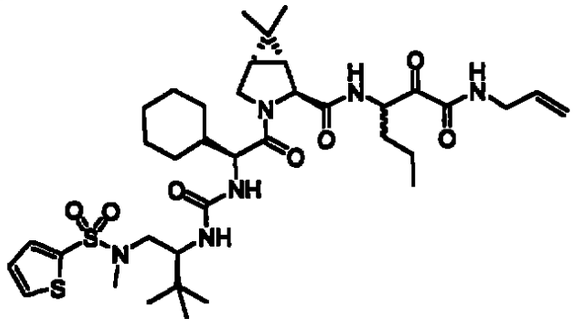
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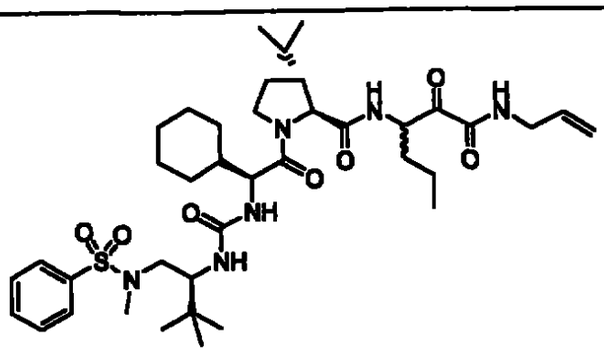
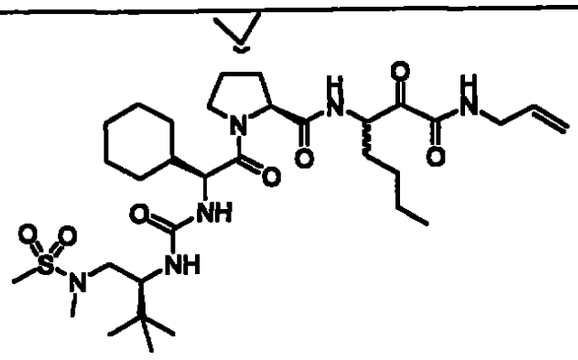
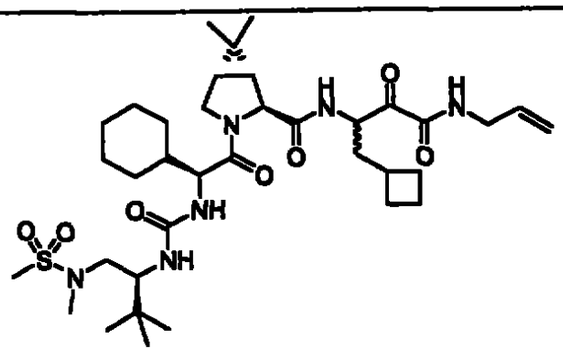
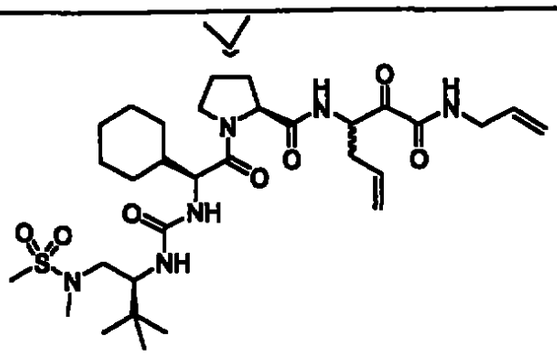
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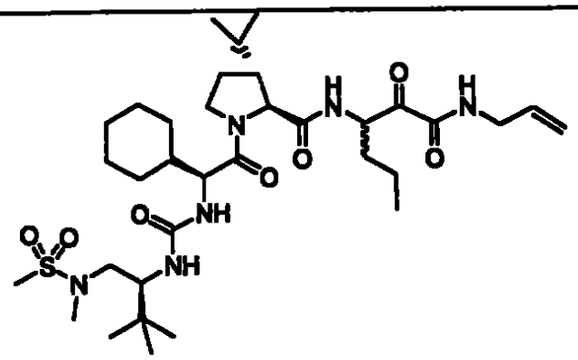
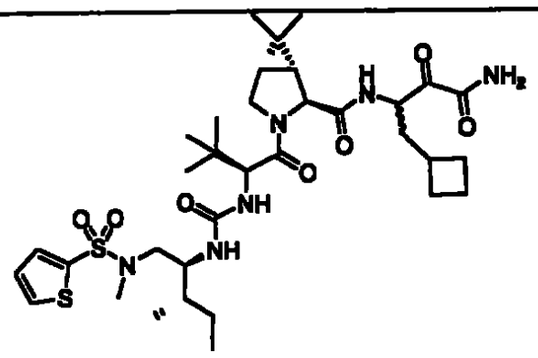
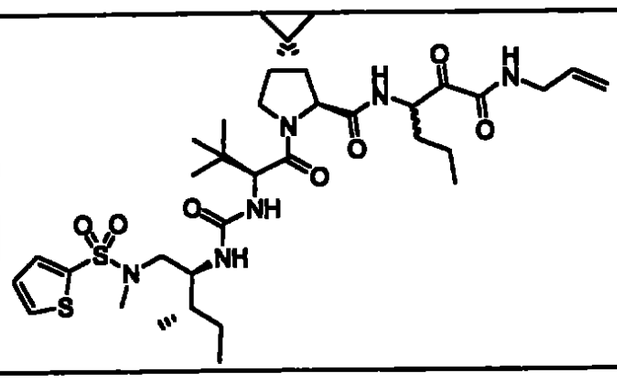
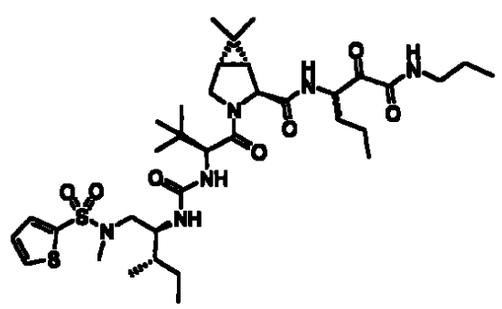
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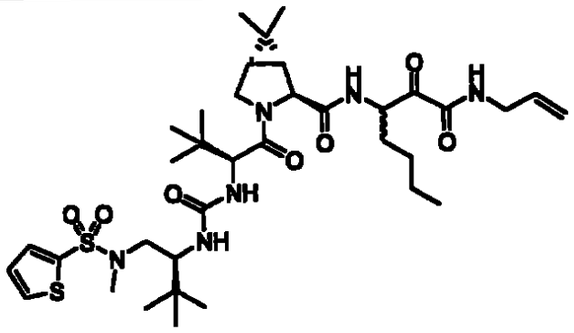
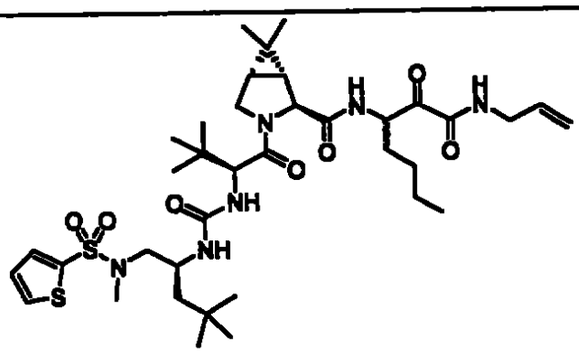
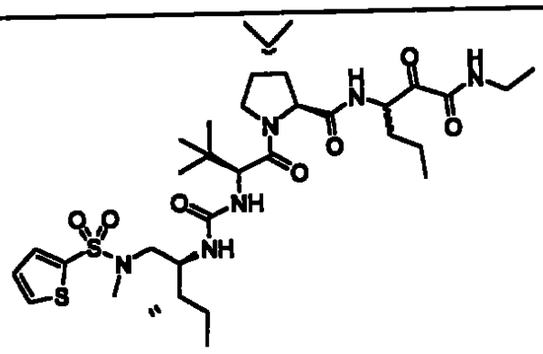
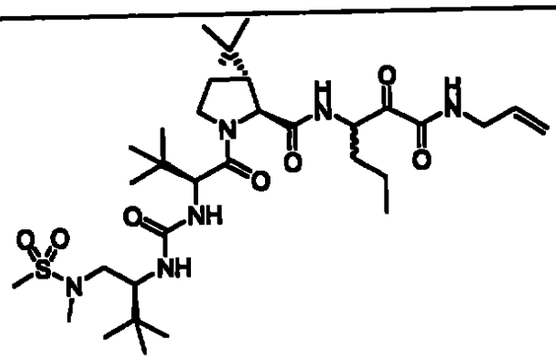
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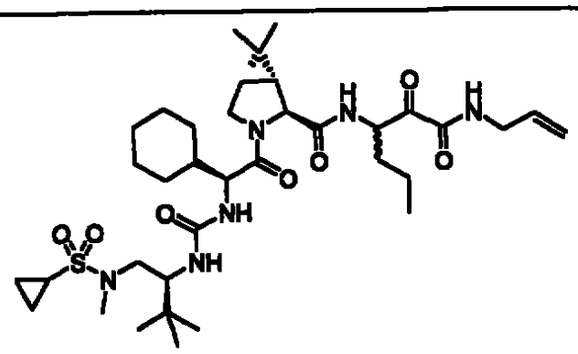
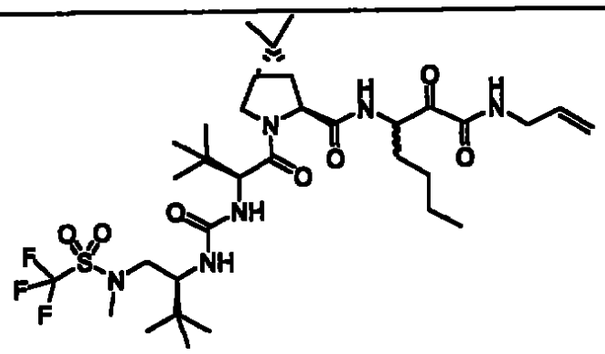
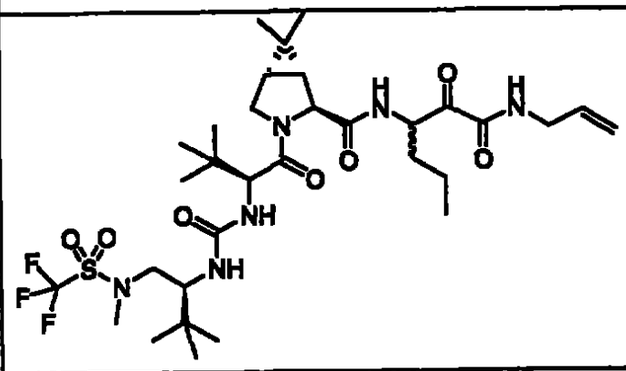
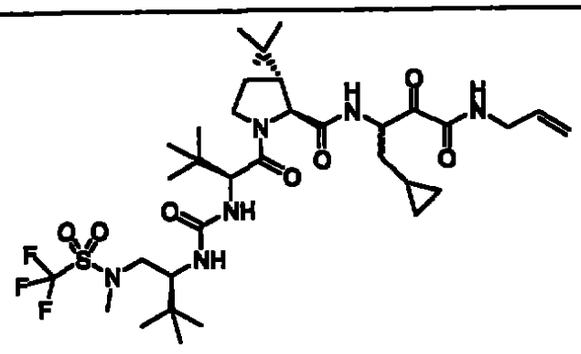
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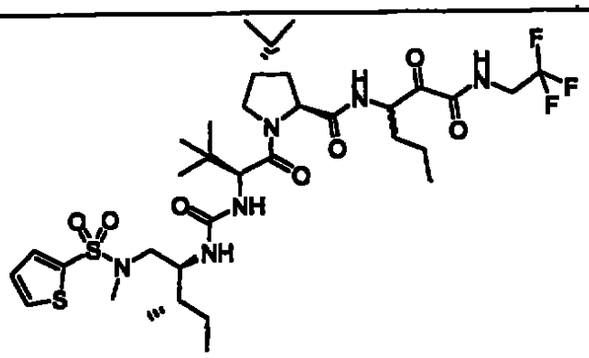
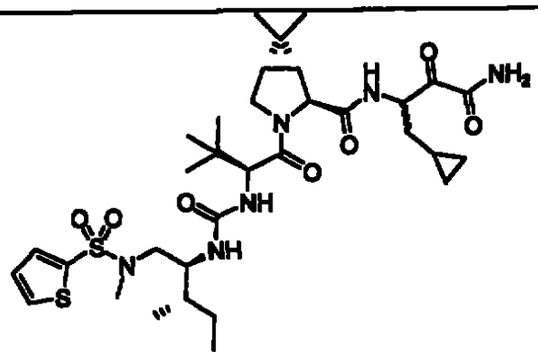
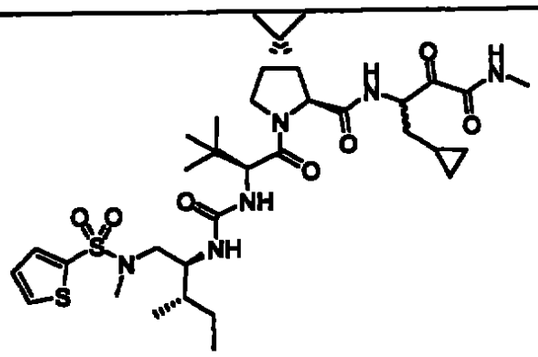
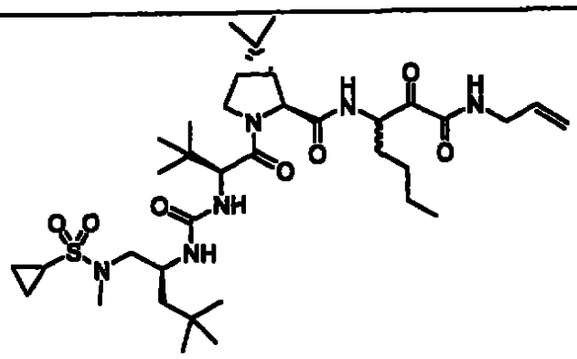
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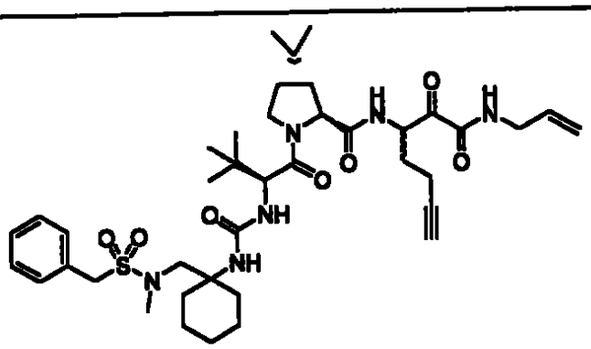
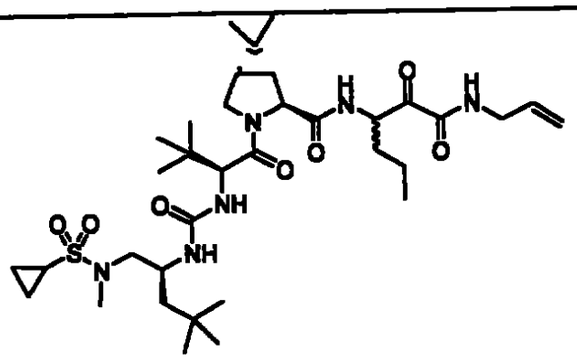
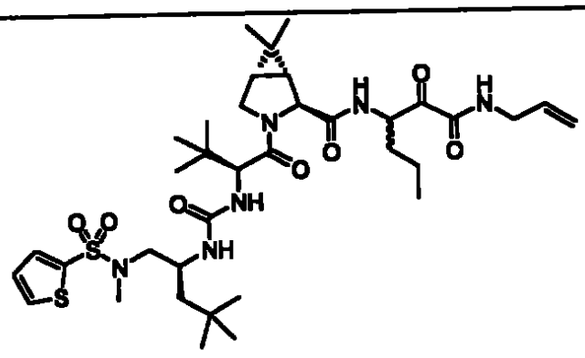
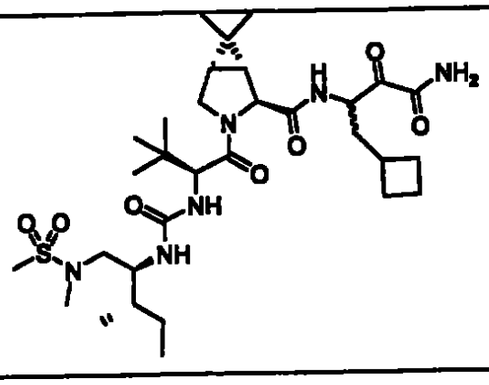
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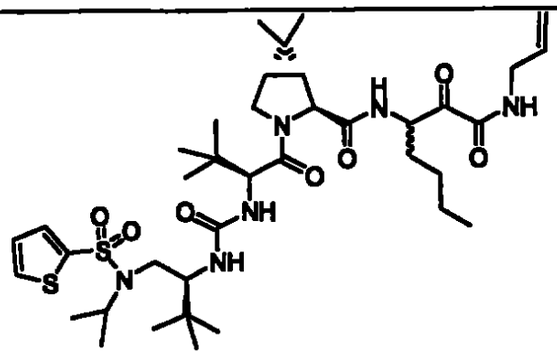
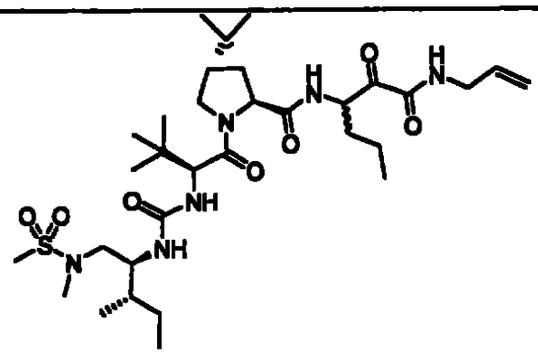
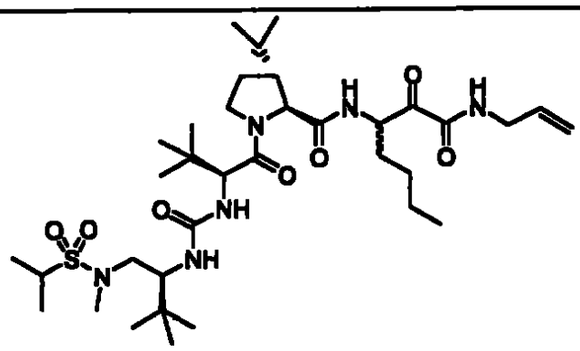
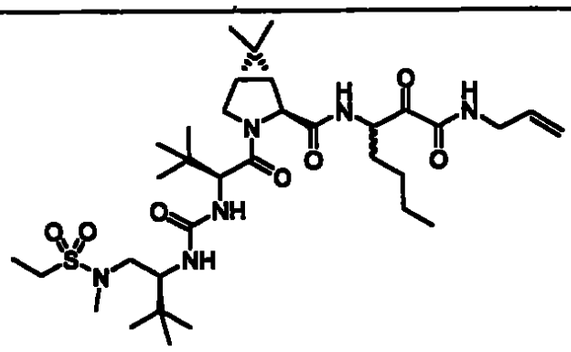
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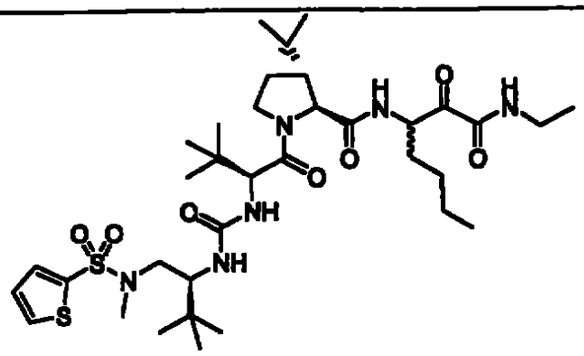
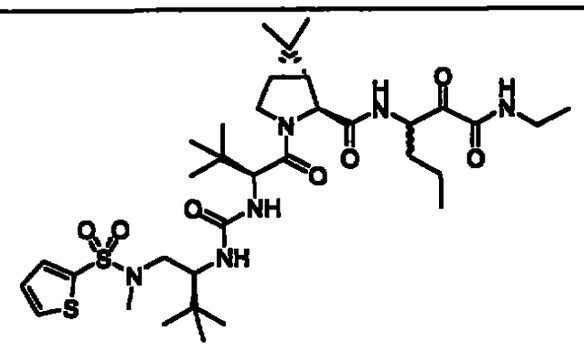
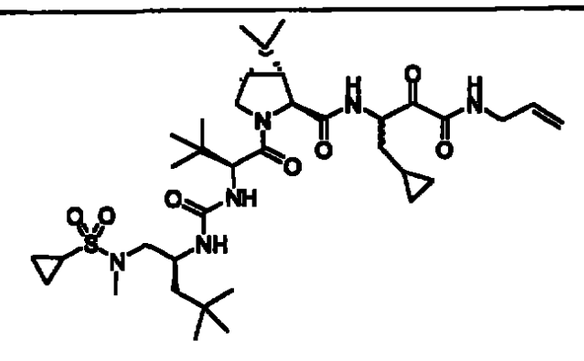
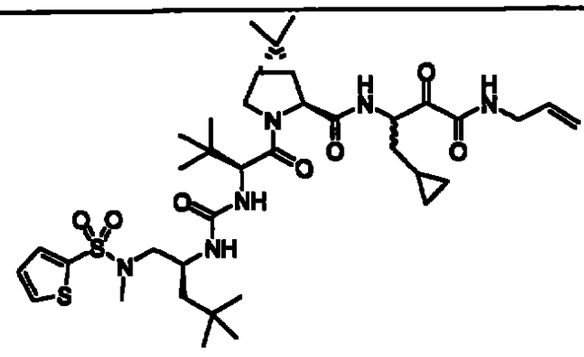
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11092		A

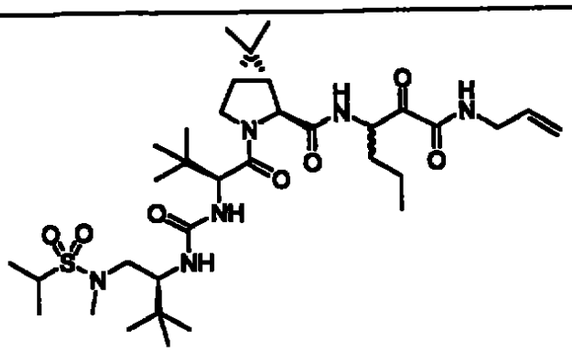
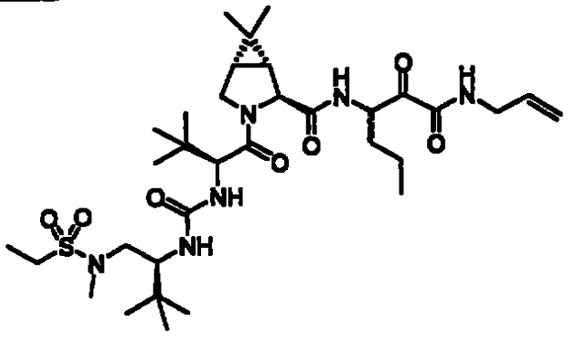
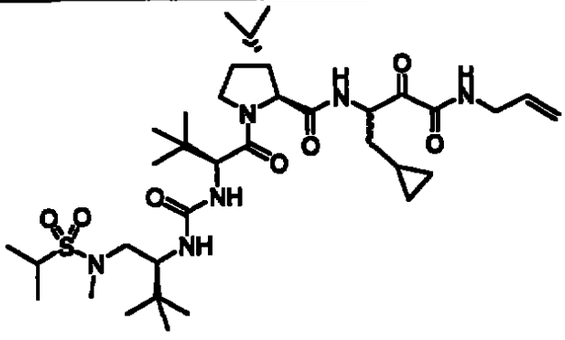
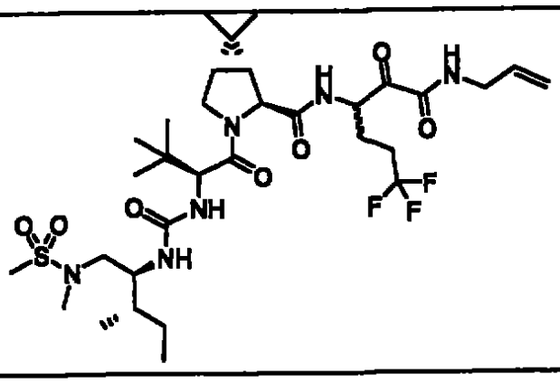
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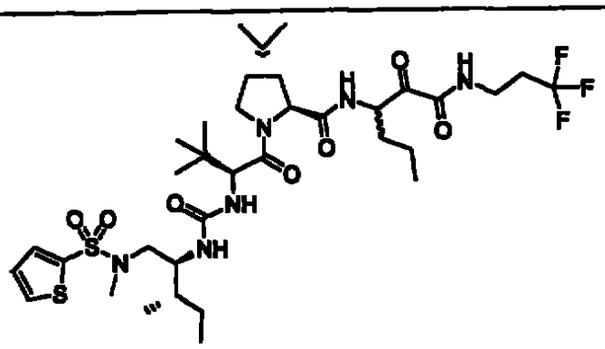
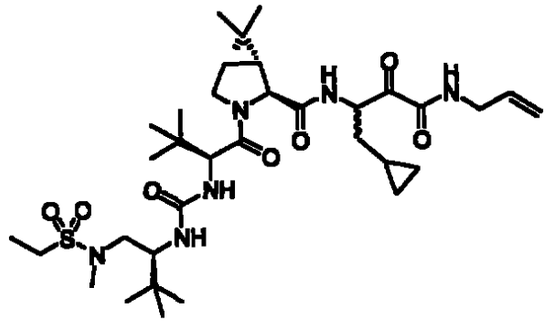
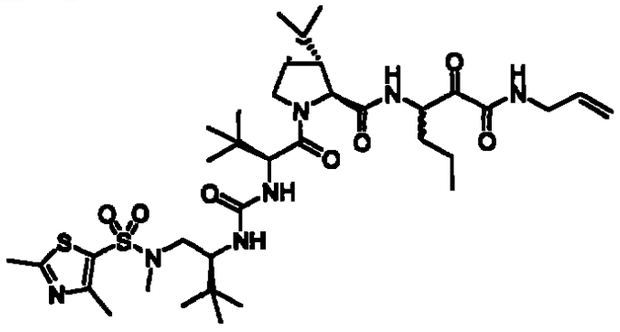
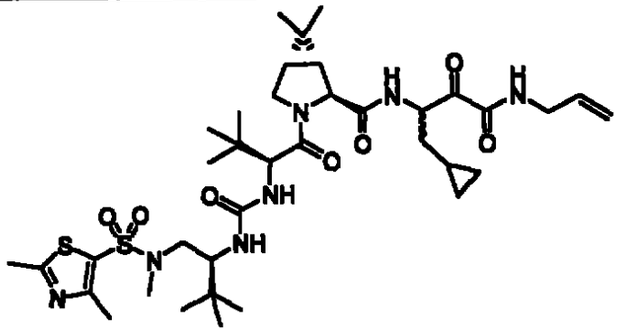
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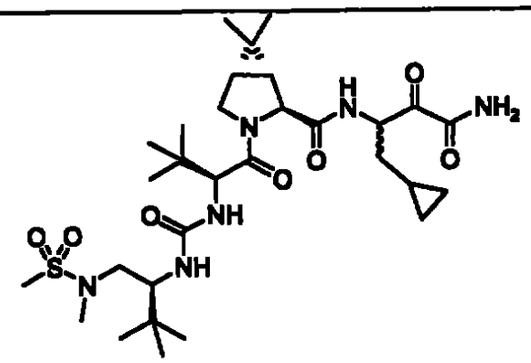
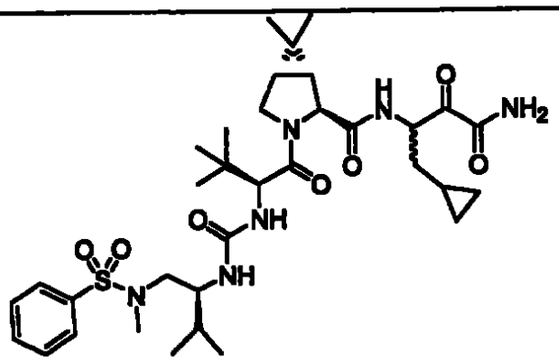
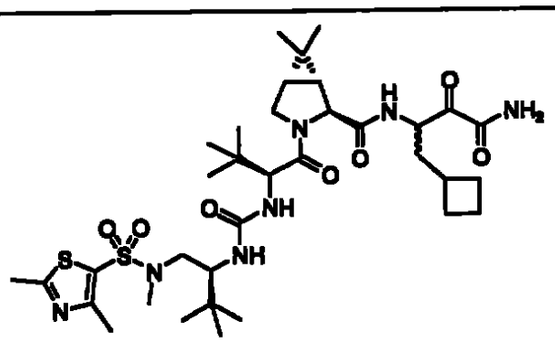
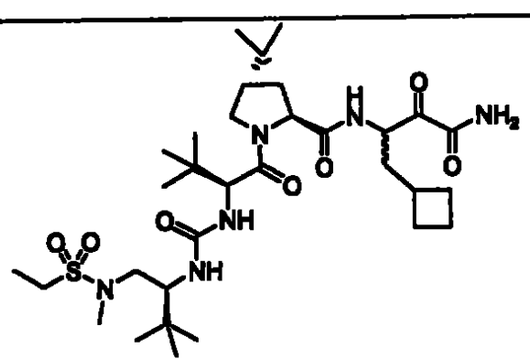
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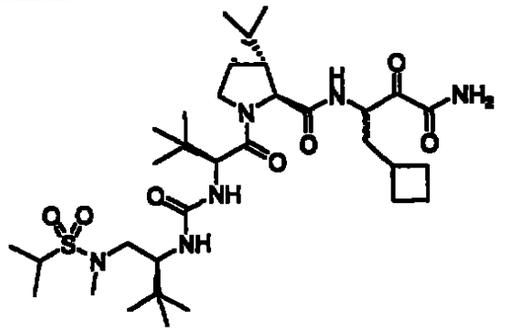
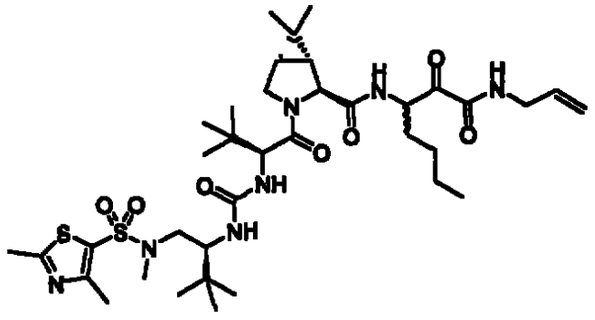
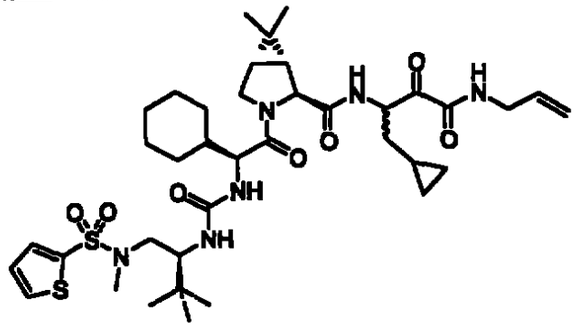
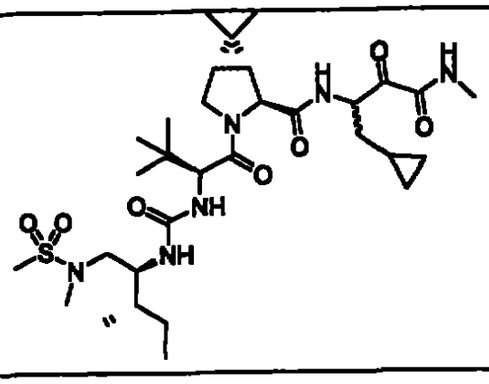
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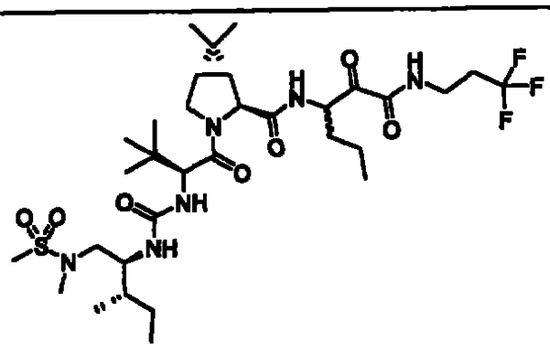
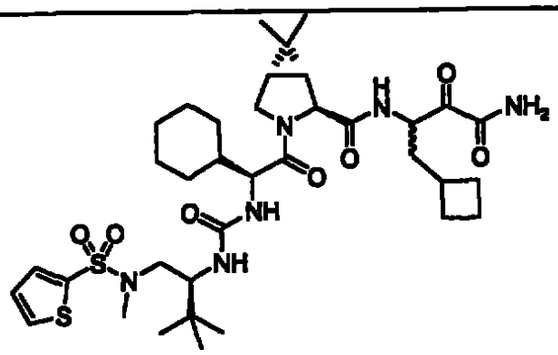
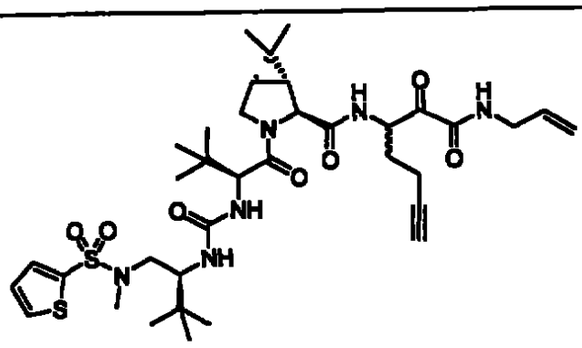
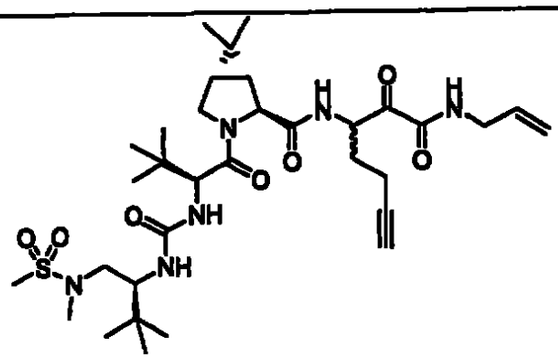
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11120		A

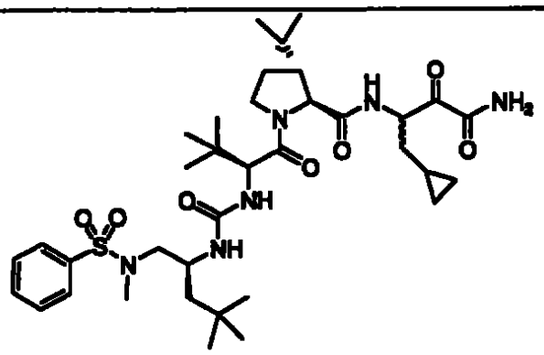
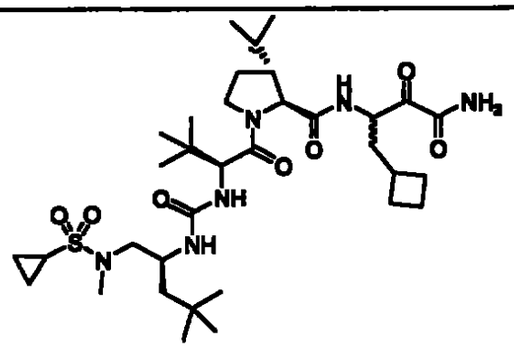
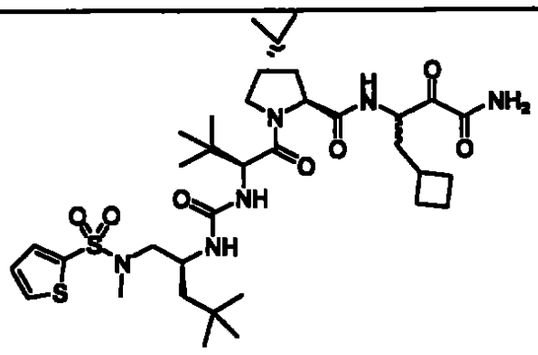
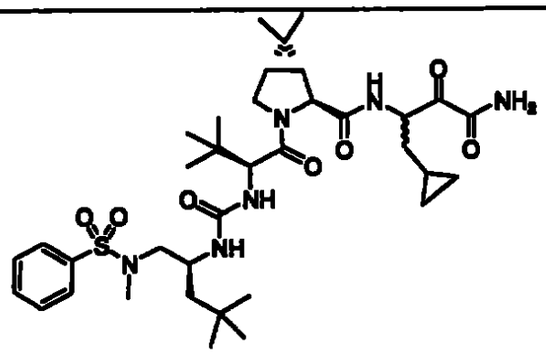
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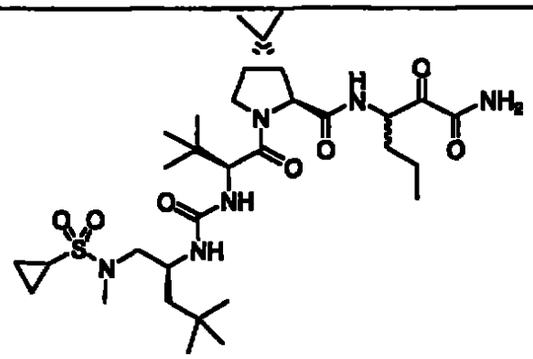
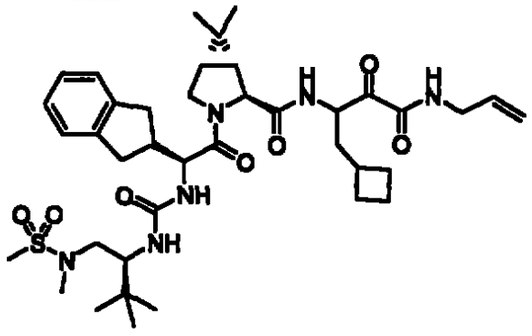
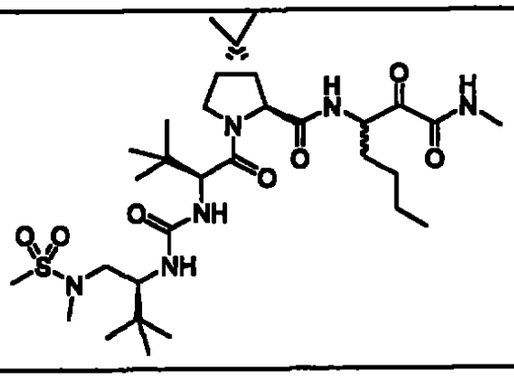
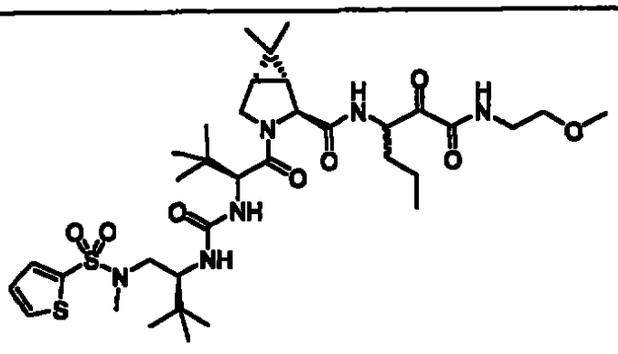
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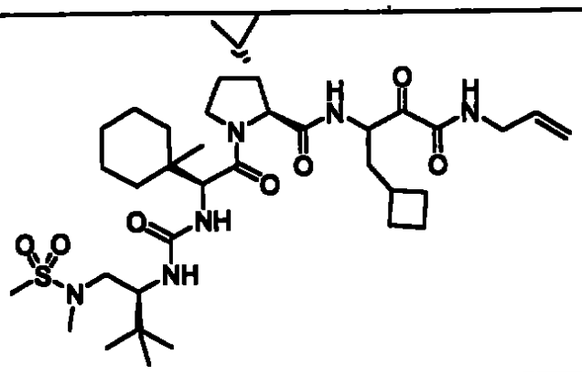
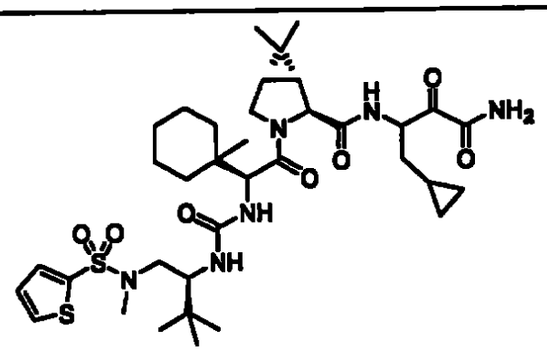
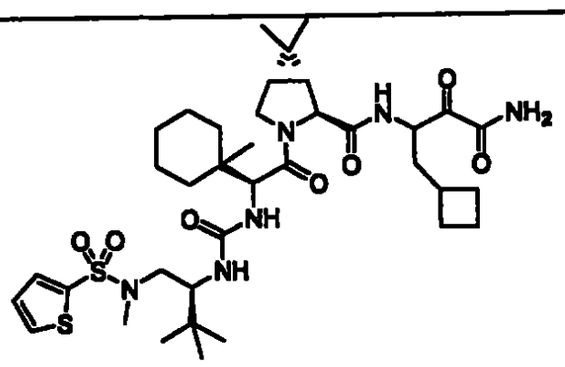
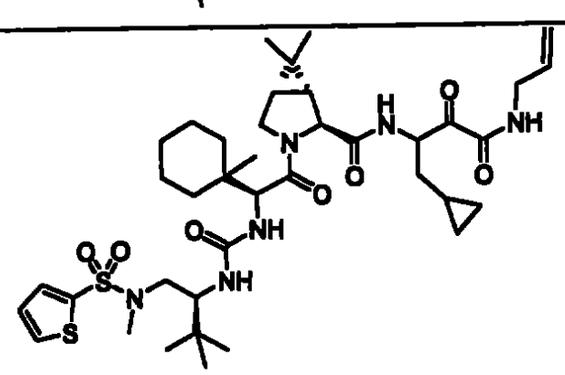
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11132		B

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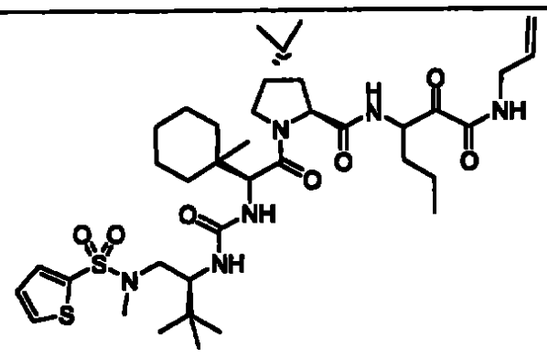
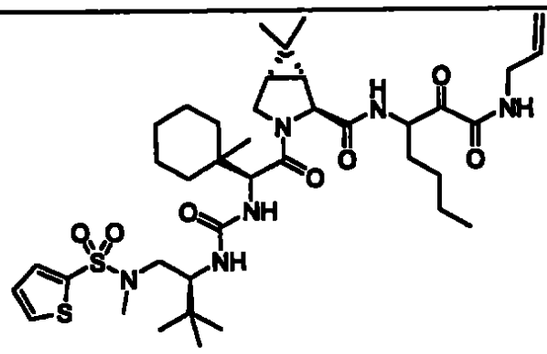
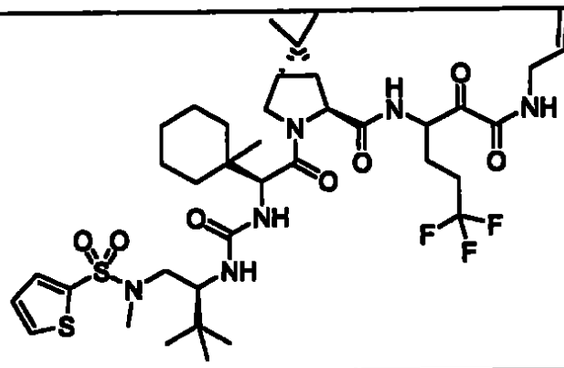
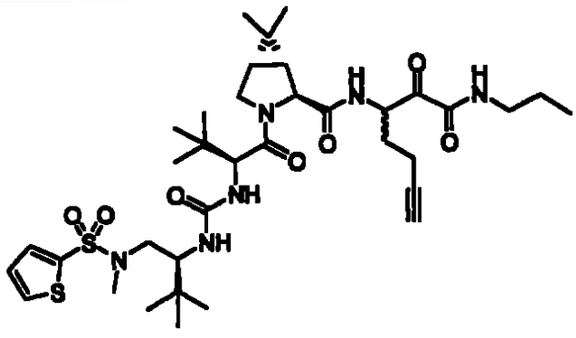
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11136		B

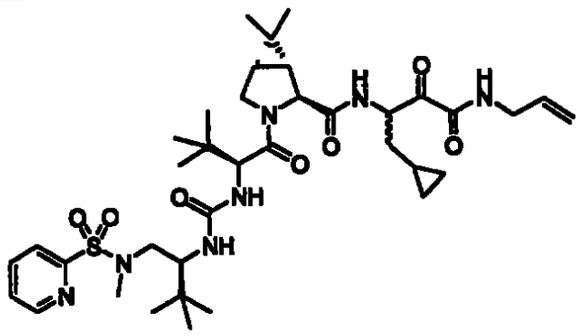
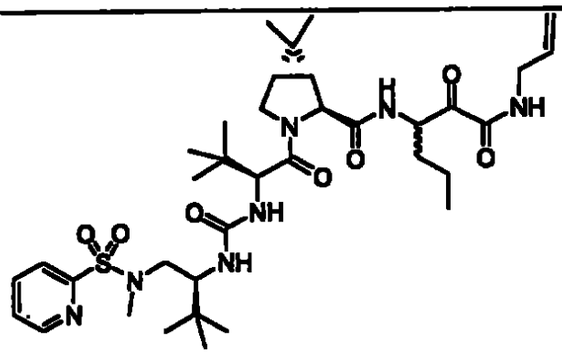
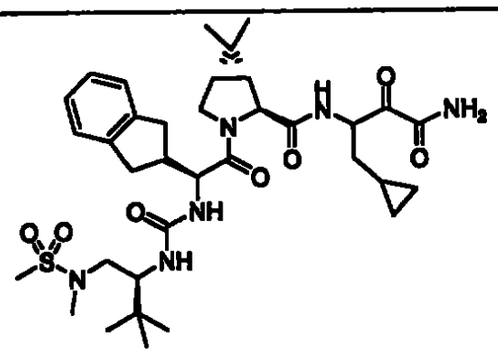
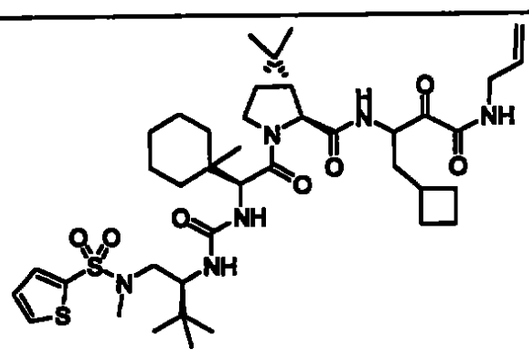
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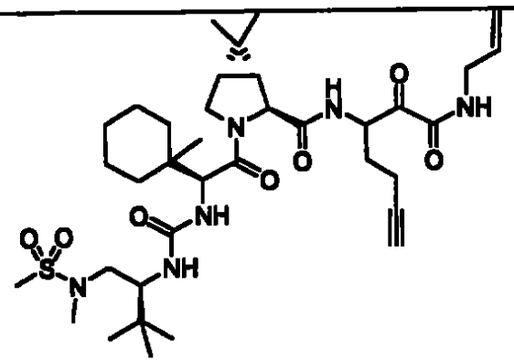
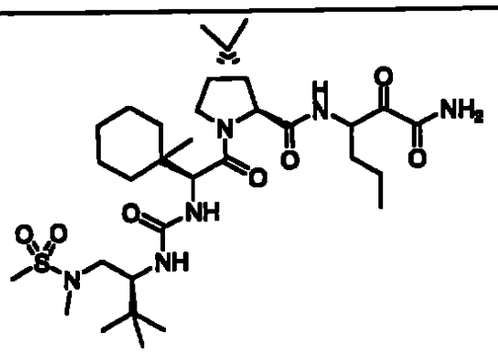
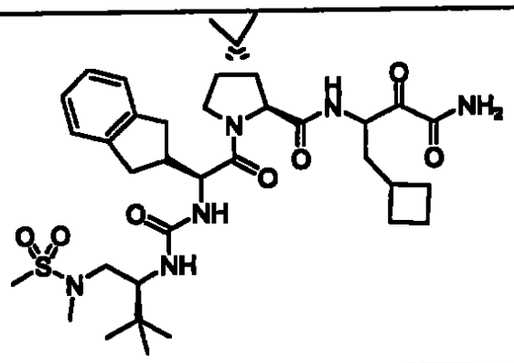
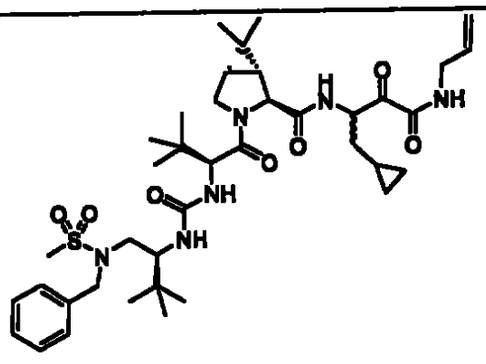
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11140		A

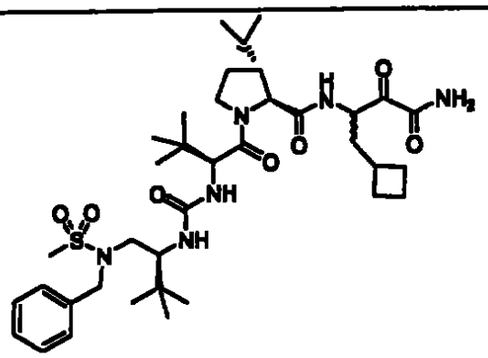
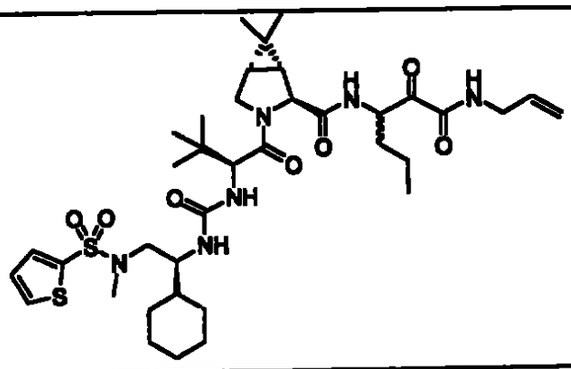
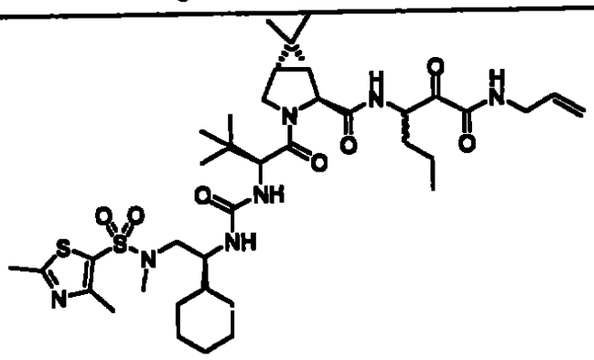
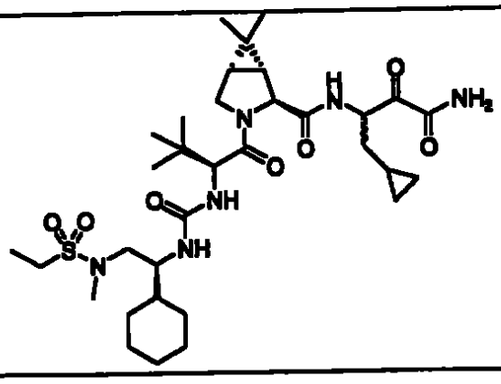
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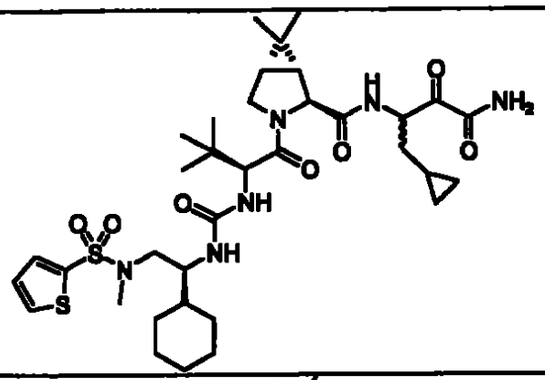
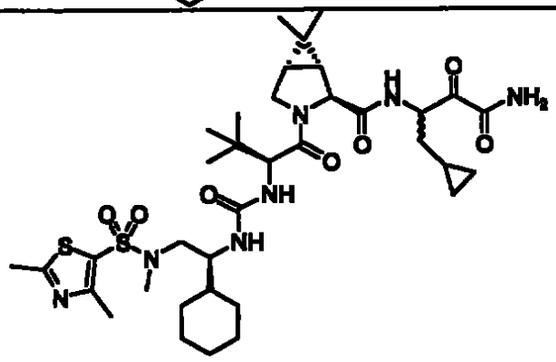
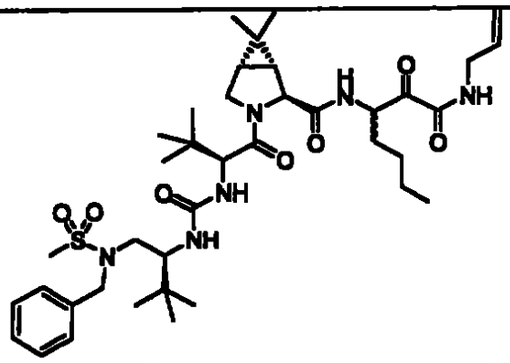
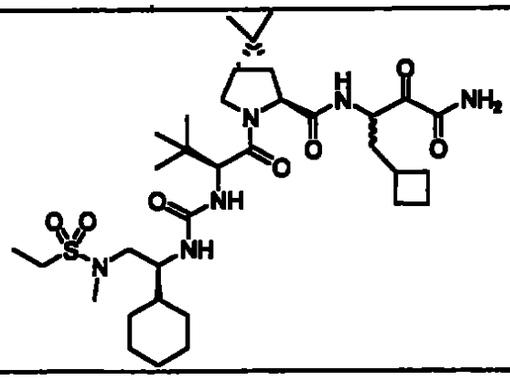
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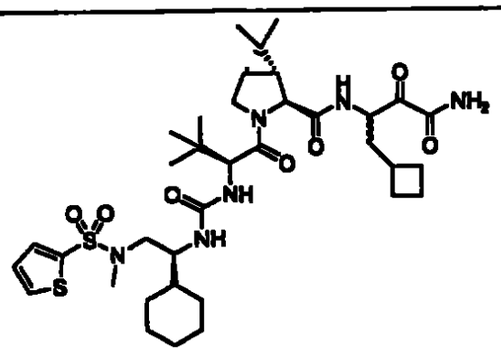
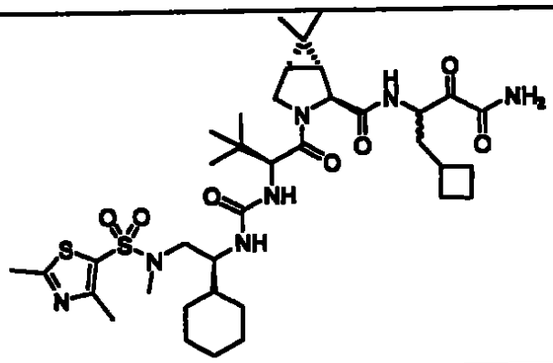
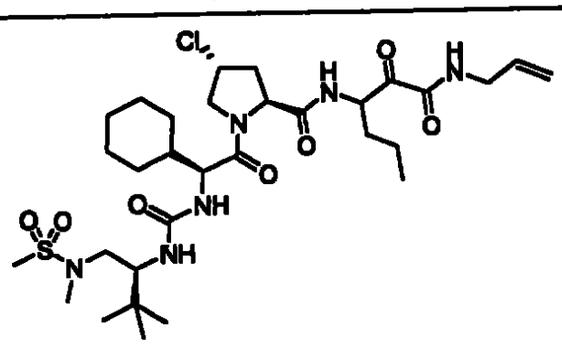
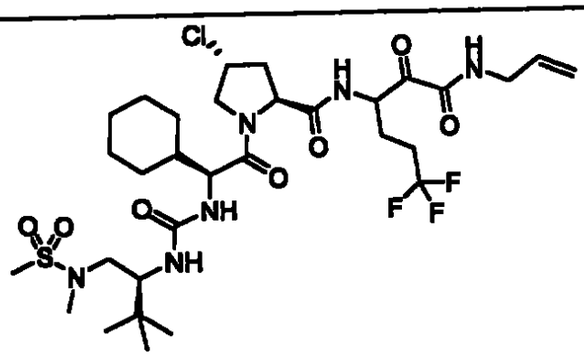
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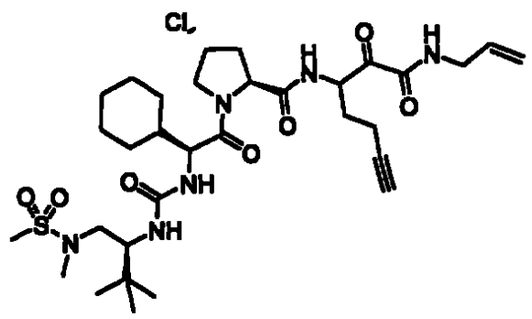
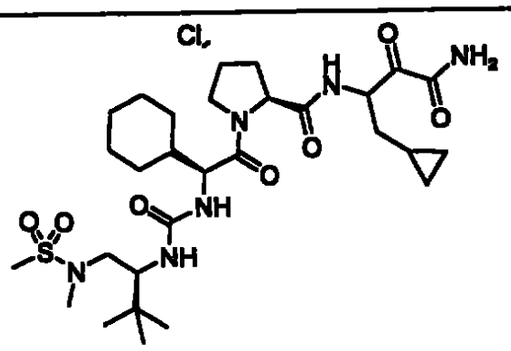
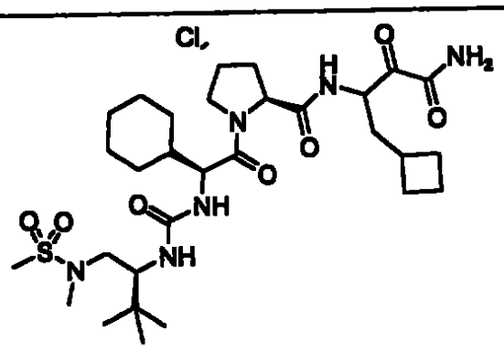
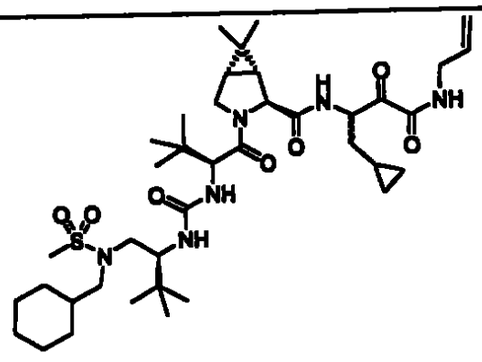
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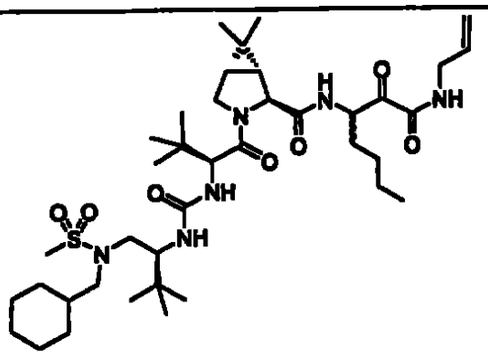
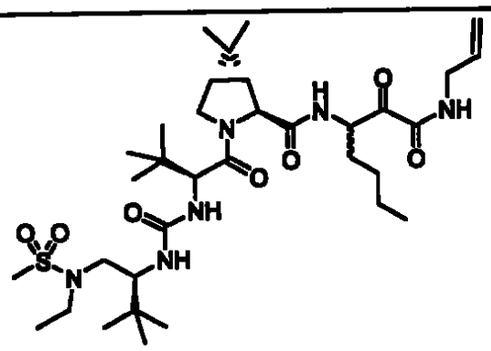
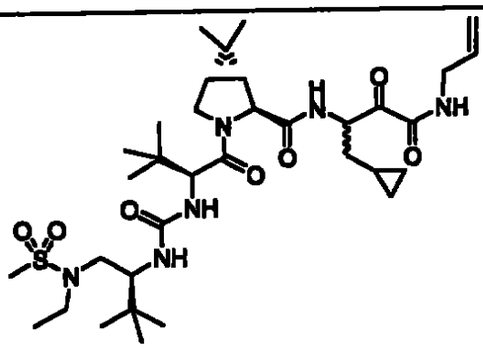
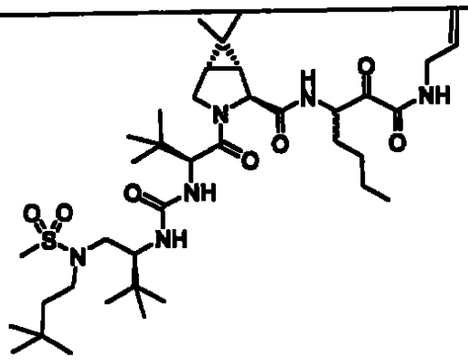
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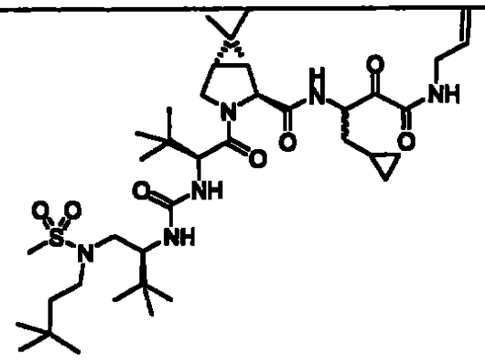
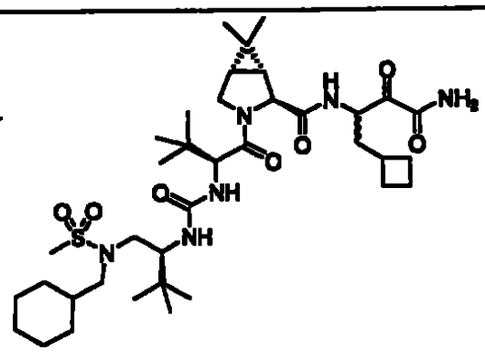
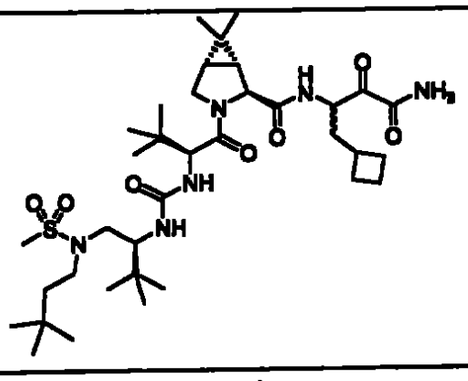
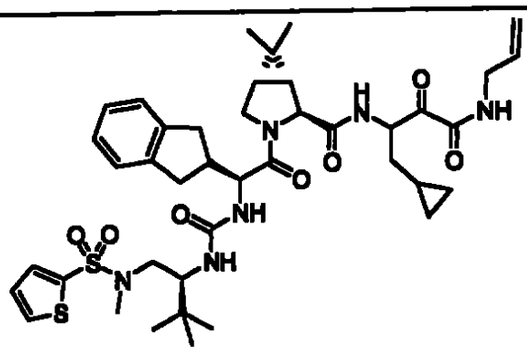
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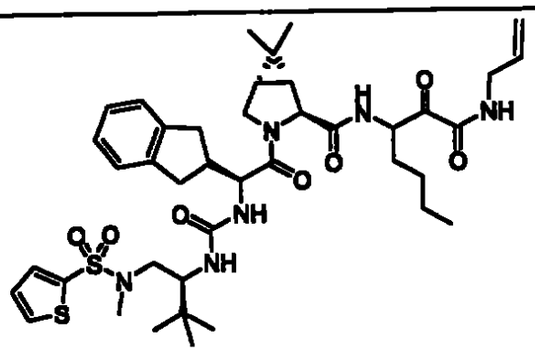
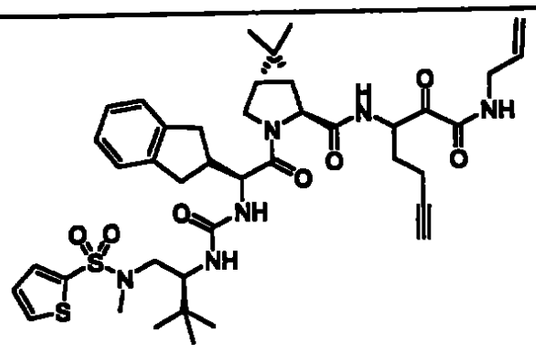
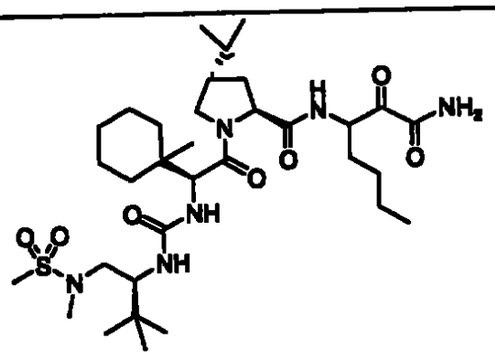
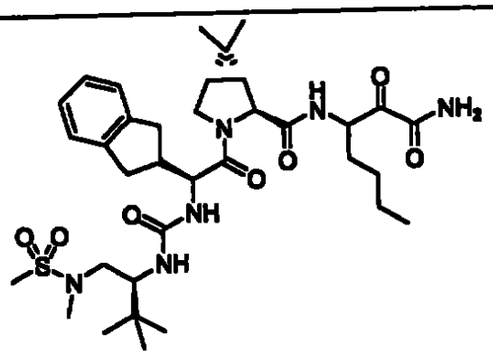
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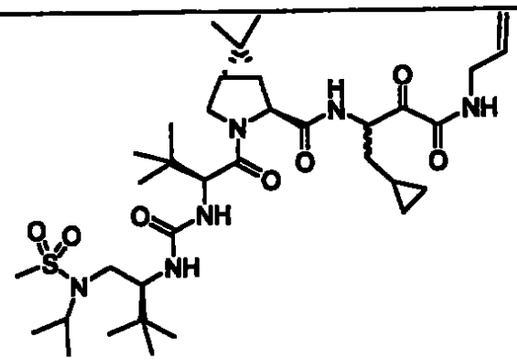
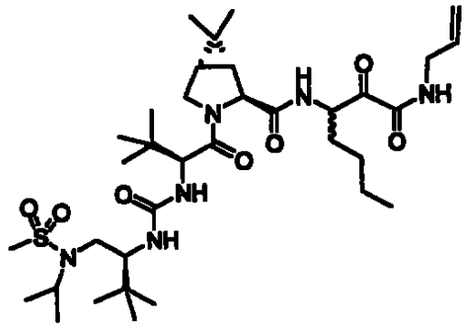
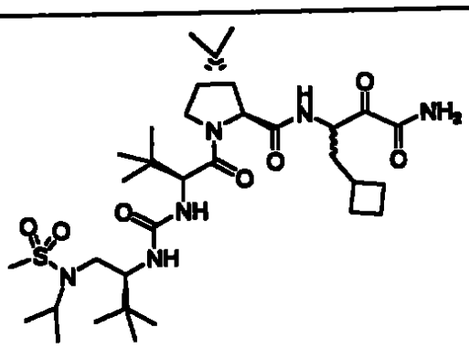
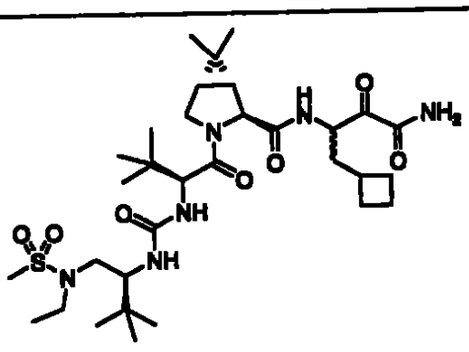
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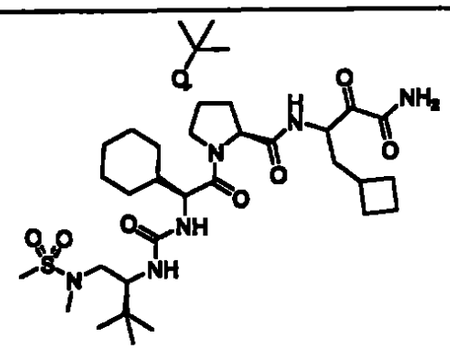
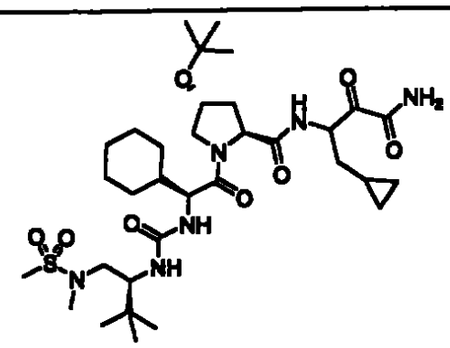
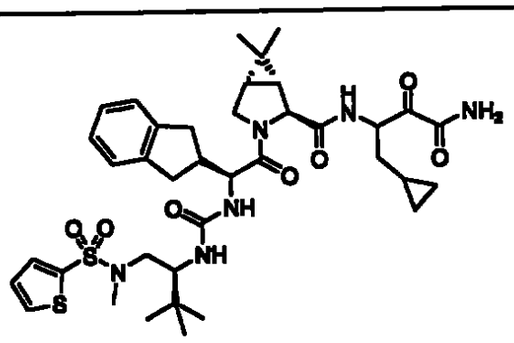
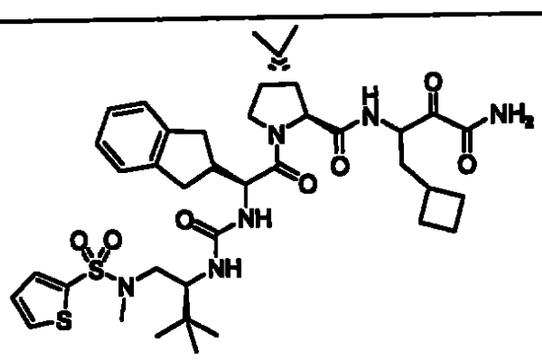
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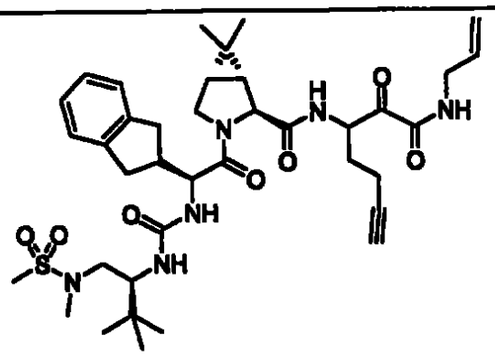
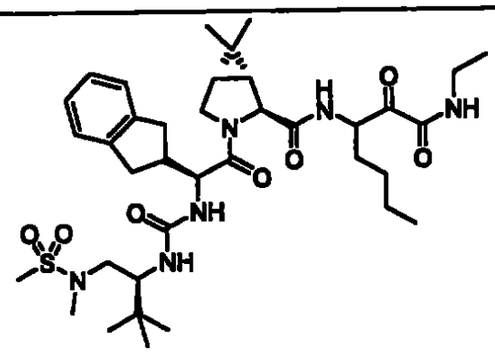
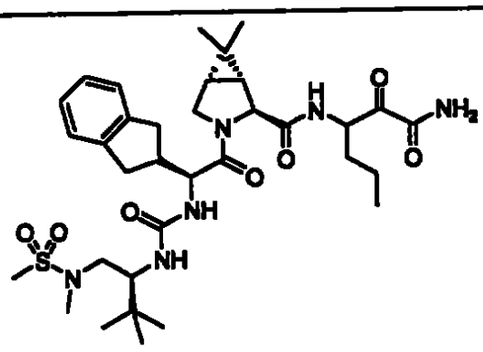
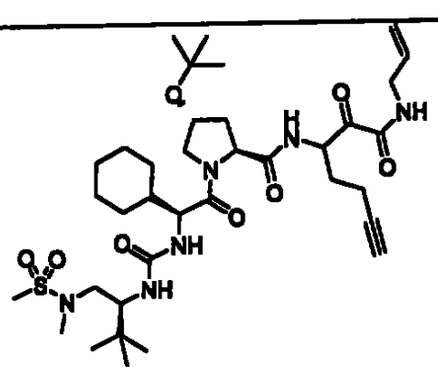
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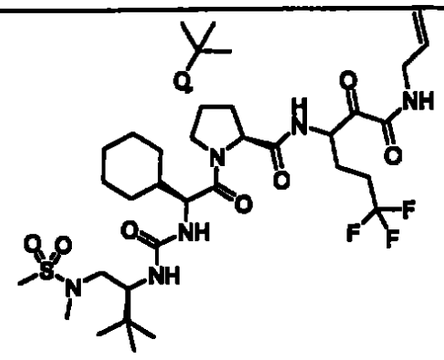
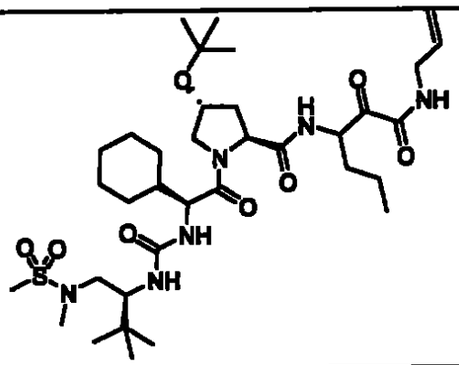
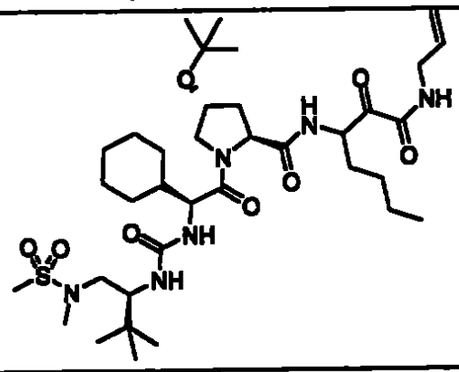
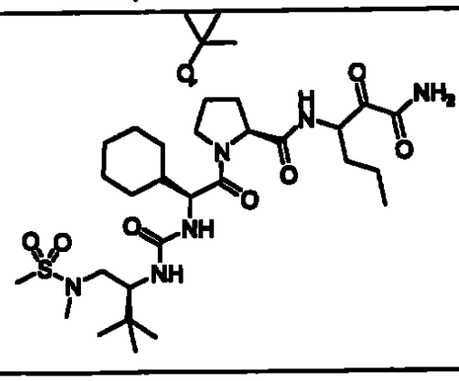
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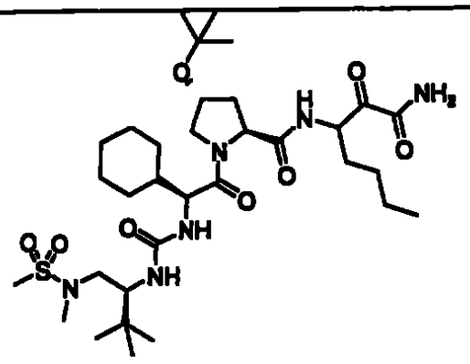
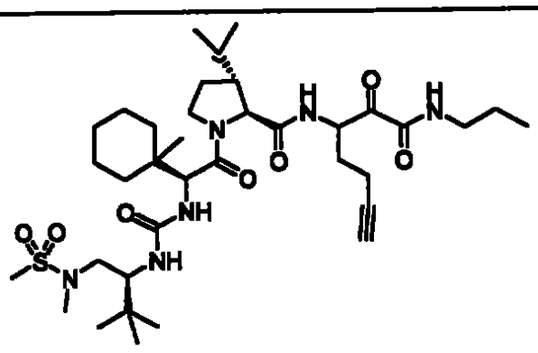
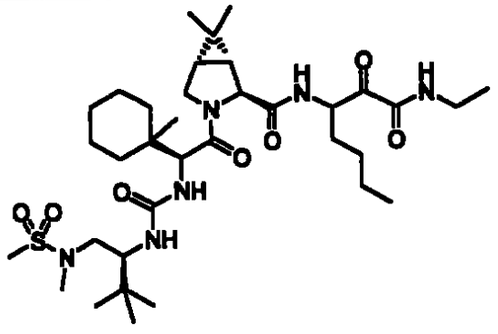
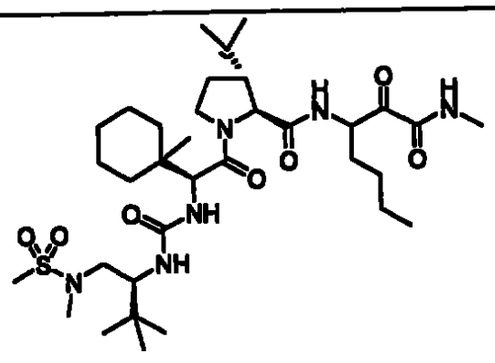
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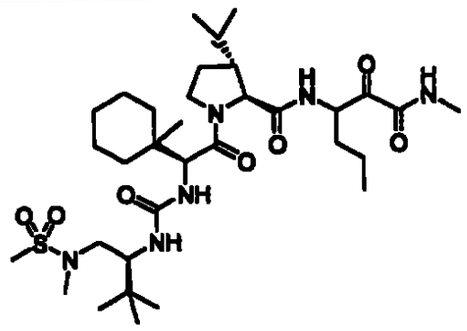
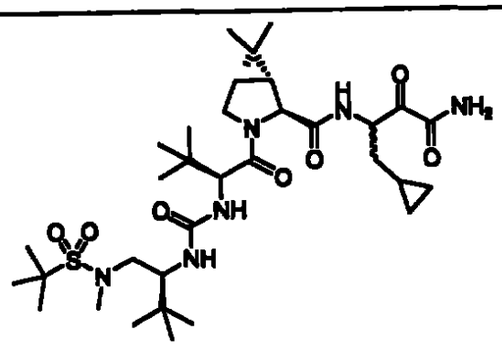
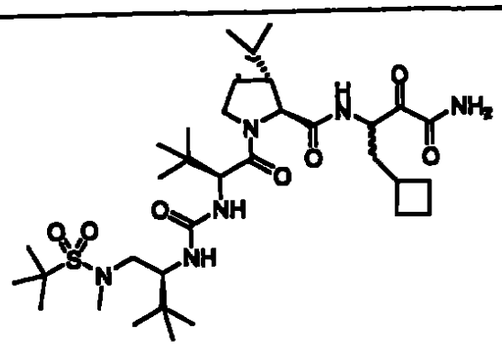
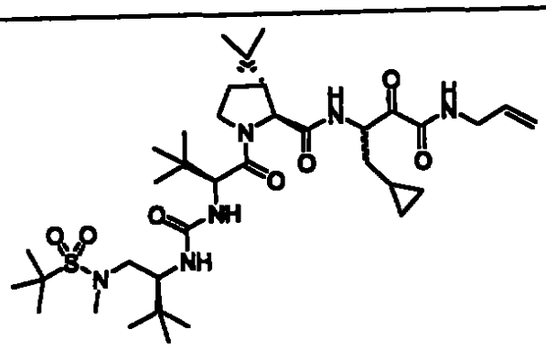
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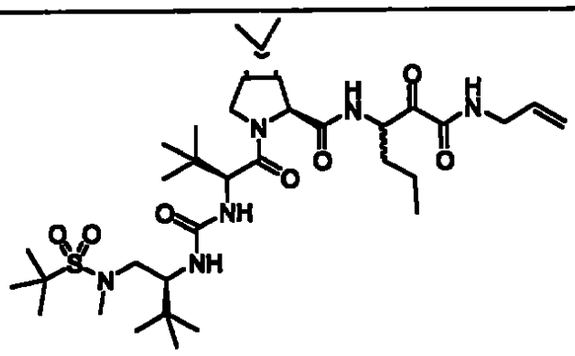
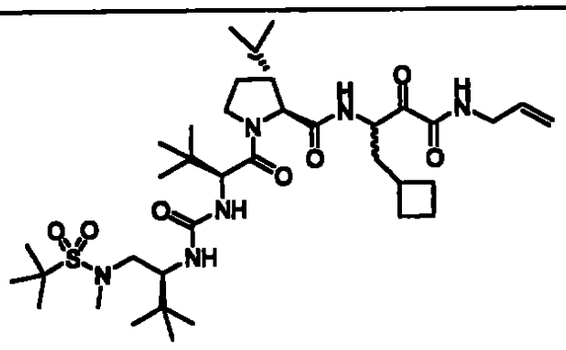
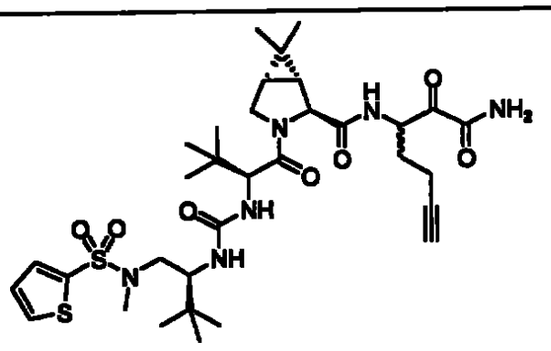
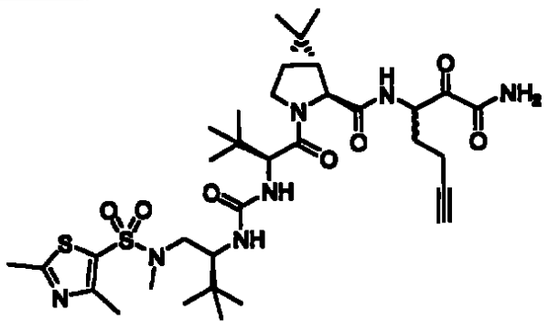
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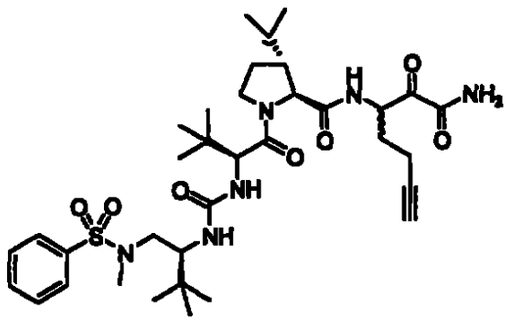
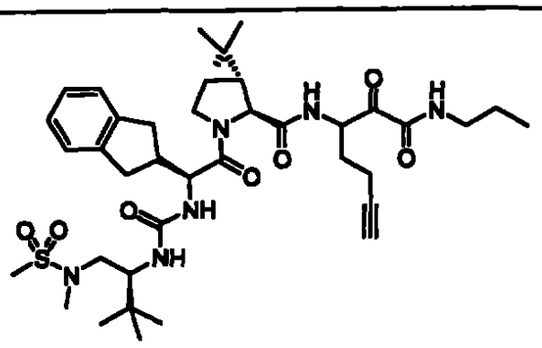
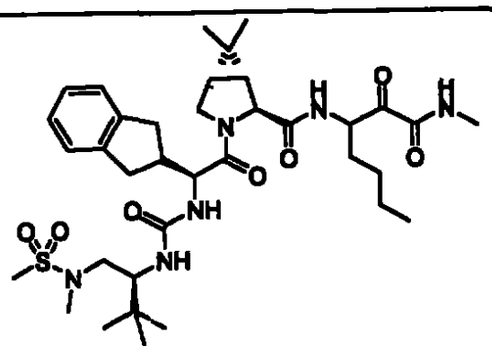
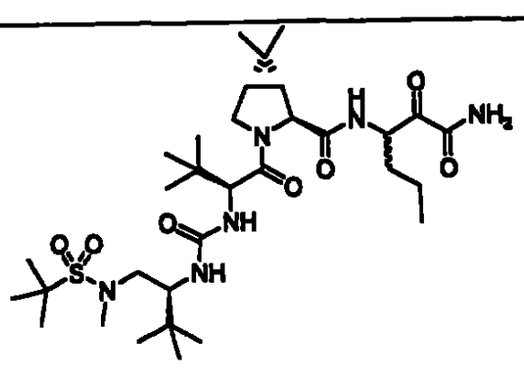
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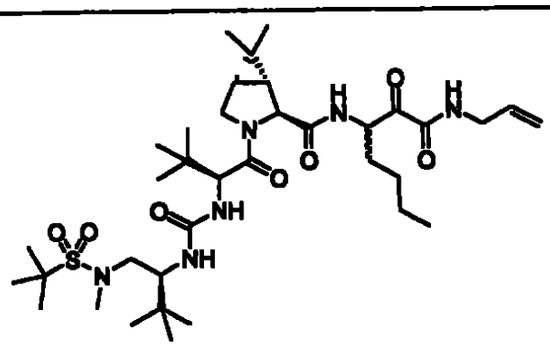
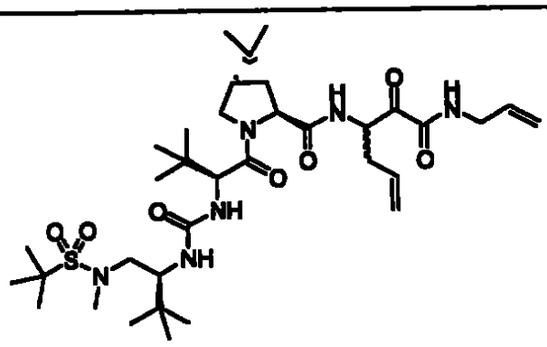
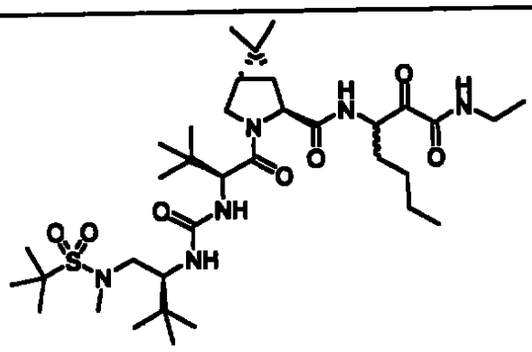
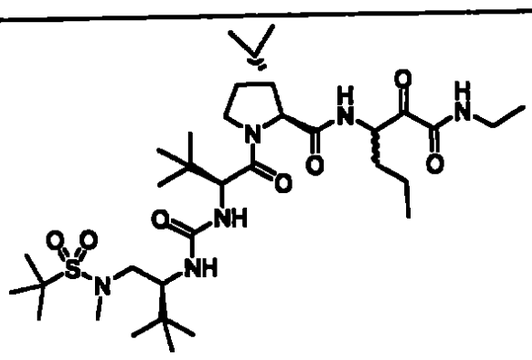
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11204		B

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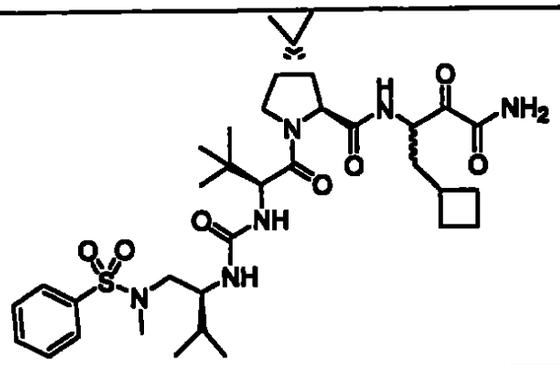
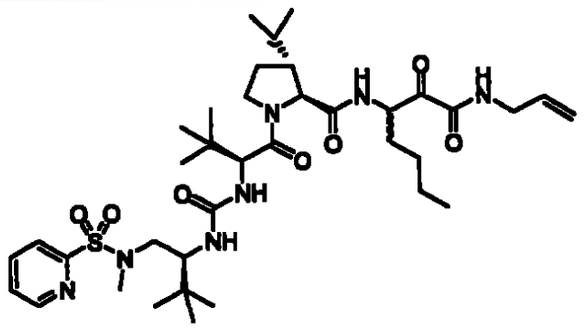
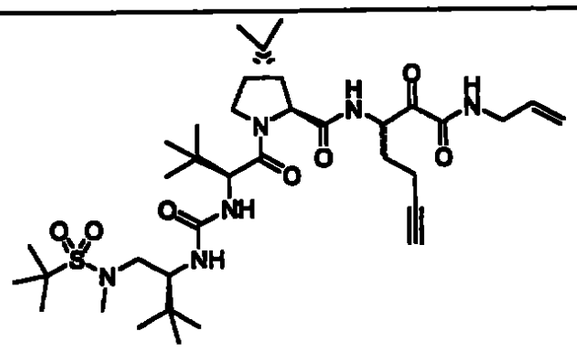
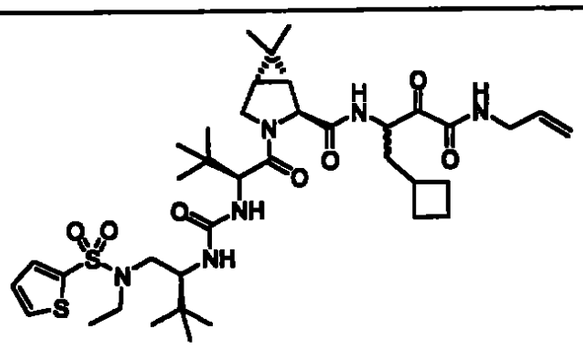
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11208		A

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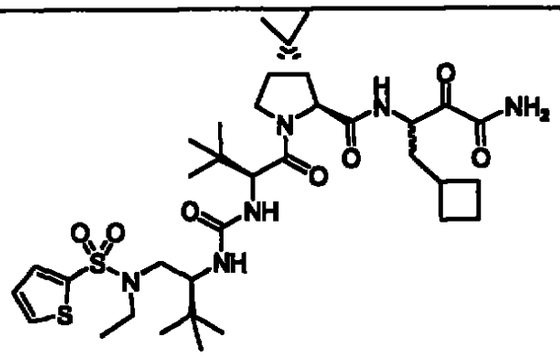
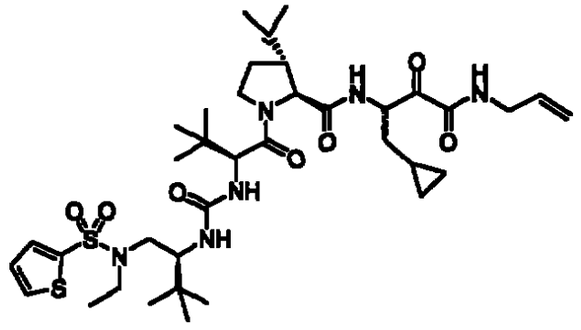
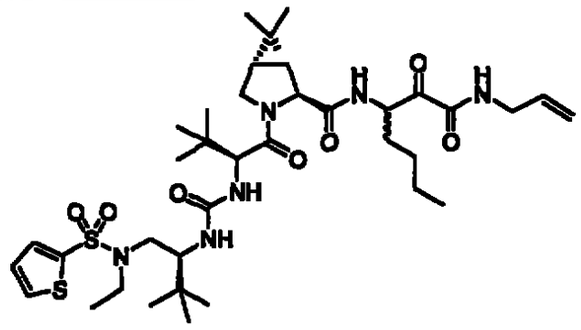
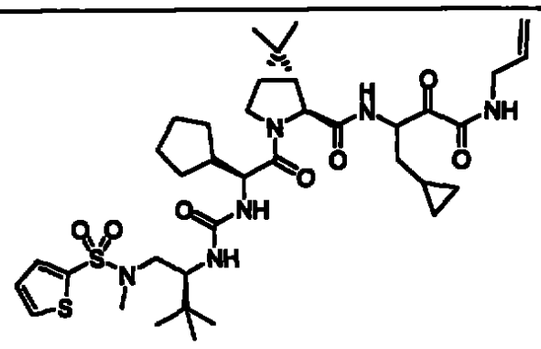
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11213		B
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11216		B

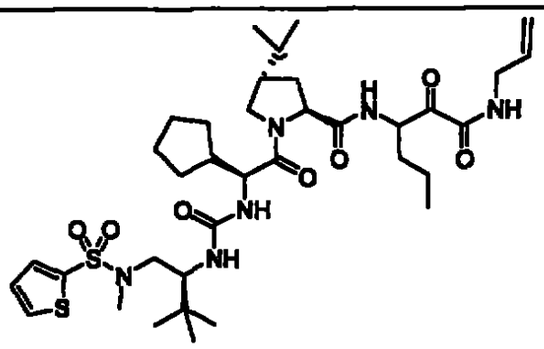
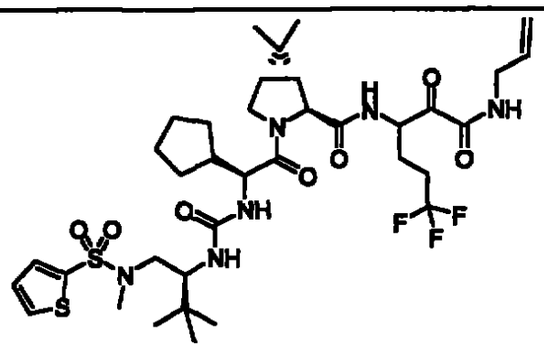
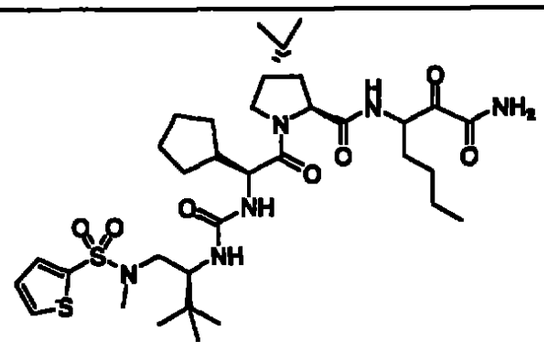
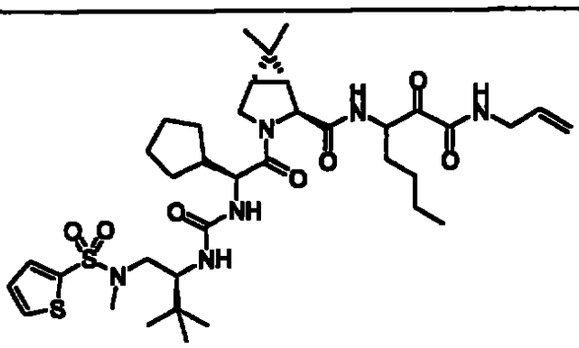
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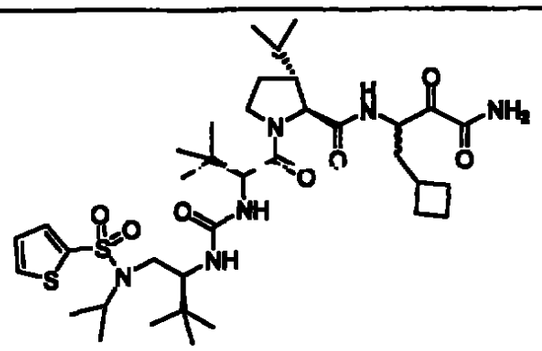
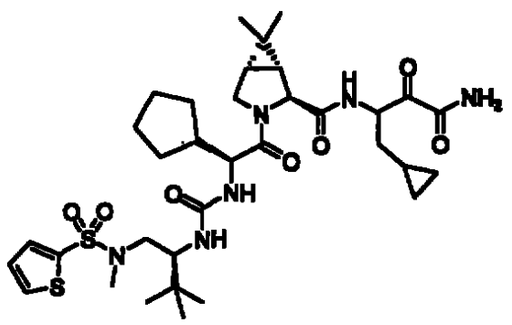
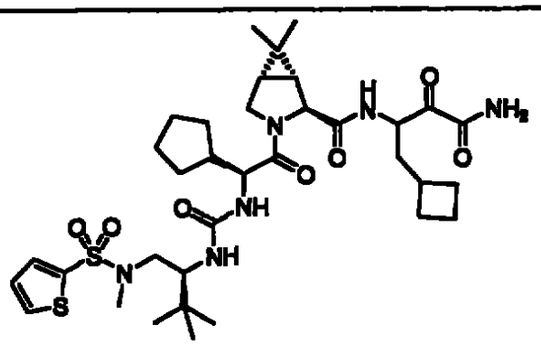
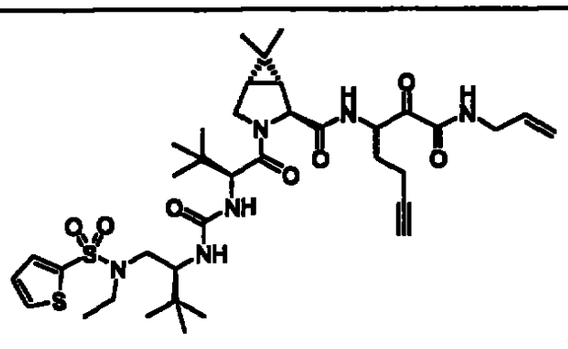
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11220		A

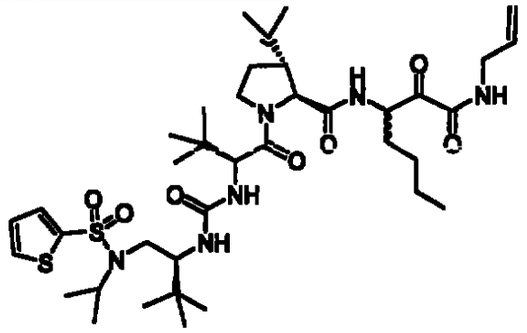
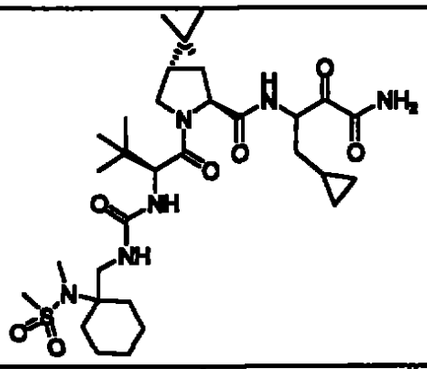
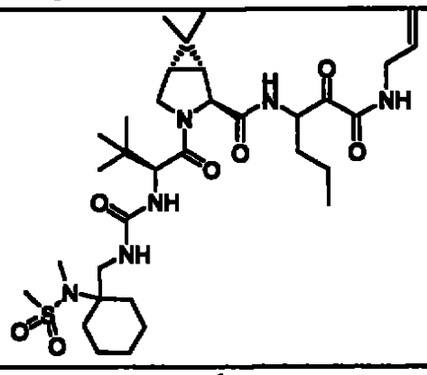
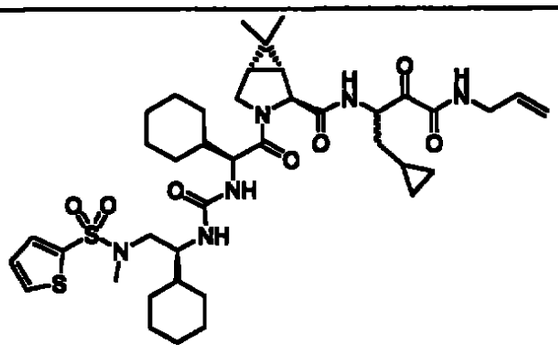
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11224		B

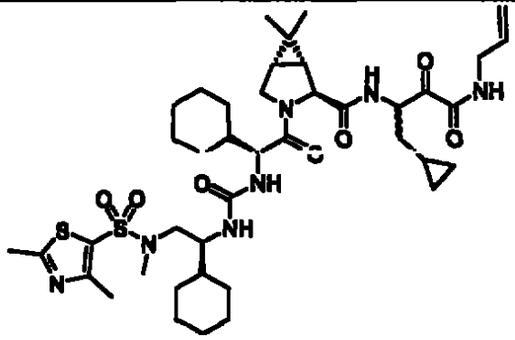
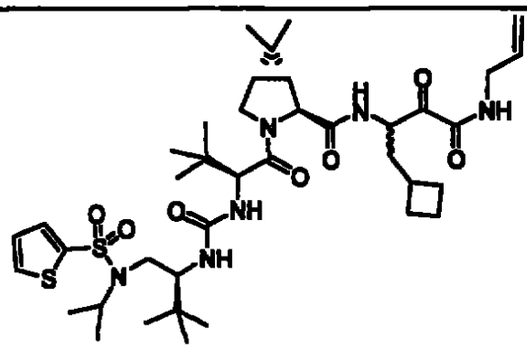
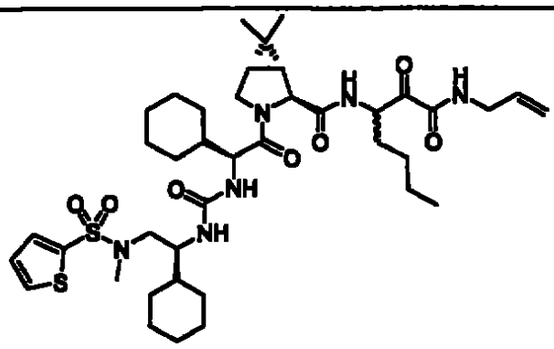
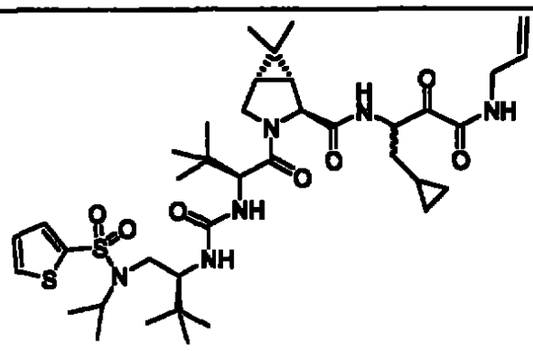
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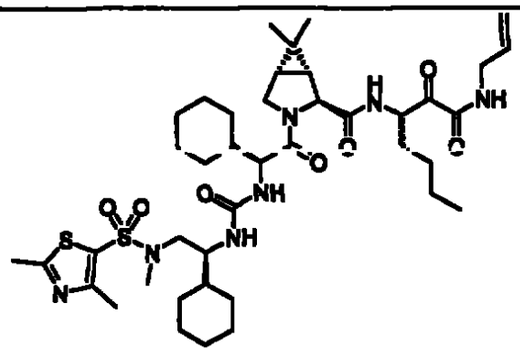
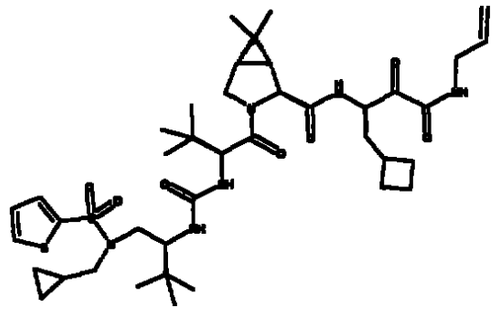
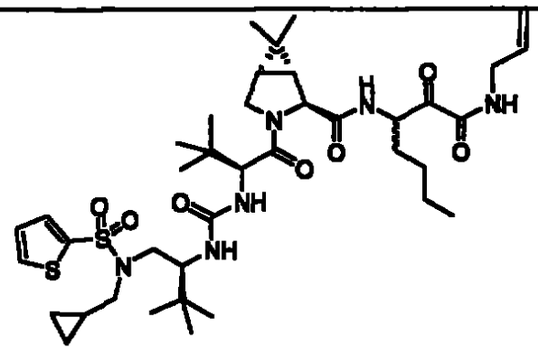
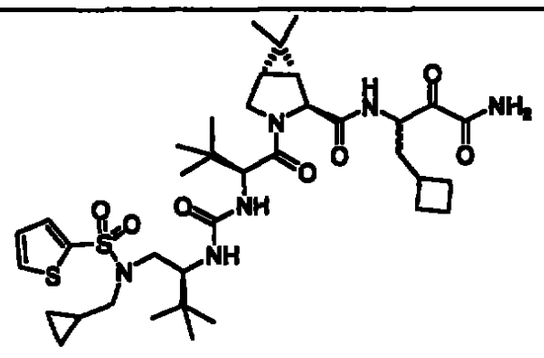
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11228		A

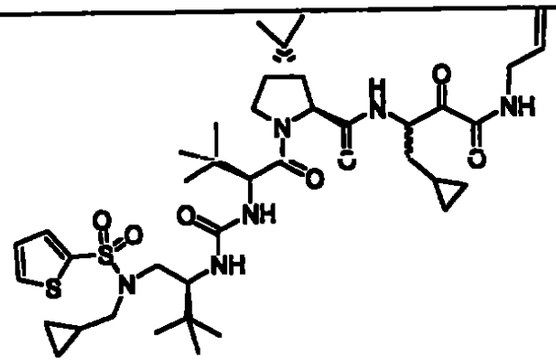
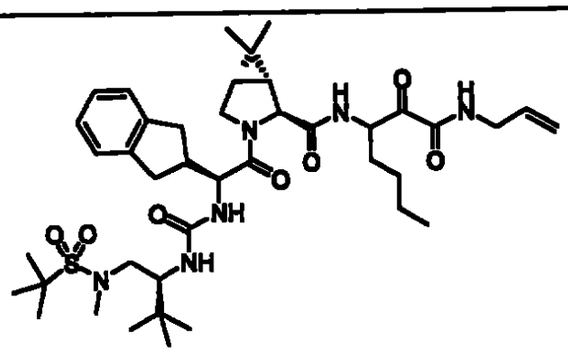
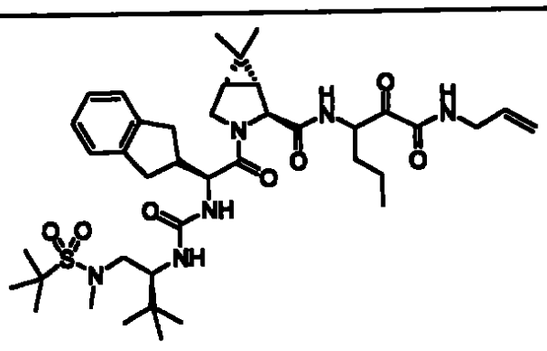
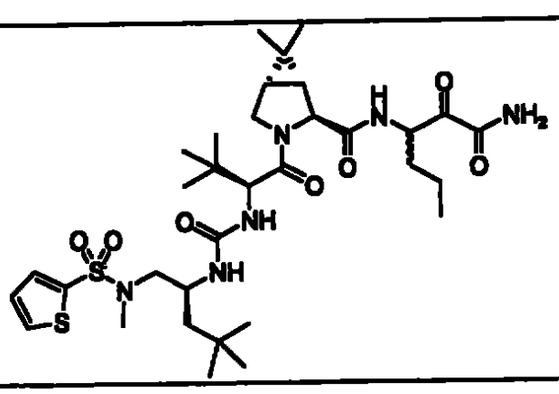
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11235		A
11236		A

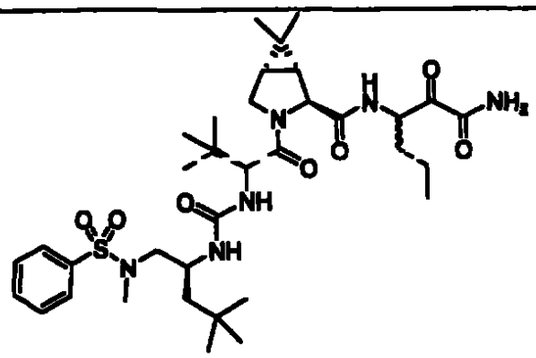
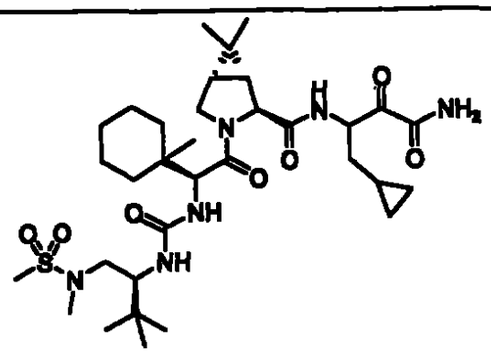
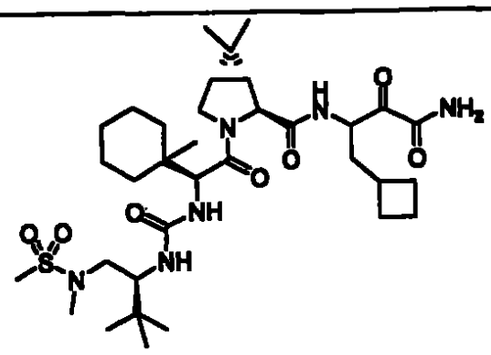
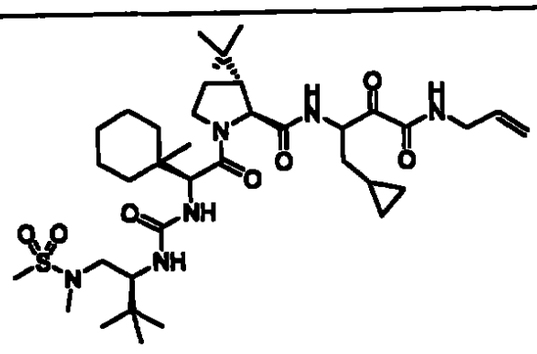
366
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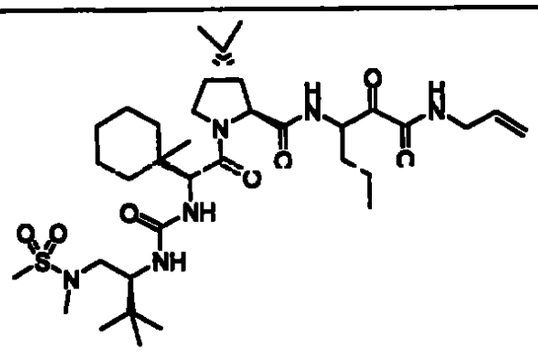
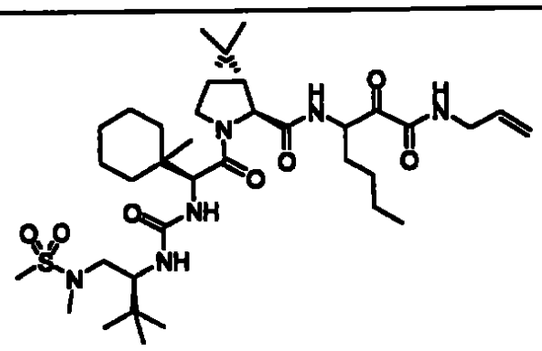
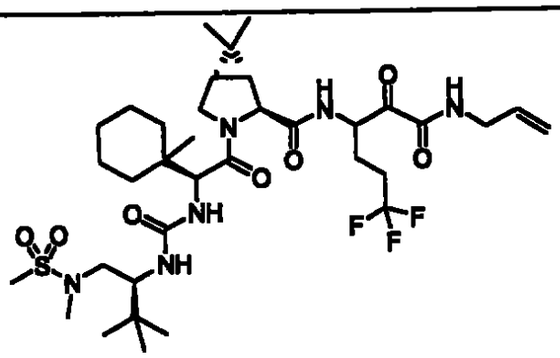
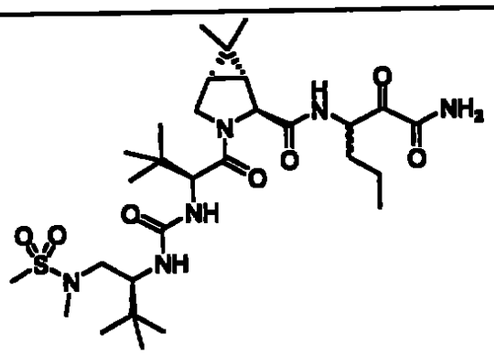
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11240		A

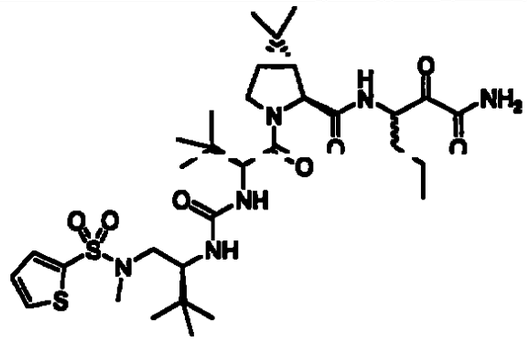
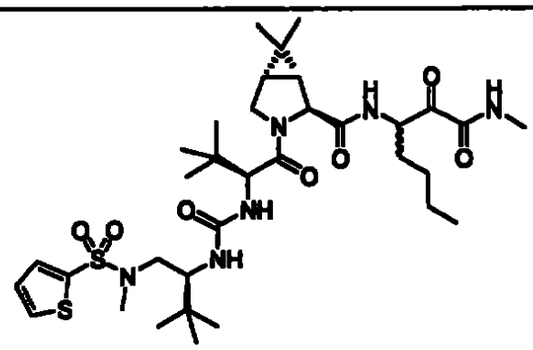
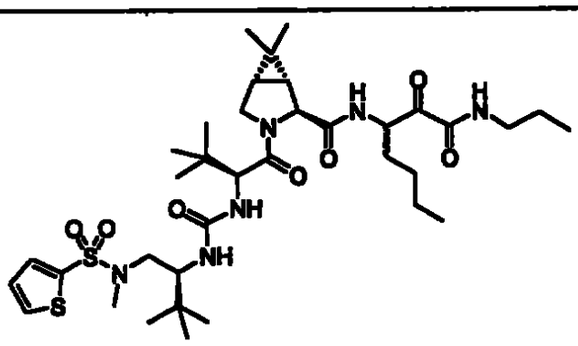
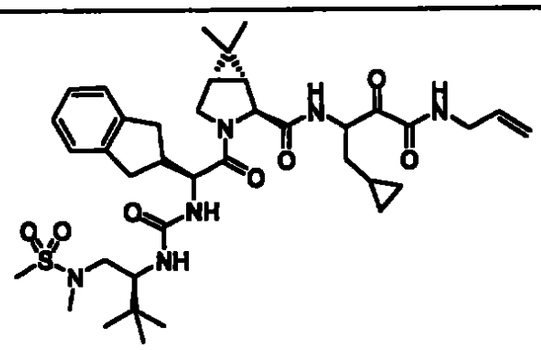
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11245		A

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11249		A

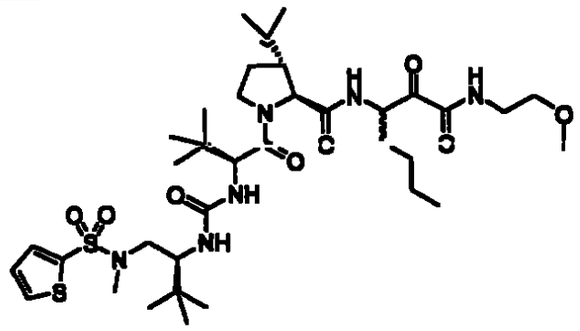
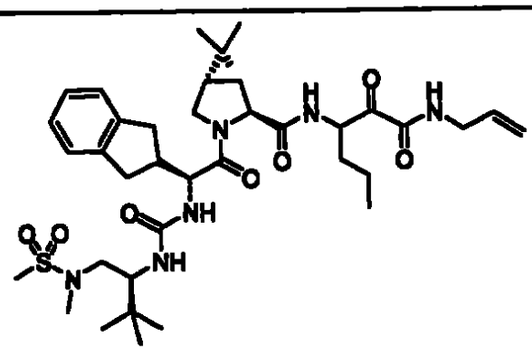
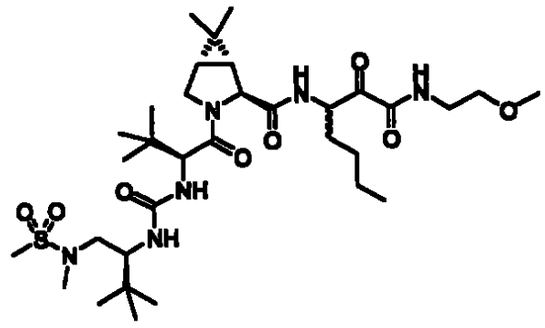
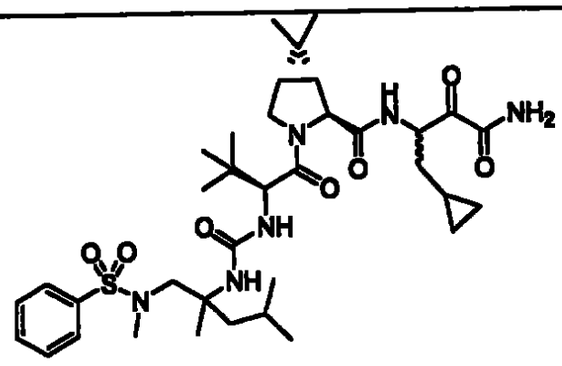
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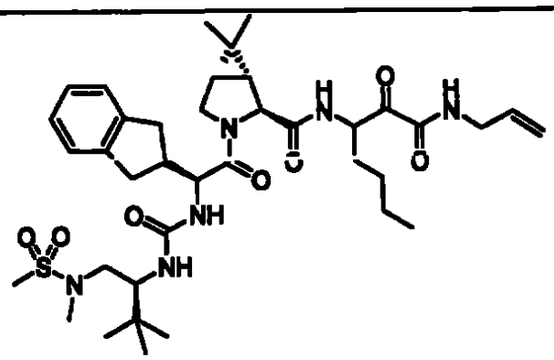
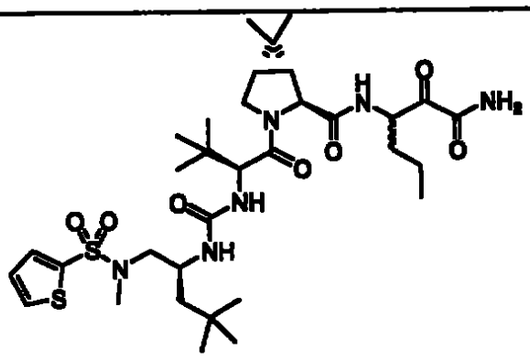
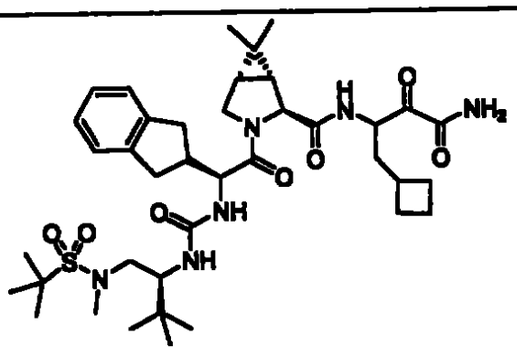
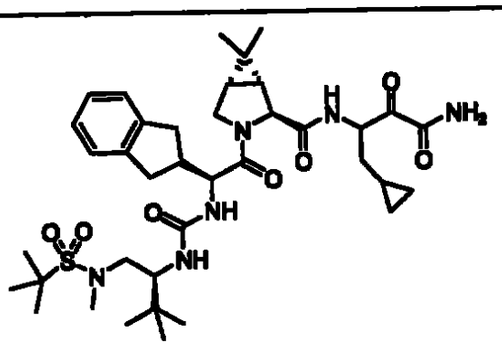
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11253		A

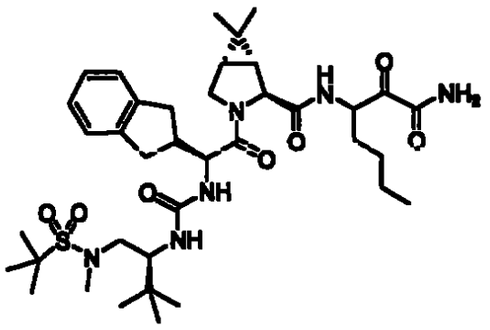
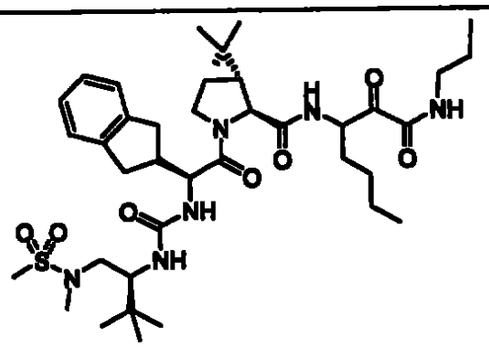
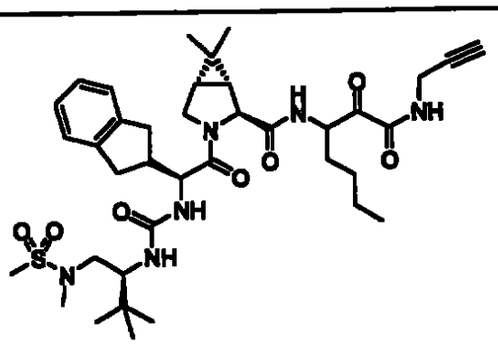
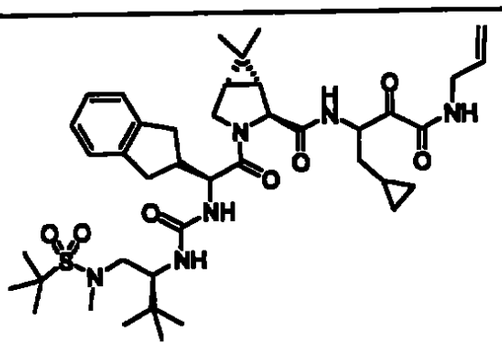
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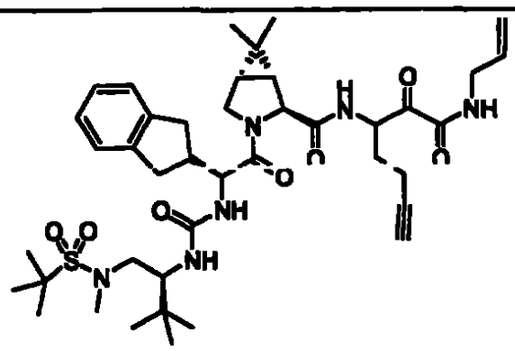
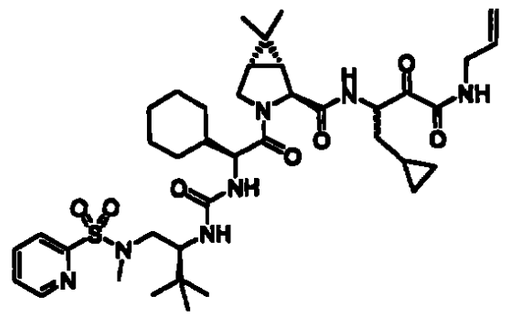
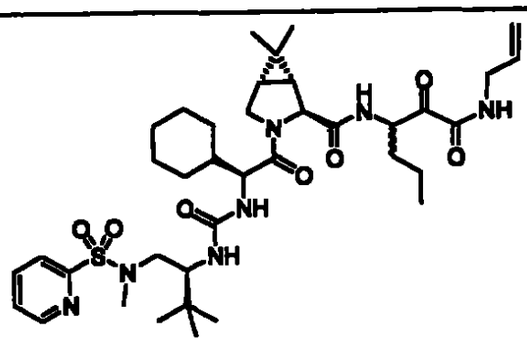
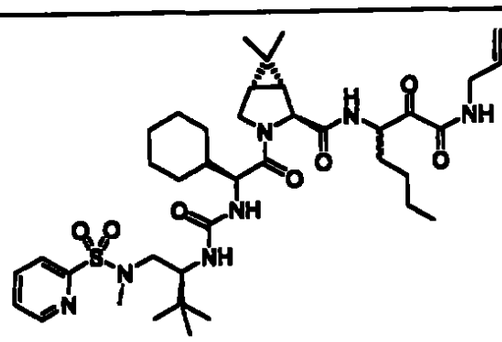
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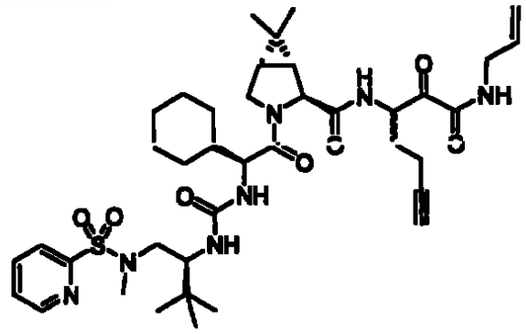
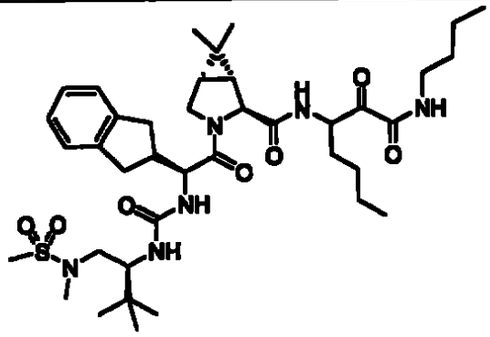
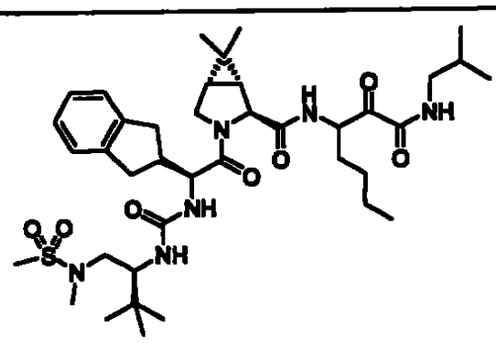
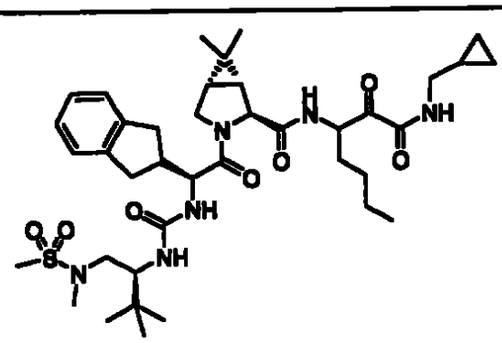
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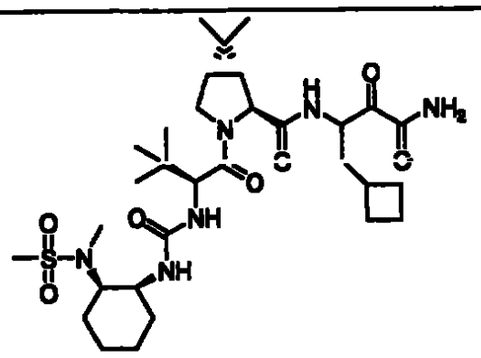
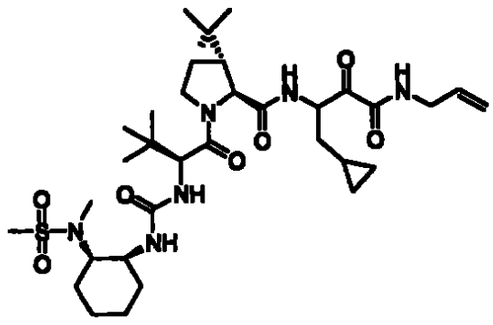
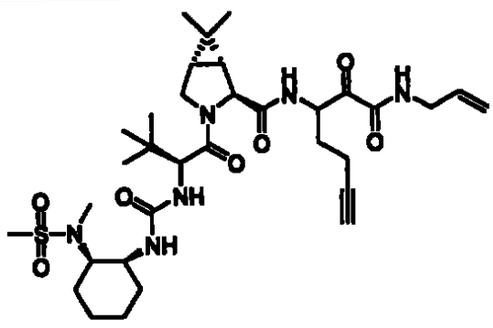
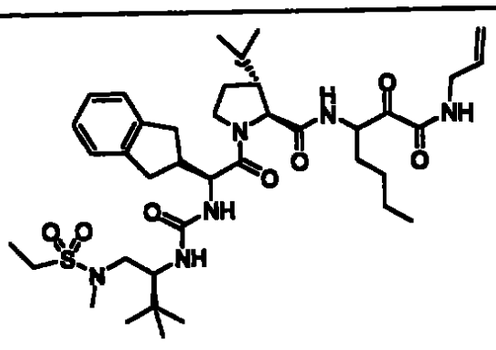
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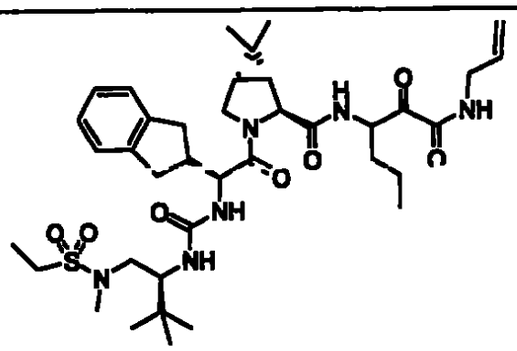
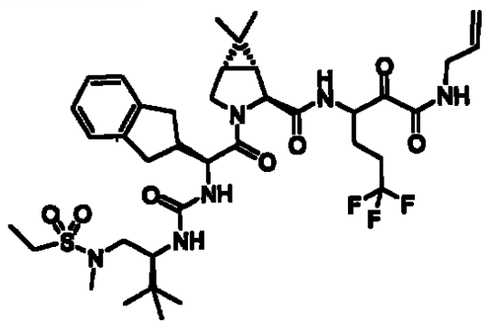
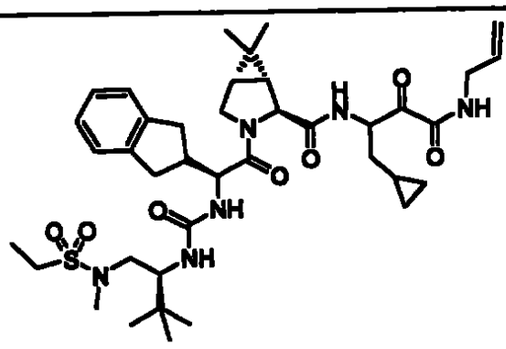
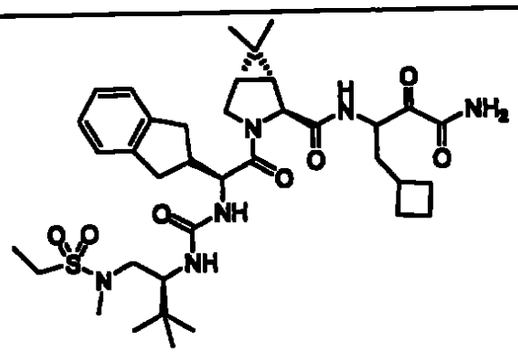
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11269		A

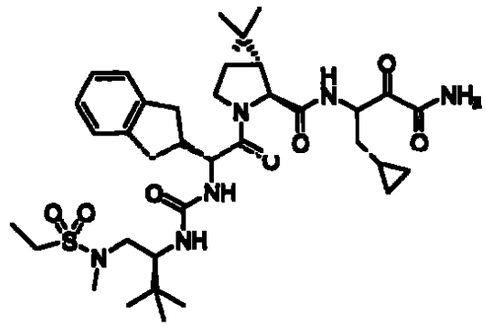
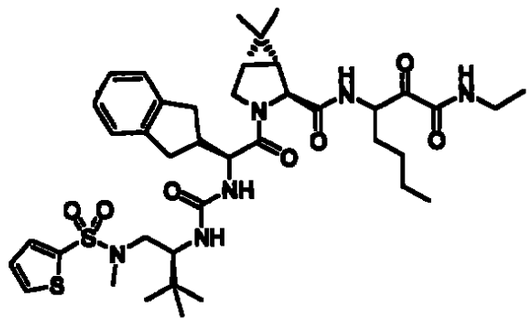
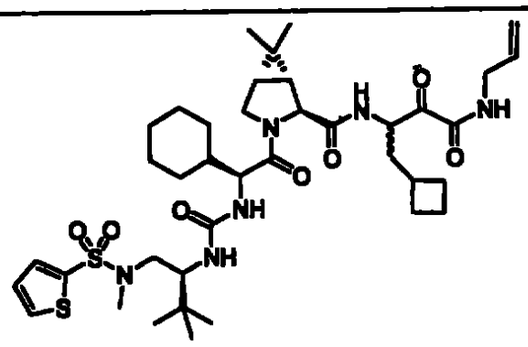
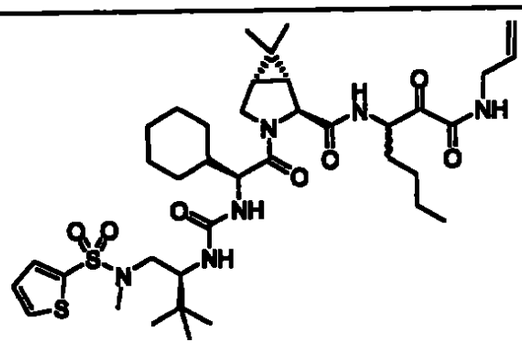
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11273		B

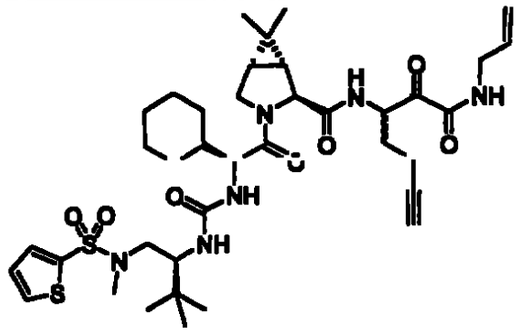
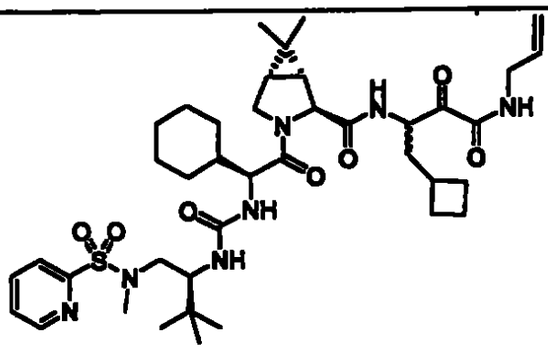
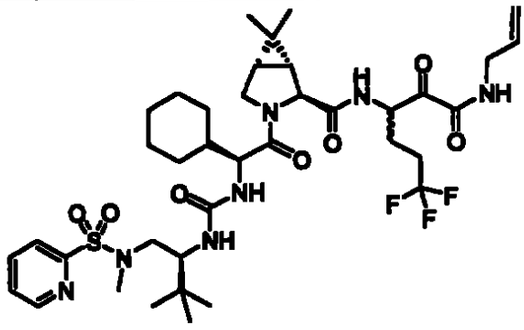
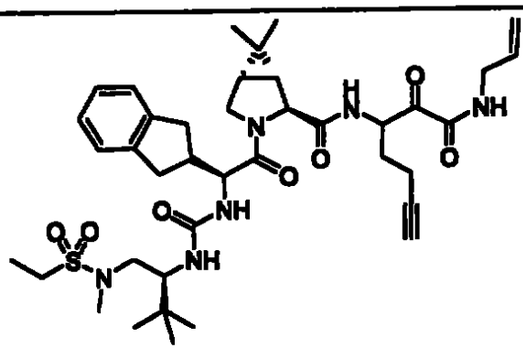
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11281		A

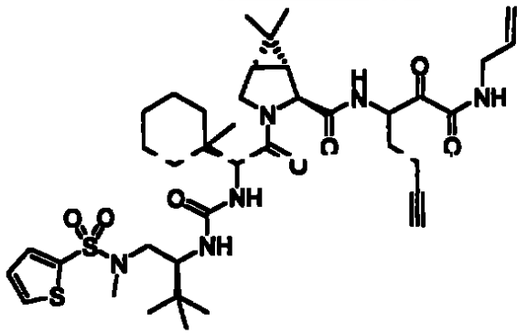
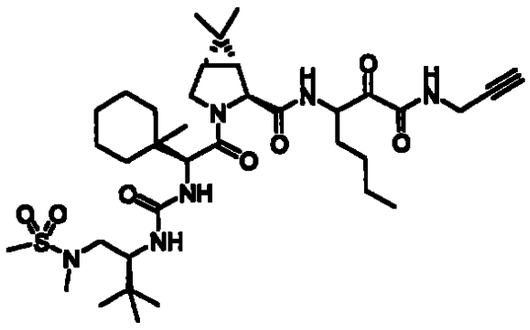
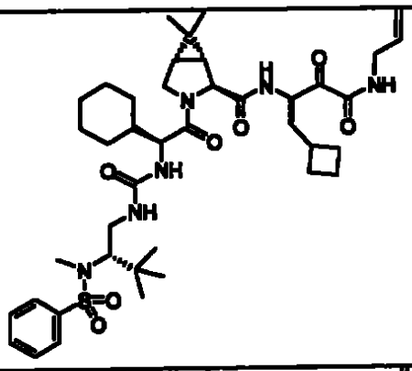
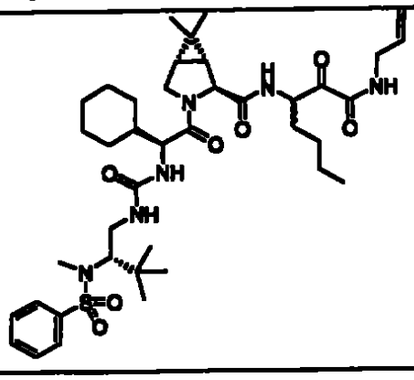
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11289		A

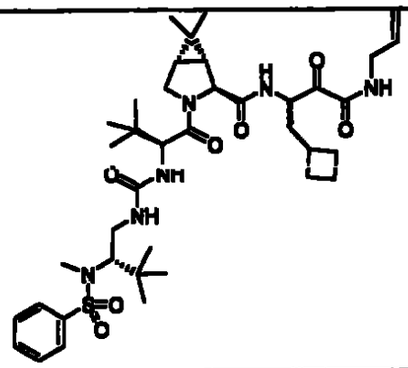
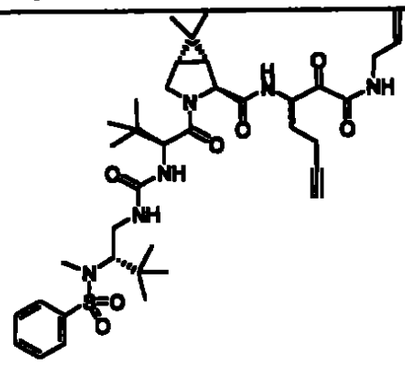
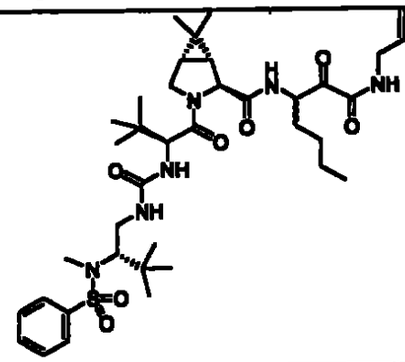
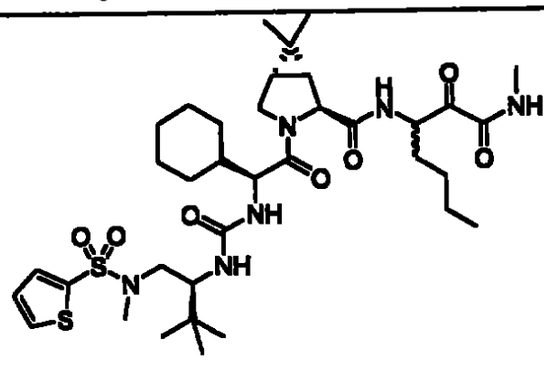
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11293		A

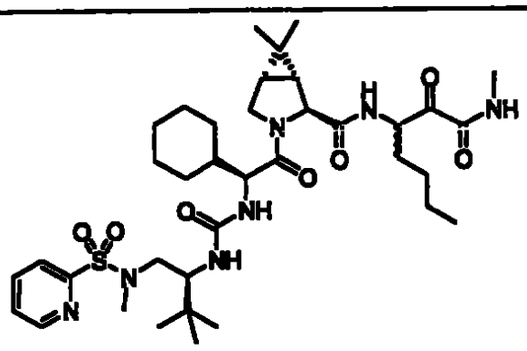
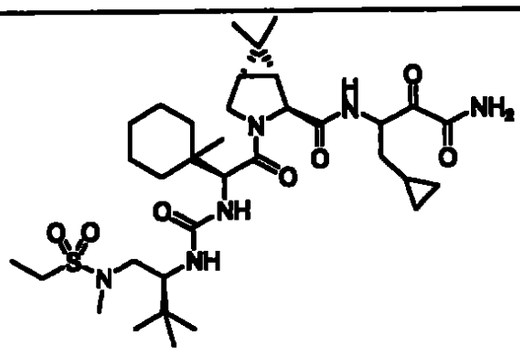
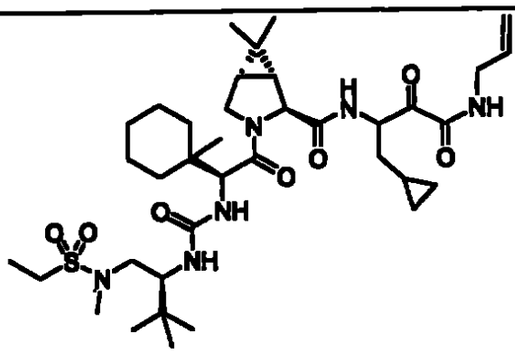
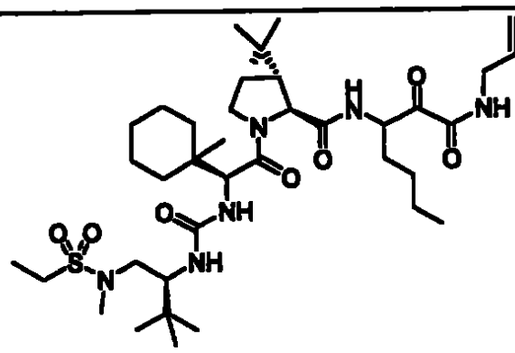
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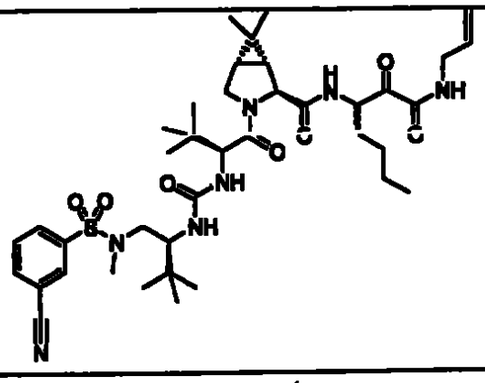
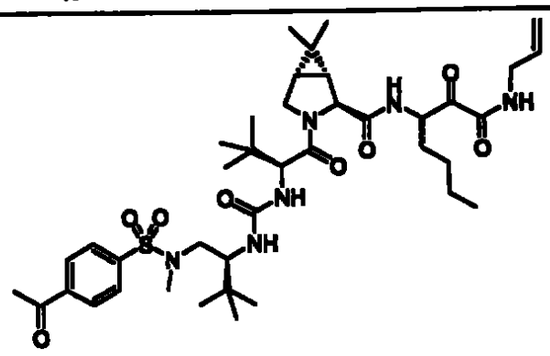
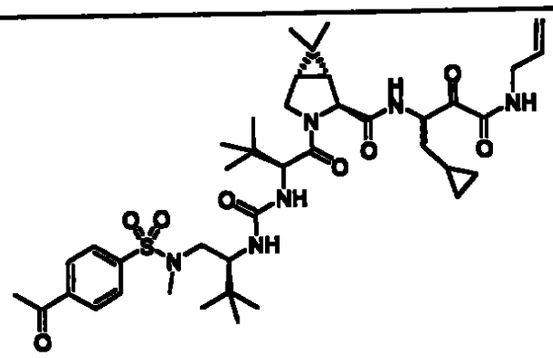
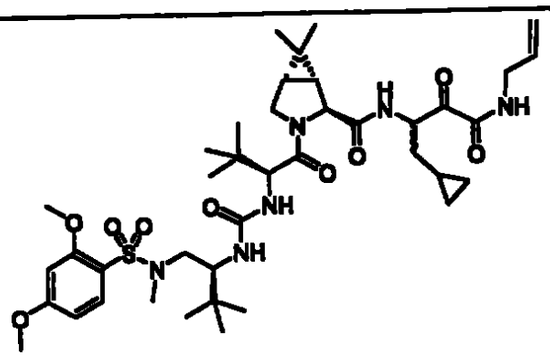
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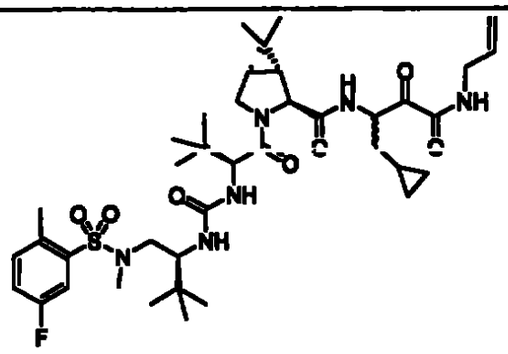
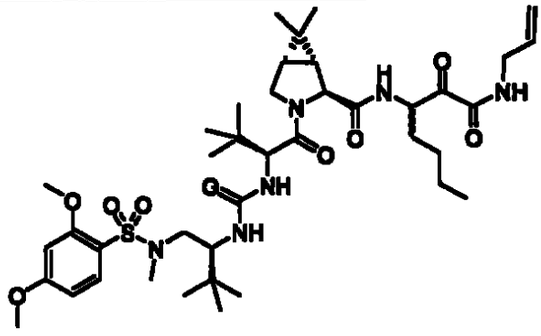
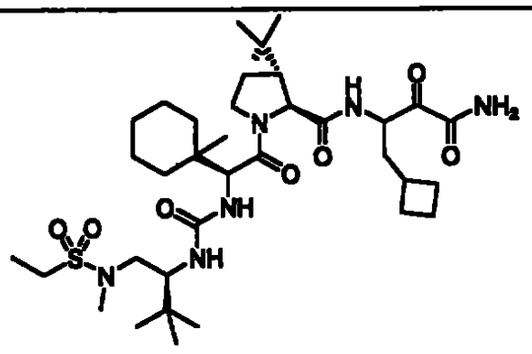
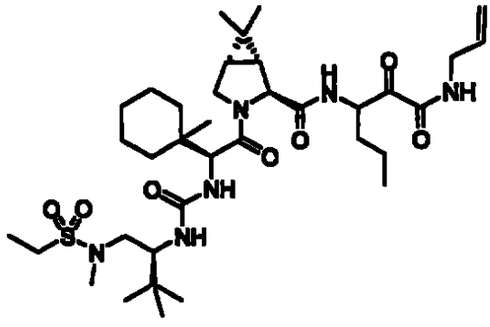
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11311		C

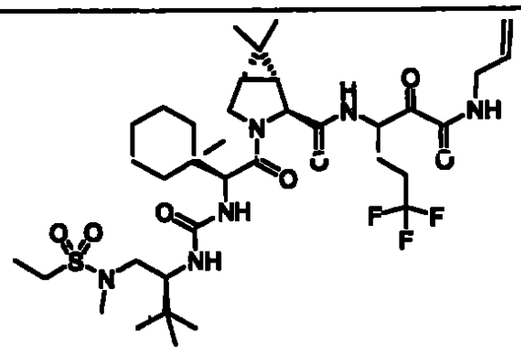
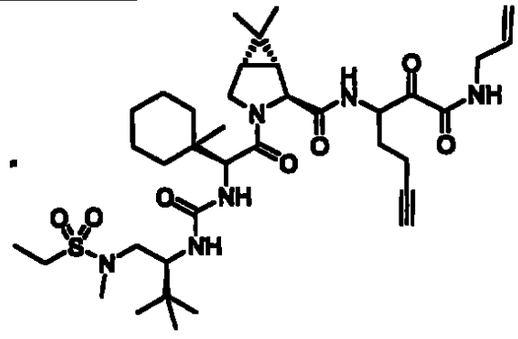
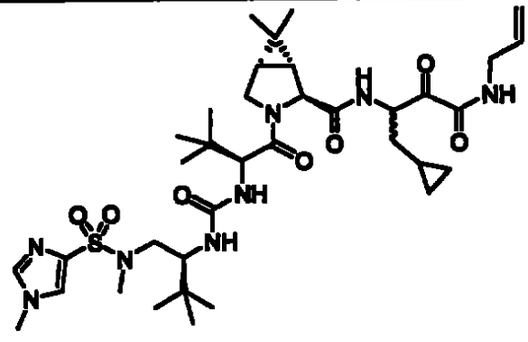
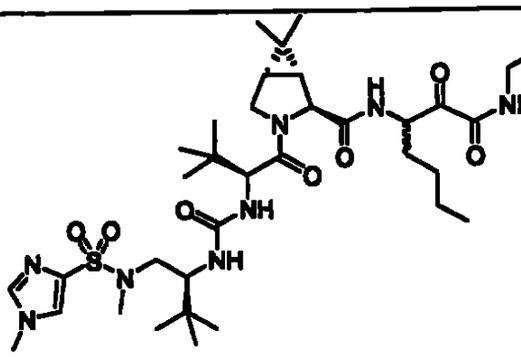
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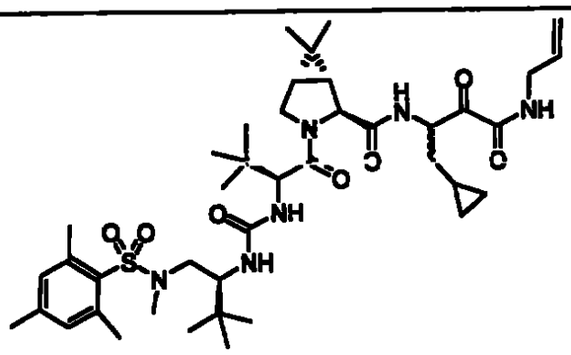
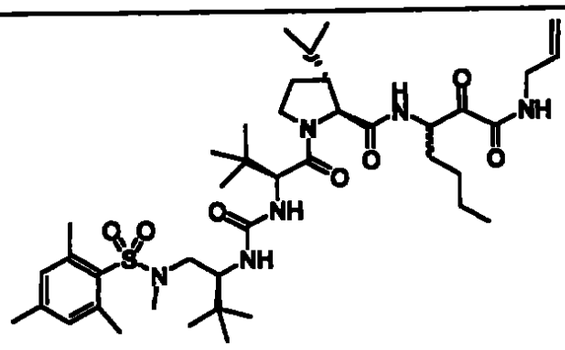
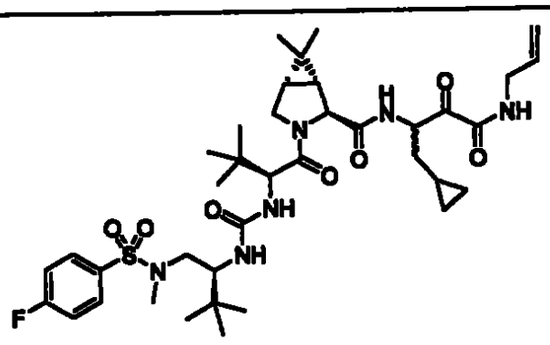
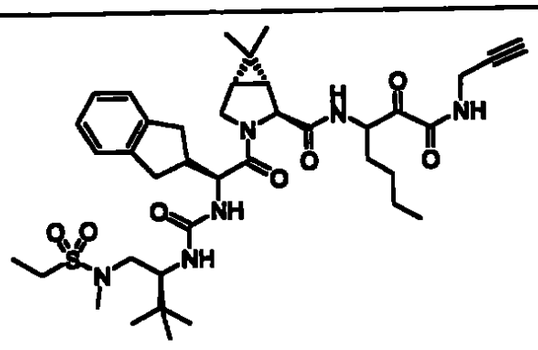
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11314		C
11315		A

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11319		A

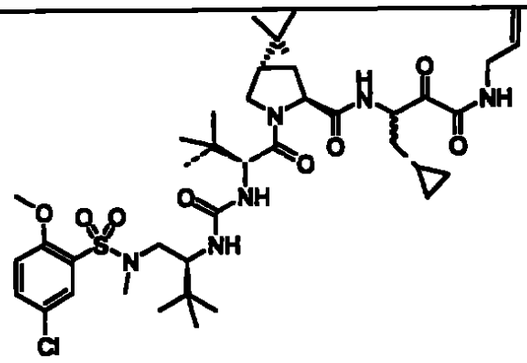
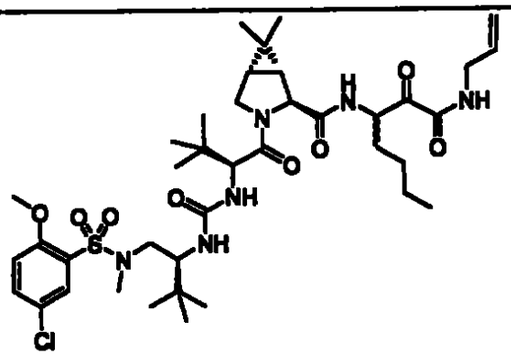
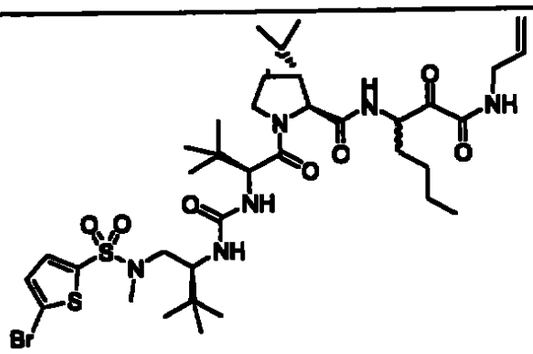
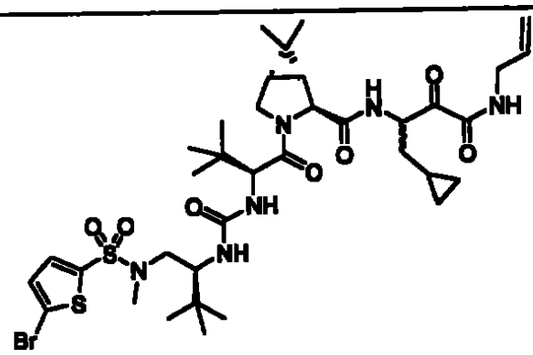
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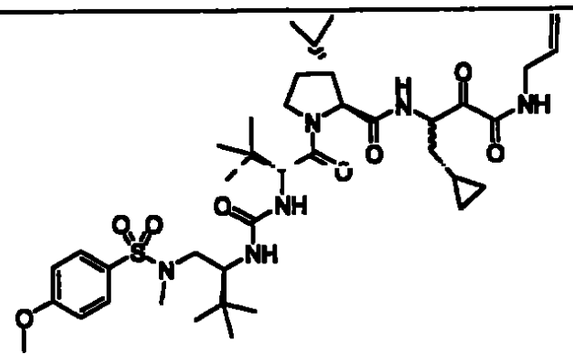
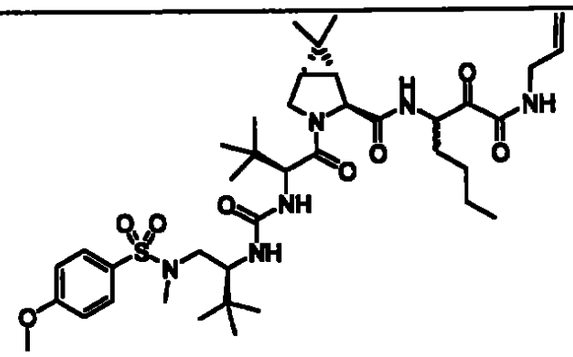
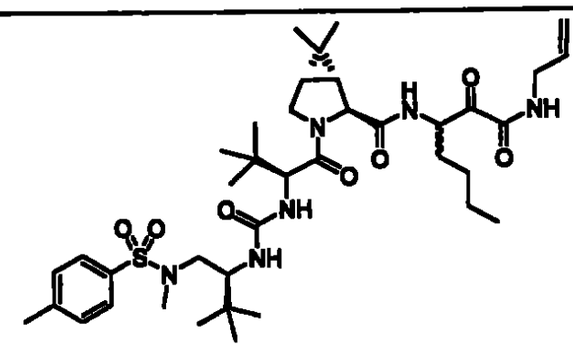
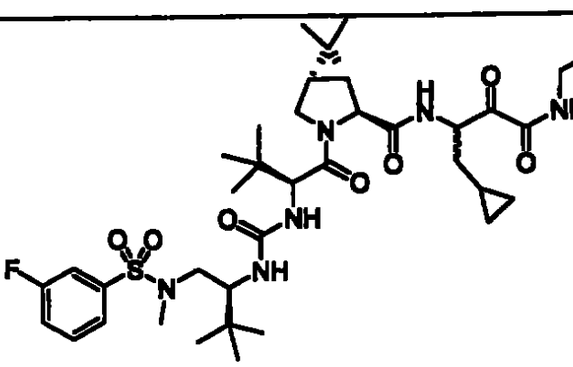
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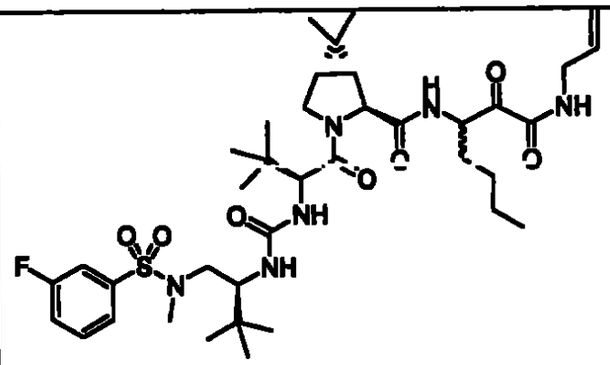
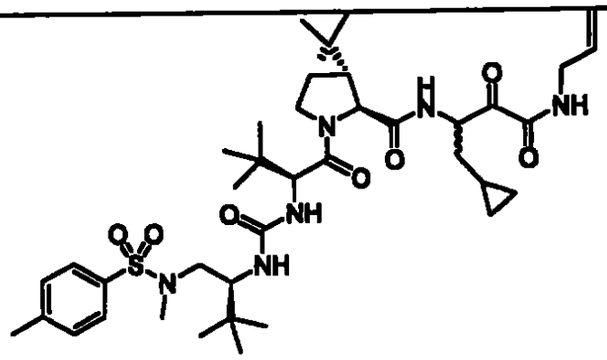
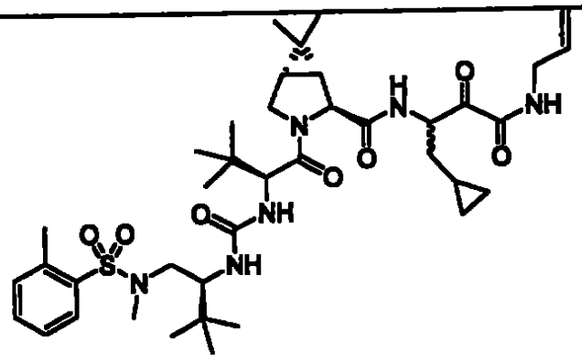
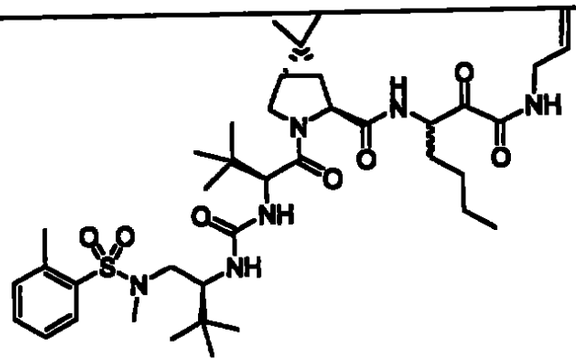
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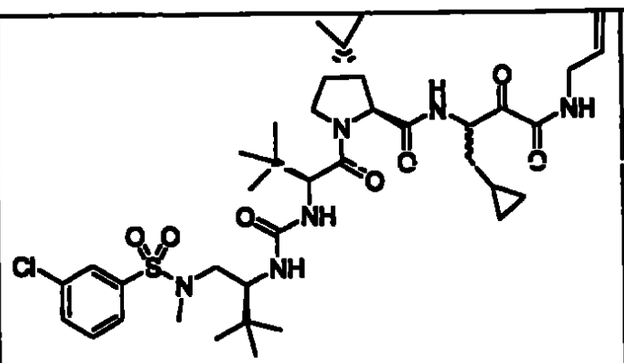
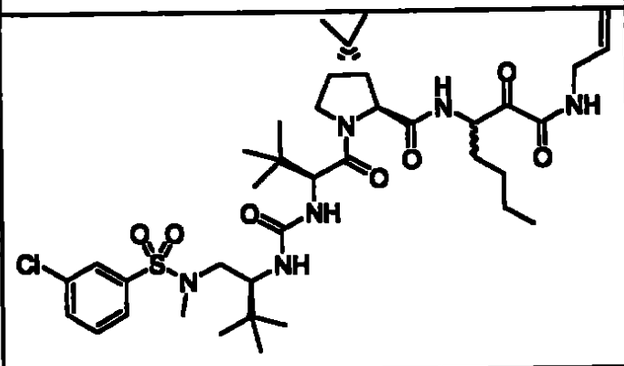
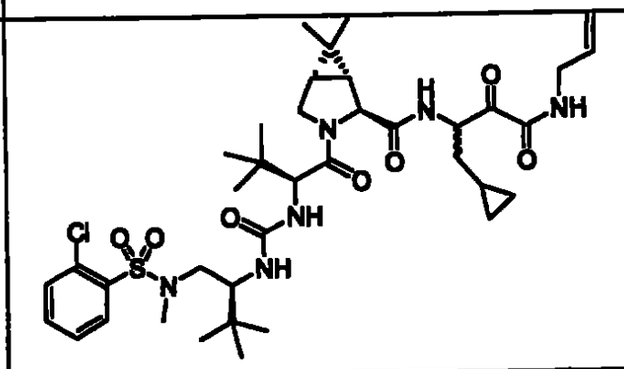
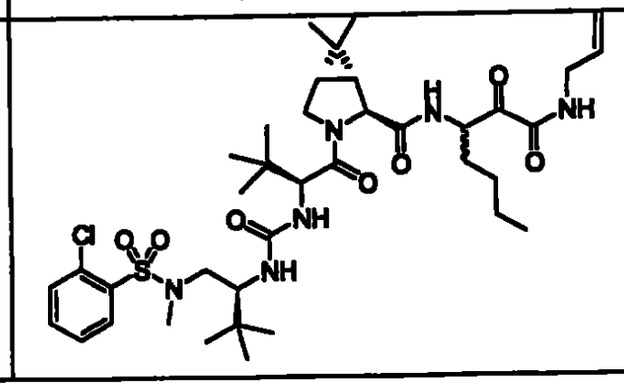
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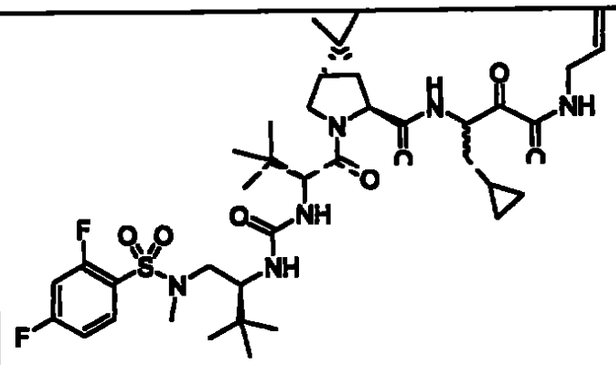
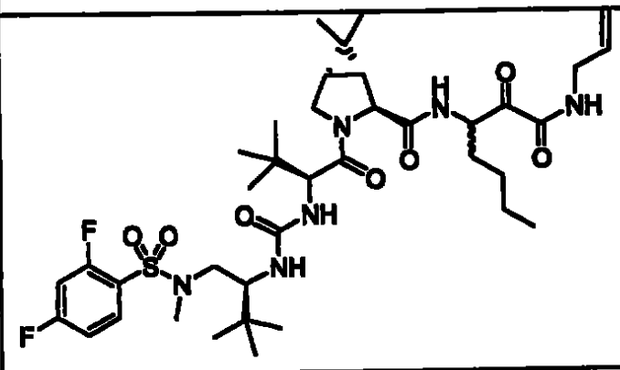
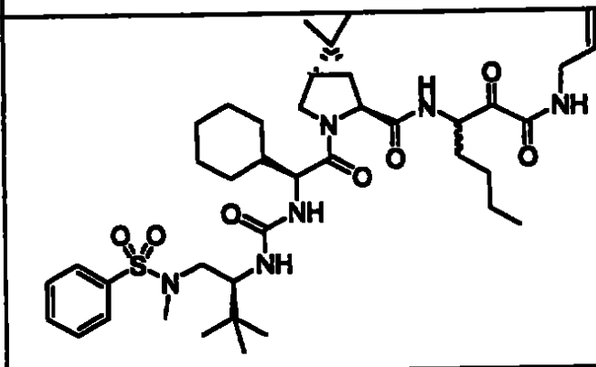
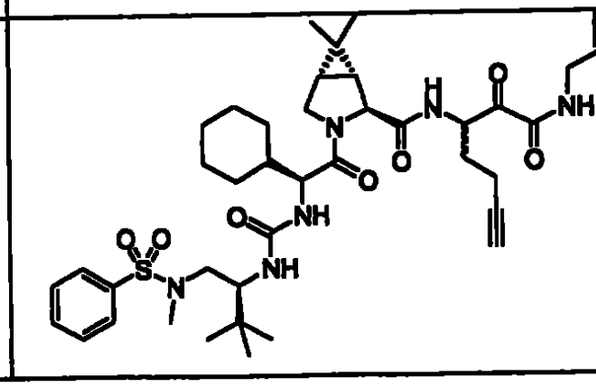
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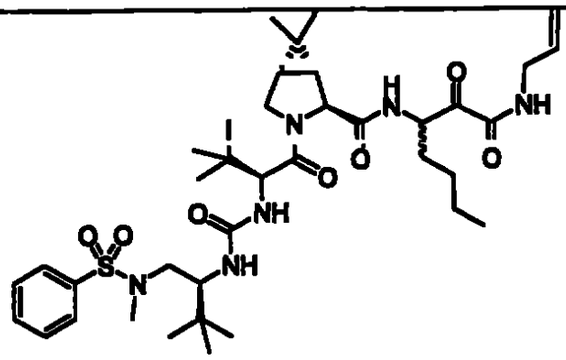
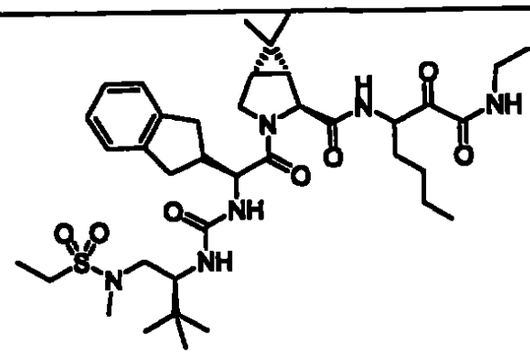
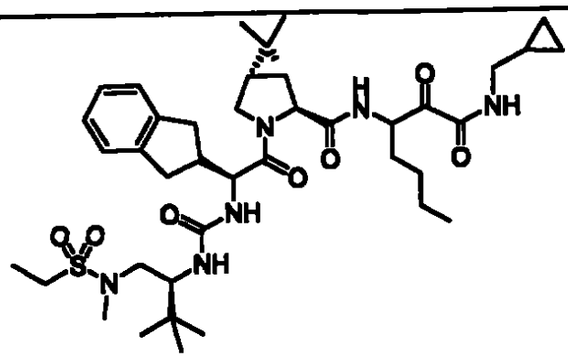
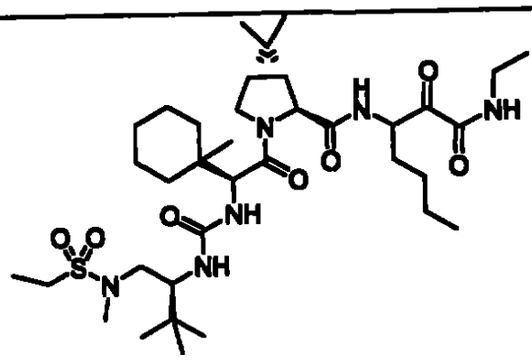
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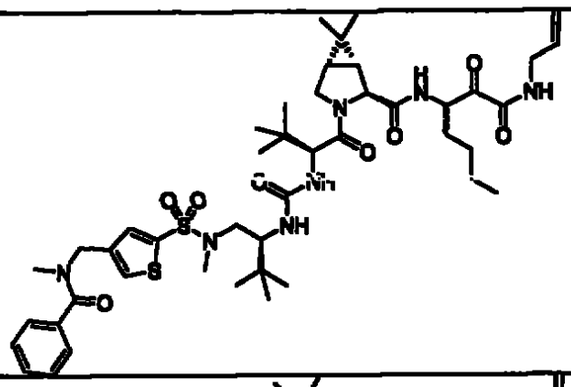
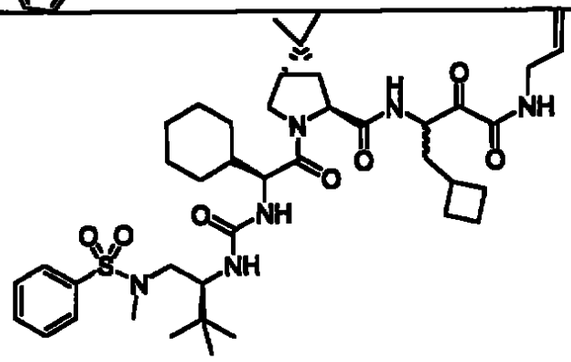
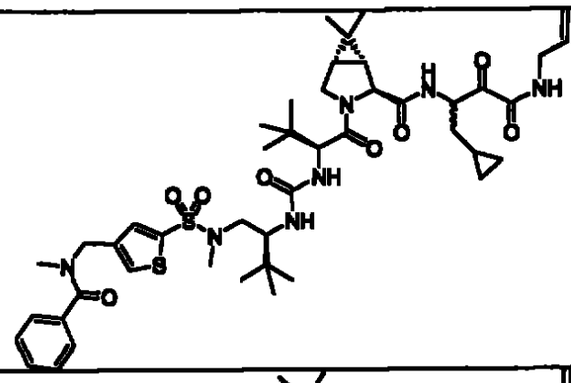
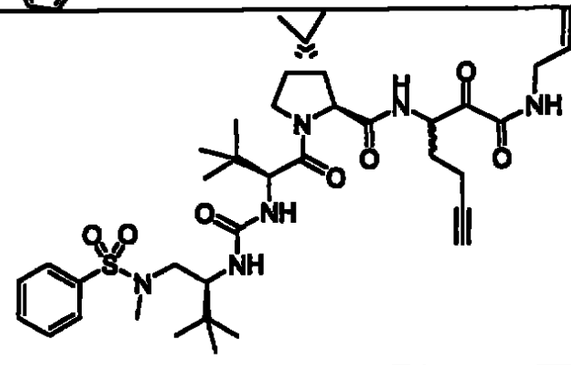
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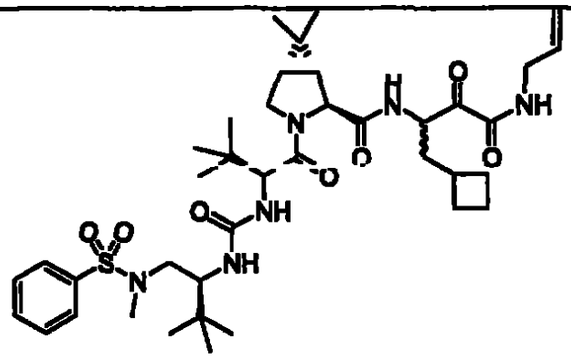
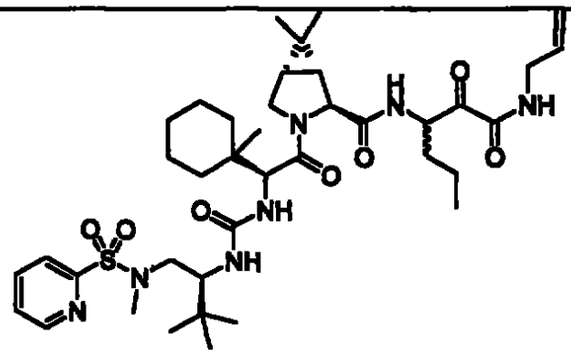
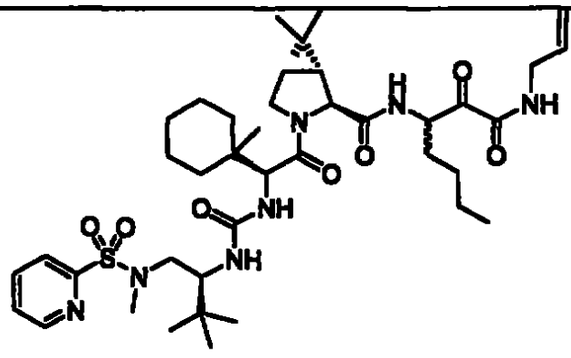
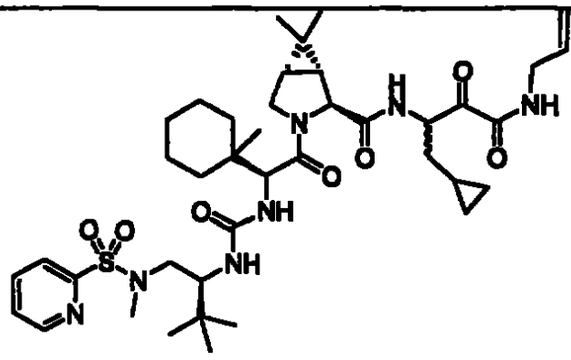
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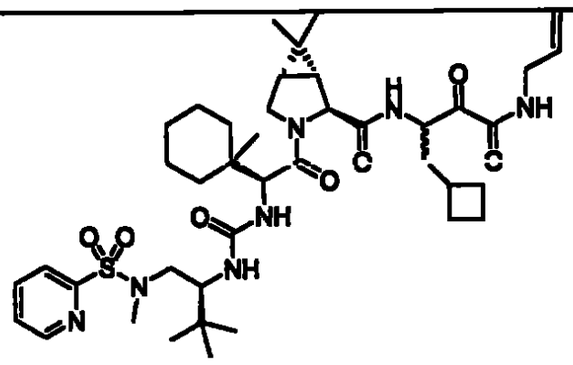
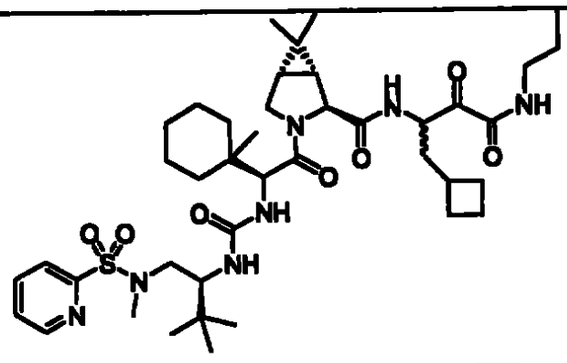
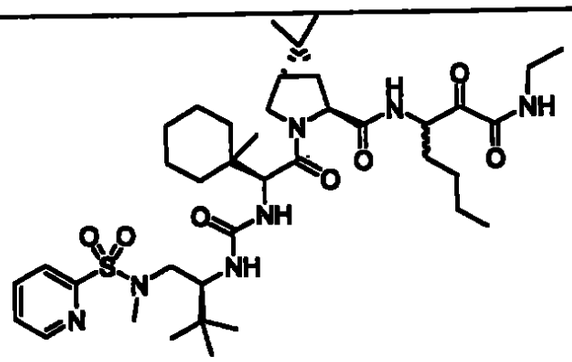
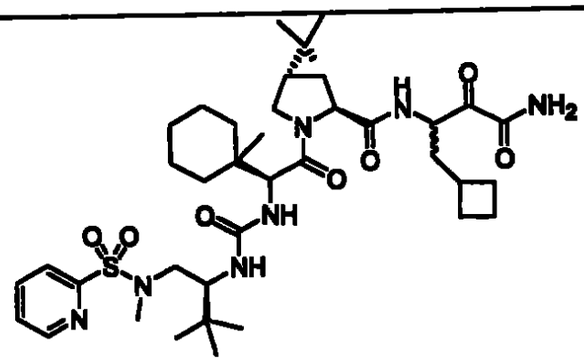
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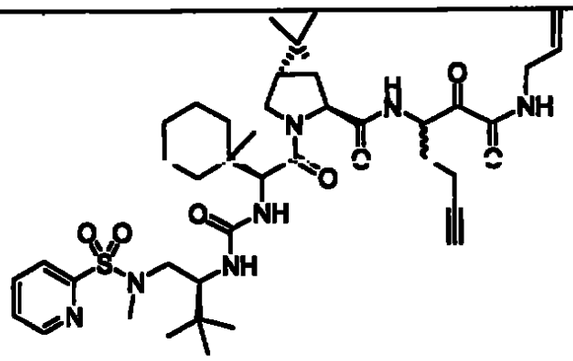
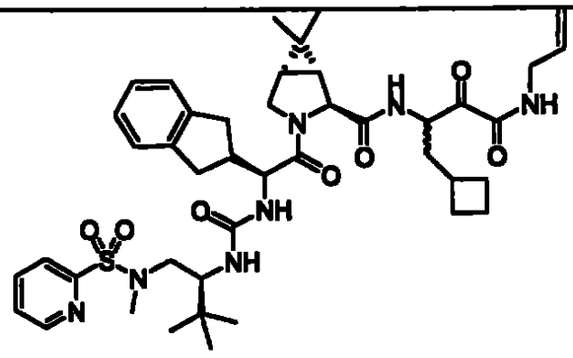
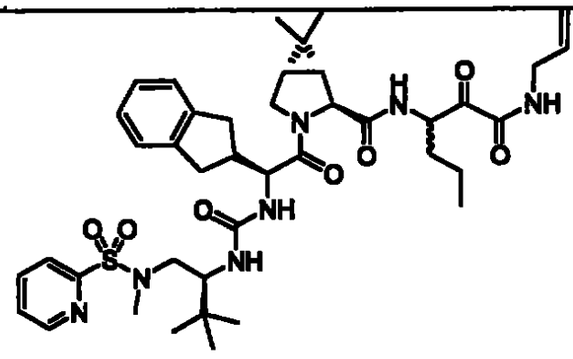
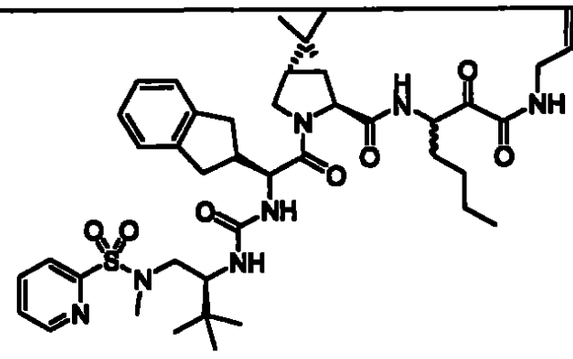
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11359		A

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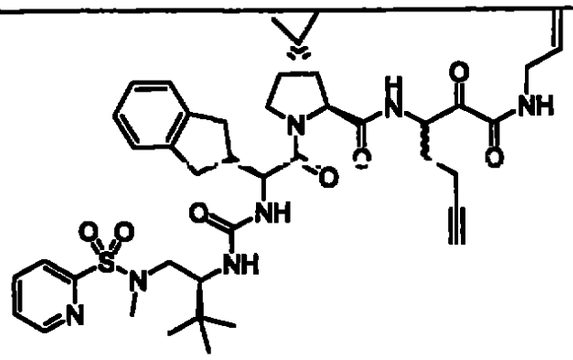
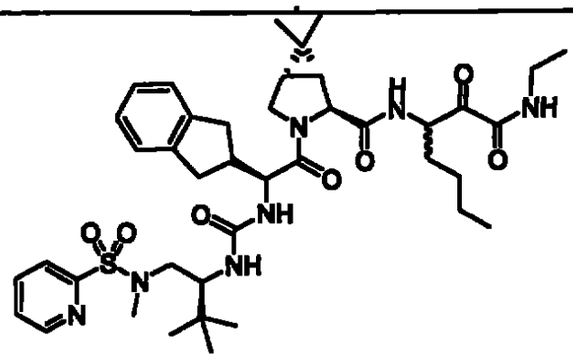
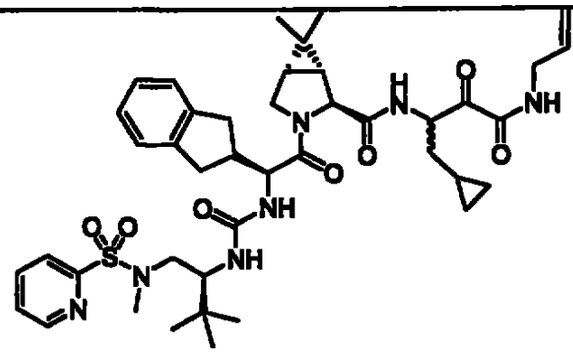
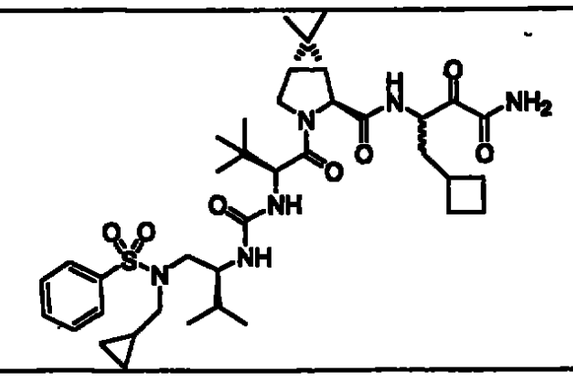
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11363		A

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11365		A
11366		A
11367		A

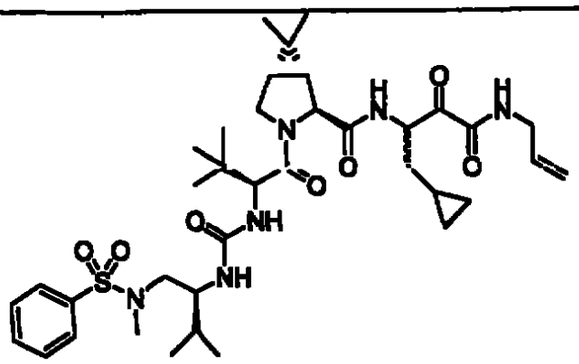
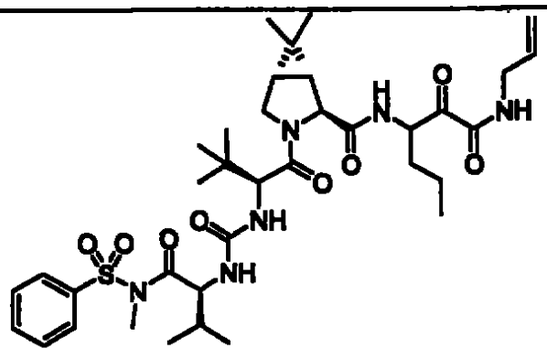
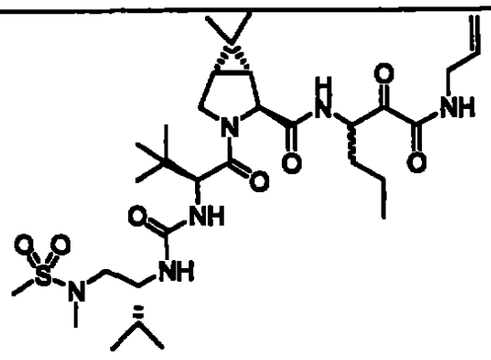
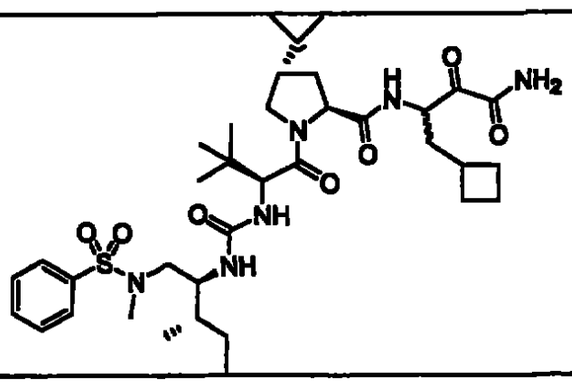
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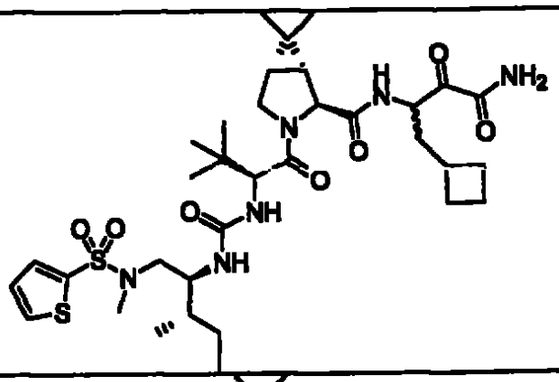
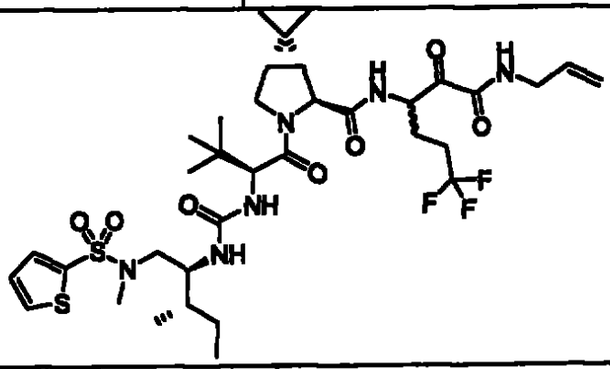
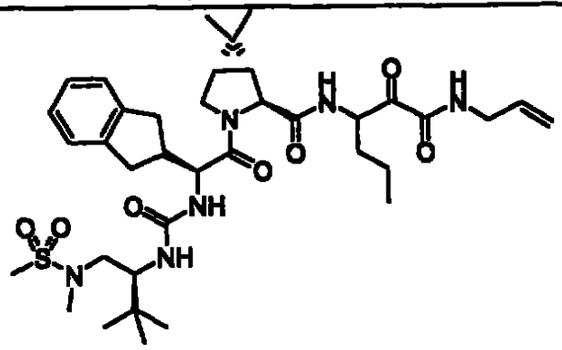
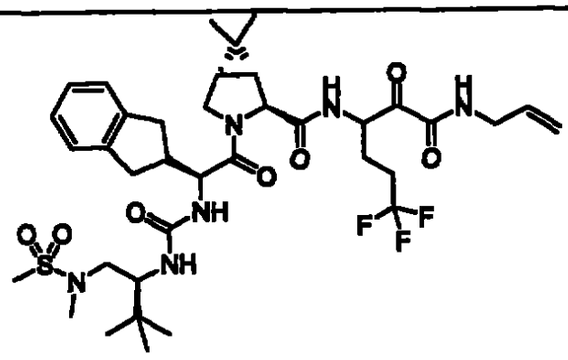
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11375		A

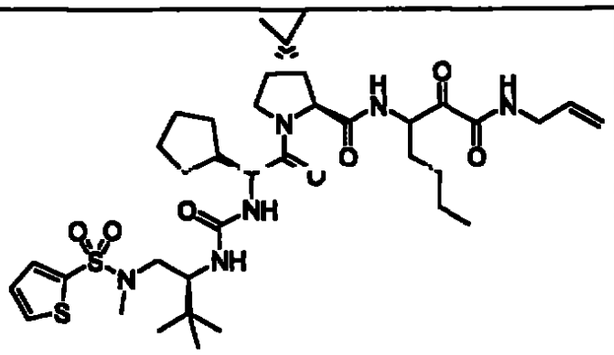
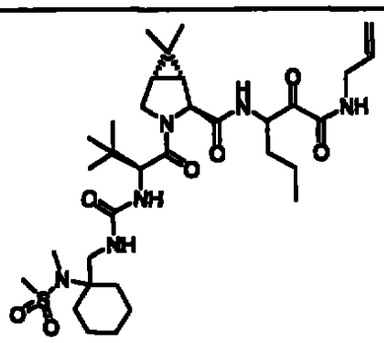
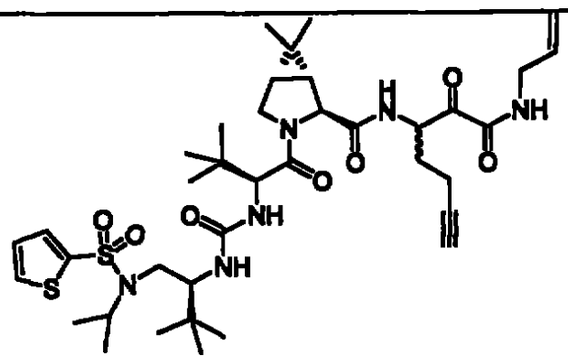
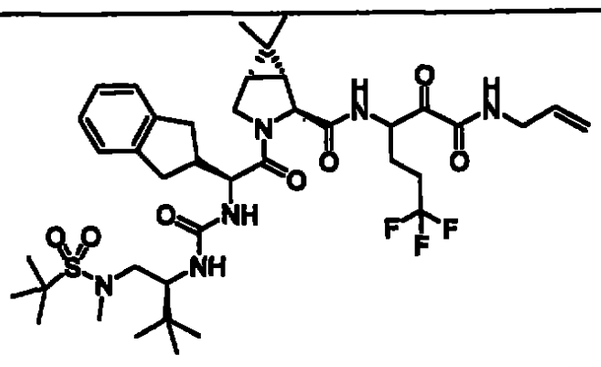
396
398

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11377		A
11378		B
11379		A

397
399

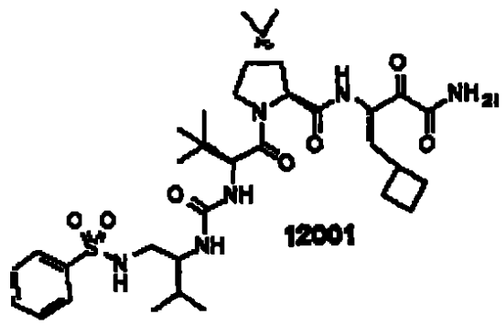
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11383		A

11384		A
11385		A
11386		A
11387		A

11388		A
11389		C
11390		A
11391		B

406
402

Ejemplo-10 Síntesis del Compuesto de la Fórmula 12001



12001

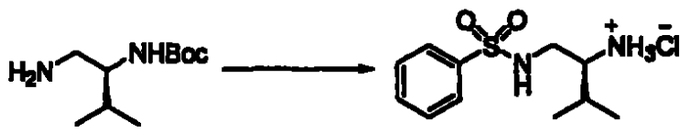
Paso A



12001a 12001b

Una solución de 12001a (2,0 g, 9,2 mmol, productos químicos Indofine) en tolueno (150 mL) se trató con BH_3•DMS (~ 10 M, 3 mL) y se calentó a 90°C durante 2 h La mezcla de reacción se enfrió hasta 0° C y se diluyó con NaOH ac. 2 M La capa orgánica se extrajo con CH_2Cl_2 y las capas orgánicas combinadas se secaron ($MgSO_4$) se filtraron y concentraron in *vacuo* para proporcionar 1,1 g de 12001b

Paso B



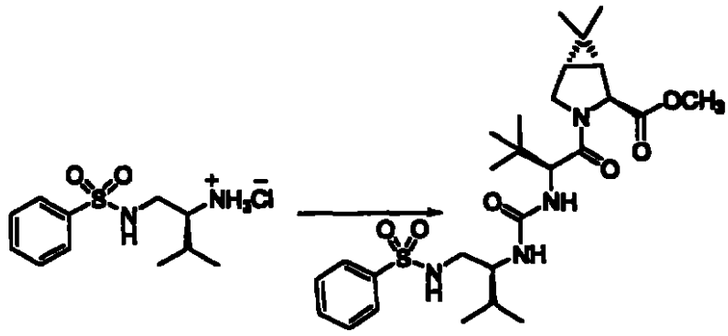
12001b 12001c

Una solución de la amina 12001b (500 mg, 2,5 mmol) en CH_2Cl_2 (10 mL) se trató con cloruro de bencensulfonilo (669 mg, 3,8 mmol) y Et_3N (384 mg, 3,8 mmol) y se agitó durante la noche a 0°C La mezcla de reacción se diluyó con HCl ac. 1 M y se extrajo con CH_2Cl_2 La capa orgánica combinada se secó, se filtró y se concentró

in *vacuo* El residuo se purificó mediante cromatografía (SiO_2, EtOAc/Hexanos 1 3) para proporcionar 552 mg de compuesto fenilsulfonamida protegida con boc.

Una solución del compuesto Boc (552 mg, 1,8 mmol) en HCl 4M en dioxano a temperatura ambiente se agitó durante 1 h y se concentró in *vacuo* El residuo se trituró con éter y el sólido que se separó se aisló mediante decantación de la capa de éter y se secó al vacío para proporcionar **12001c**

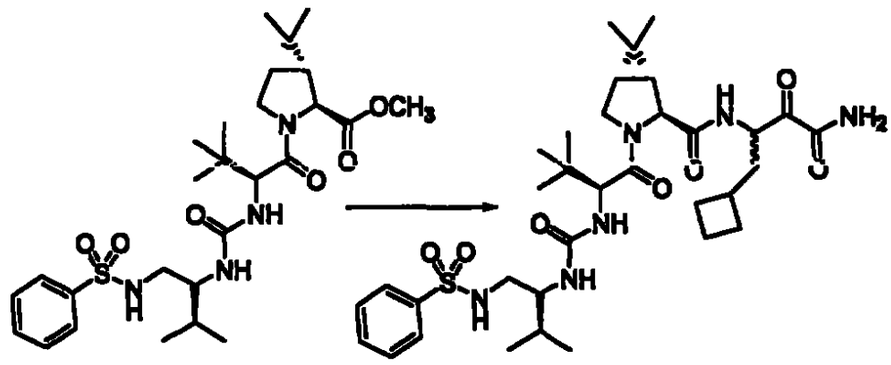
Paso C



12001c **12001d**

Una solución de la amina desprotegida **12001c** (139 mg, 0,5 mmol) en CH_2Cl_2/DMF (1 1, 20 mL) se trató con 4-nitrofenilcarbamato **1.16** (1,879 g, 4,20 mmol), NMM (1,062 g, 10,5 mmol) y se agitó a temperatura ambiente durante la noche La mezcla de reacción se concentró in *vacuo* y se diluyó con CH_2Cl_2 (200 mL) y se lavó con HCl ac (1M, 2x125 mL), $NaHCO_3$ saturado ac. (2x125 mL), salmuera (100 mL), se secó ($MgSO_4$), se filtró, y se purificó mediante cromatografía (SiO_2, Hexanos/EtOAc 1 2) para proporcionar **12001d.**

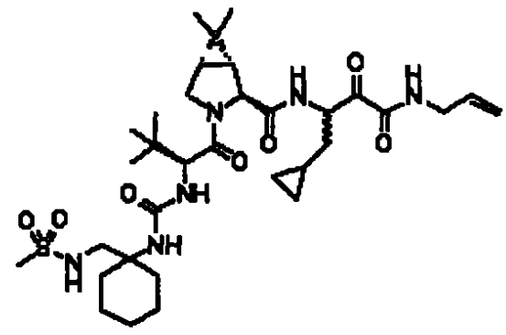
Paso D



12001d 12001

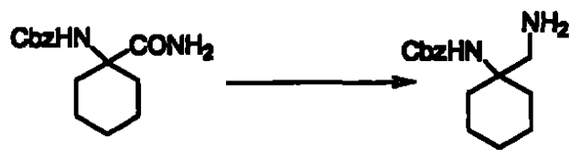
El intermediario 12001d fue convertido en 12001 mediante acoplamiento al intermediario 10 11 seguido por oxidación Moffett idéntica a los procedimientos descntos en el ejemplo preparativo 6 de la síntesis de 11001, Paso D y Paso E

Ejemplo 11. Síntesis del Compuesto de la Fórmula 12002



12002

Paso A

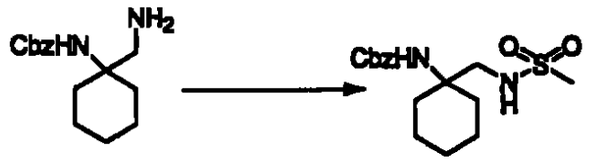


12002a 12002b

Una solución 12002a (Gregory, H *et al*, *J Chem Soc* 1968, 531) (11,62 g, 42,08 mmol) en tolueno seco se trató con BH_3•DMS (soluc. ~10 M, 6,3 mL) y se calentó a 70°C durante la noche La mezcla de reacción se enfrió hasta temperatura

ambiente y se templó con NaOH ac y se extrajo con CH_2Cl_2. Las capas orgánicas combinadas fueron extraídas con salmuera y se concentraron in *vacuo* para proporcionar 12002b 8,77 g (00%)

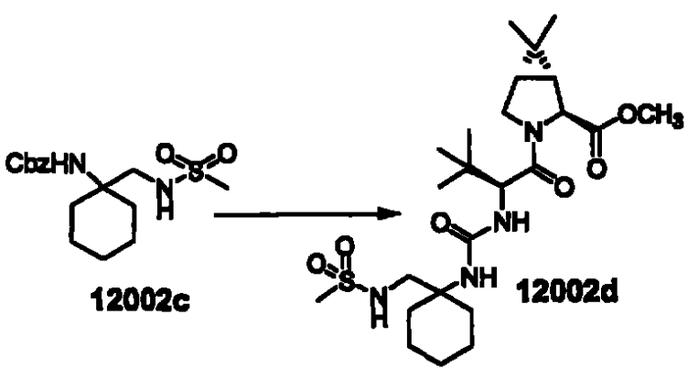
Paso B



12002b 12002c

Una solución de 12002b (2 g, 7,24 mmol) en cloruro de metileno se trató con piridina (7,9 g, 100 mmol) y cloruro de metansulfonilo (1,24 g, 10,86 mmol) y se agitó a temperatura ambiente durante 24 h La mezcla de reacción se lavó con HCl ac, $NaHCO_3$ saturado y salmuera La capa orgánica se secó ($MgSO_4$) se filtró, se concentró in *vacuo* y se purificó mediante cromatografía (SiO_2, acetona/Hexanos 1 2) para proporcionar 12002c.

Paso C



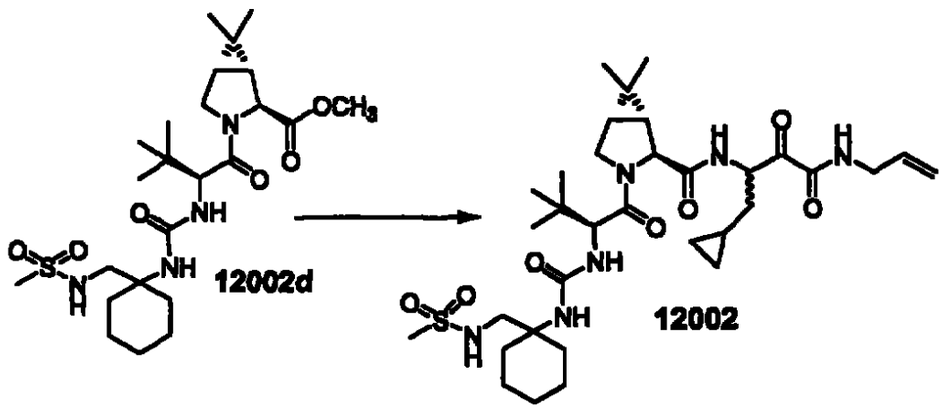
12002c 12002d

Una solución de 12002c (465 mg, 1,37 mmol) en metanol se trató con paladio sobre carbono y se hidrogenó durante 2 h a 340 kPa (50 *psi*) La mezcla de reacción se filtró a través de un tapón de celite® y se concentró in *vacuo* para aislar a la amina desprotegida la cual se utilizó en la siguiente reacción sin más purificación

404
406

Una solución de la amina desprotegida en CH_2Cl_2/DMF (1 1) se trató con 4-nitrofenilcarbamato 1 16 (612 mg, 1,37 mmol), NMM (548 mg, 5,48 mmol) y se agitó a temperatura ambiente durante 12 h. La mezcla de reacción se concentró in *vacuo* y se diluyó con CH_2Cl_2 (200 mL) y se lavó con HCl ac. (1M, 2x125 mL), NaHCO3 acuoso saturado (2x125 mL), salmuera (100 mL), se secó ($MgSO_4$), se filtró and se purificó mediante cromatografía (SiO_2, Hexanos/acetona 1 4) para proporcionar 12002d (560 mg)

Paso D

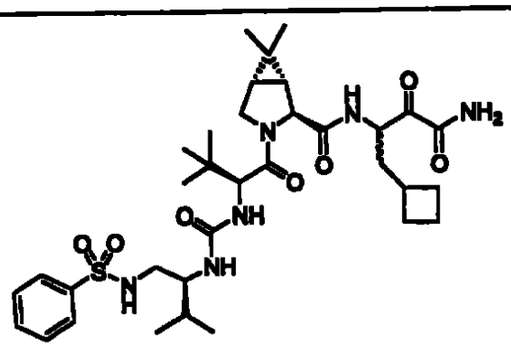
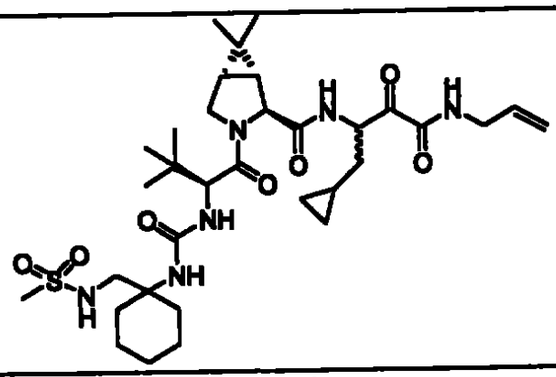
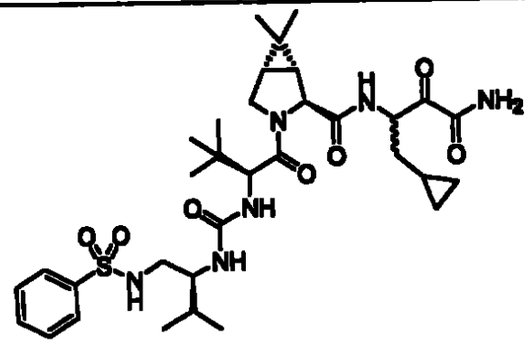


El intermediario 12002d fue convertido en 12002 mediante acoplamiento al intermediario 12 04 seguido por oxidación de Dess-Martin idéntica a los procedimientos descritos en el ejemplo preparativo de la síntesis de 11003, Paso C y Paso D

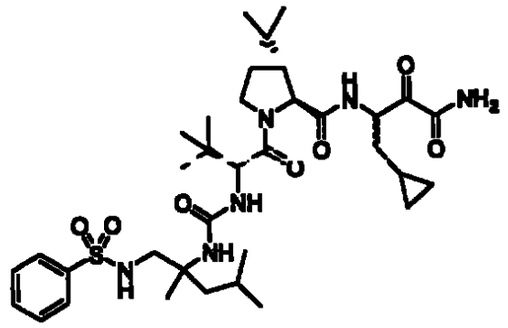
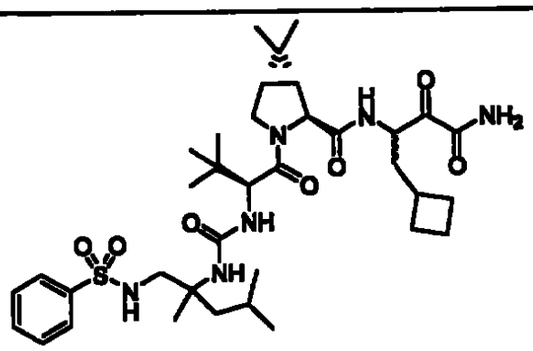
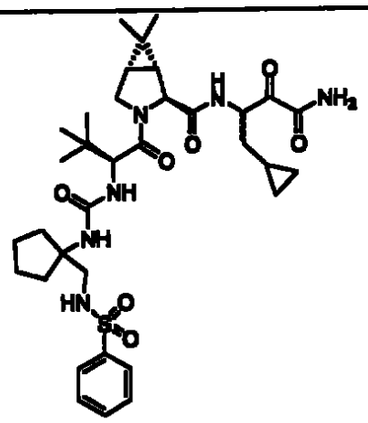
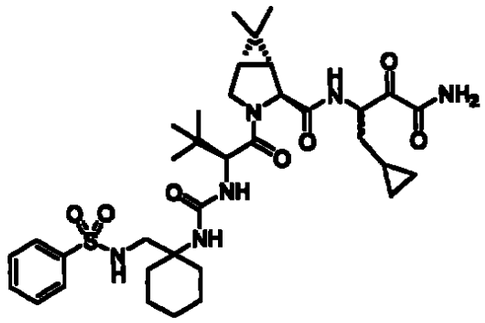
Los compuestos mostrados en la siguiente Tabla 3 se sintetizaron utilizando reacciones similares como se muestra en los Ejemplos anteriores. El rango de KI* indicó A≤75 nM, 75<B≤250 nM, C>250 nM

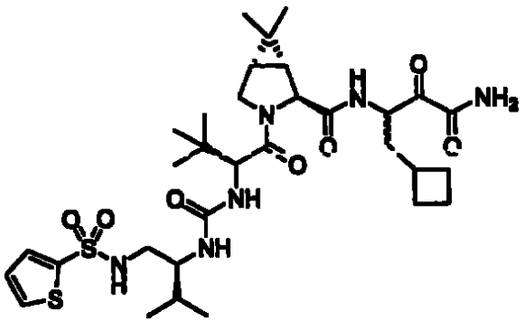
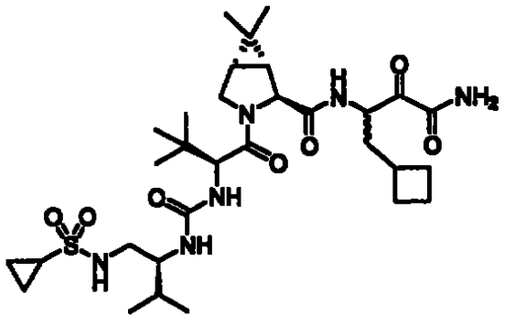
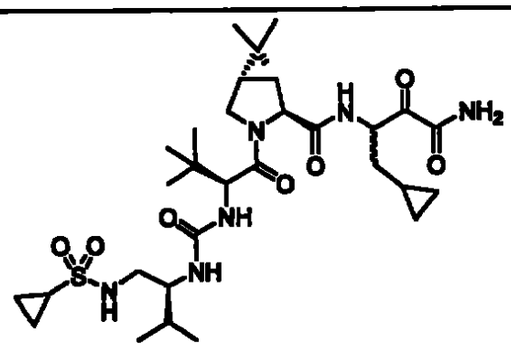
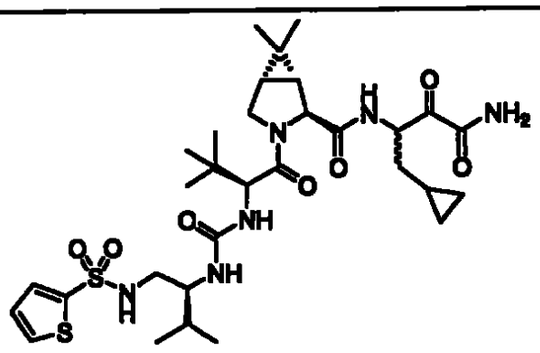
405
407

Tabla 3

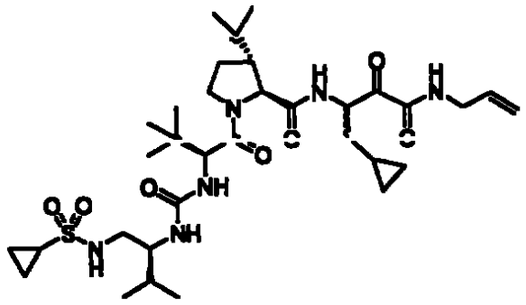
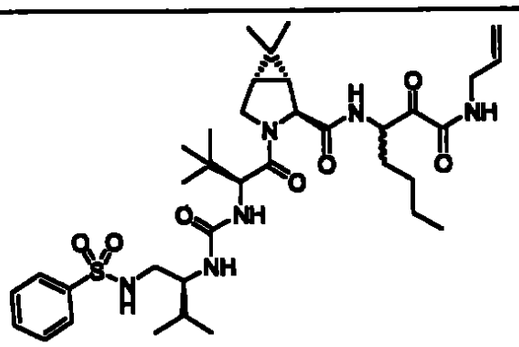
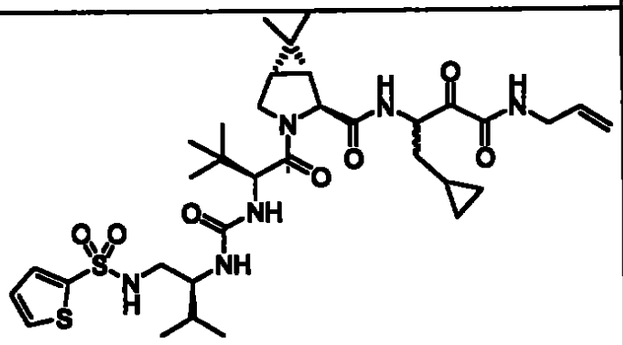
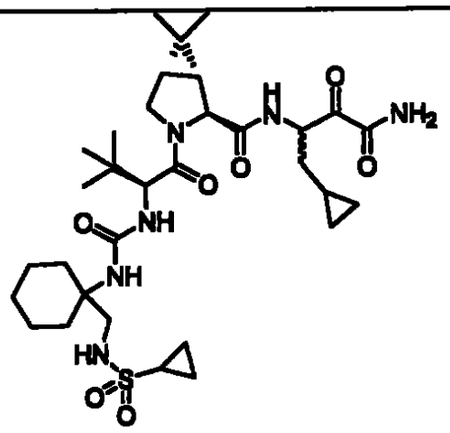
Item	Estructura	Ki*
12001		A
12002		A
12003		A

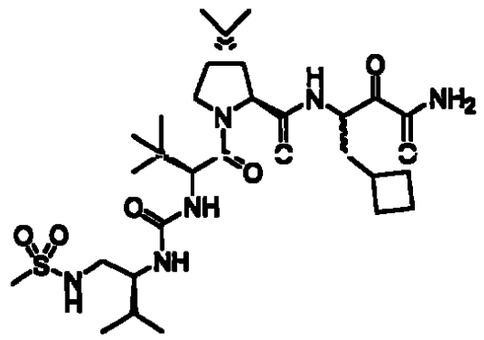
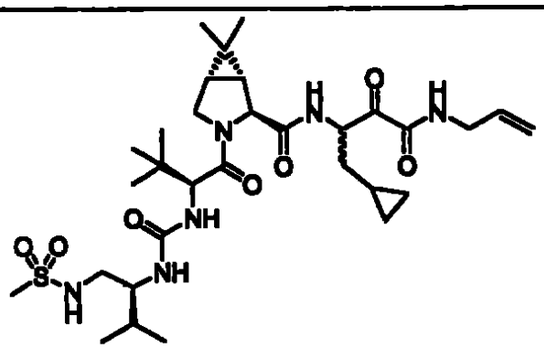
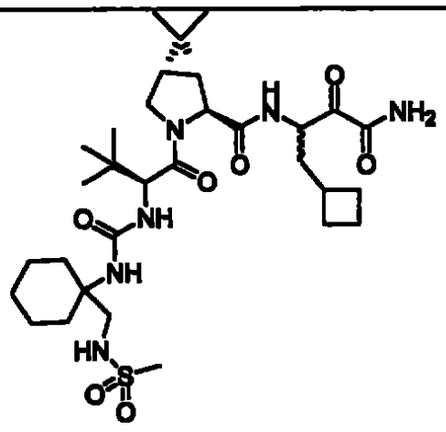
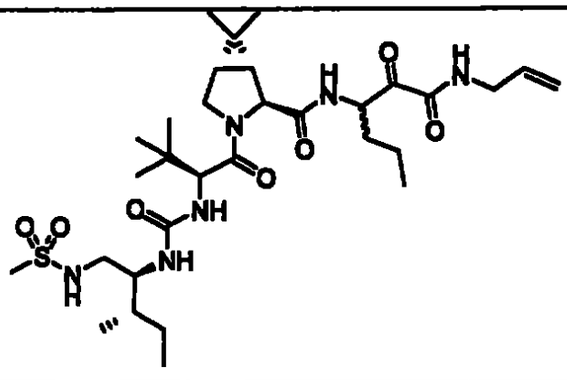
406
408

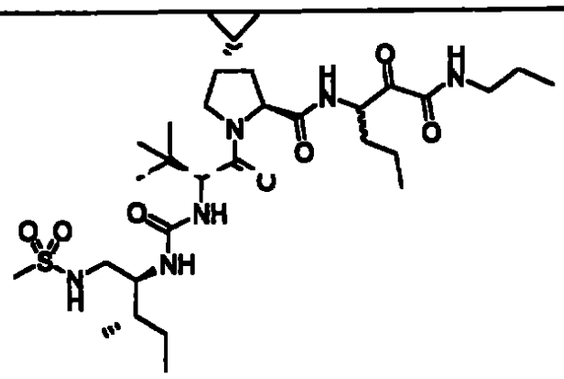
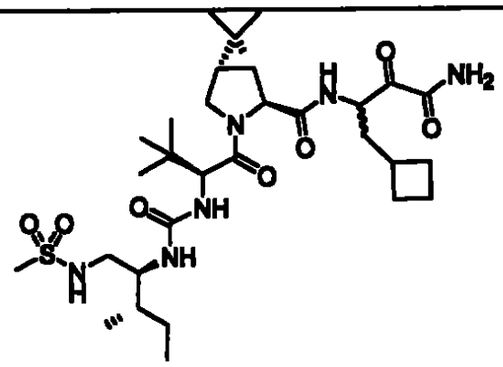
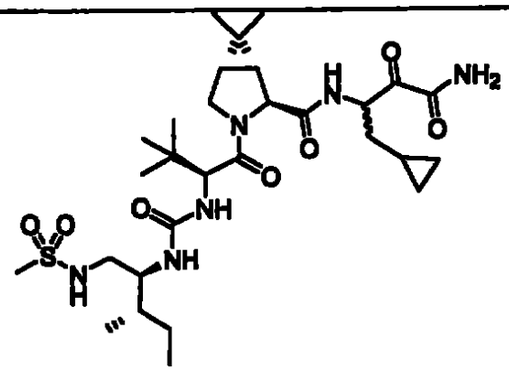
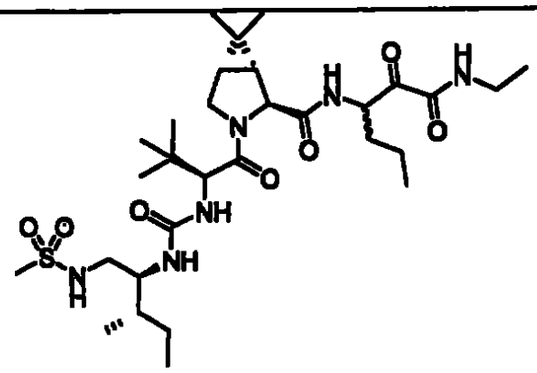
12005		B
12006		B
12007		A
12008		A

12009		A
12010		A
12012		A
12013		A

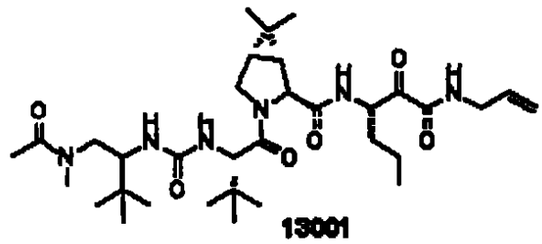
408
410

12014		C
12015		C
12016		B
12017		A

12018		A
12019		A
12020		A
12021		A

12022		C
12023		A
12024		B
12025		C

Ejemplo 12 Síntesis del compuesto de fórmula molecular 13001



13001

Paso A



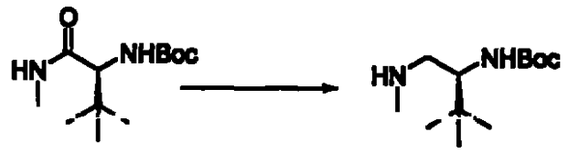
13001a 13001b

El ácido, 13001a, (5 g, 21,6 mmol, 1 equiv Fluka) y clorhidrato de metilamina (1,2 equiv,, 25,92 mmol) se disolvieron en N, N-dimetilformamida seco (20 ml) y se enfrió hasta 0°C Se agregó HATU (1,2 equiv , 25,92 mmol) seguido por DIPEA (Sigma-Aldrich), (172,8 mmol , 8 equiv) bajo atmósfera de N_2 La temperatura se elevó lentamente hasta temperatura ambiente y se agitó otras 4 horas a temperatura ambiente Se diluyó con EtOAc y se lavó con HCl 1N, $NaHCO_3$ y finalmente con salmuera Se secó sobre sulfato de sodio anhidro, se filtró y se separó por evaporación el solvente El producto crudo aislado se purificó mediante columna flash (10-50% EtOAc-Hexano) para proporcionar 5,27 g de 13001b Rendimiento, (99%)

^{1}H RMN ($CDCl_3$, 300 MHz) δ, 6,0(bs, 1 H), 5,35(d, 1 H,), 3,82 (d, 1 H), 2,8 (s, 3H), 1,4 (s, 9H), 0,98 (s, 9 H)

414

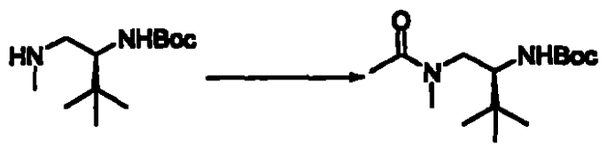
Paso B



13001b 13001c

A la amida 13001b (3,37g,13,8 mmol, 1 equiv) en tolueno (100 mL) a temperatura ambiente, se le agregó $BH_3 \cdot Me_2S$ (10M, 3 equiv , 41,4 mmol, 4,14 mL) y se refluió a 80 °C durante 3 hrs El solvente se separó por evaporación y el producto crudo se templó con hidróxido de sodio ac 2 M y se extrajo con diclorometano La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio anhidro El solvente se filtró y evaporó para proporcionar 1,8 g de 13001c El producto crudo se utilizó para el siguiente paso sin purificación Rendimiento, (55%)

Paso C



13001c 13001d

Al compuesto amino Boc-protegido 13001c (540 mg, 1 equiv) en diclorometano (25 mL) a temp del hielo se agregó trietilamina (3 equiv) y acetil cloruro (3 equiv) Se agitó durante 1 hr a temperatura del hielo y luego a temperatura ambiente durante la noche Se templó con bicarbonato de sodio ac. y se extrajo con EtOAc Se lavó con HCl 1N y luego con salmuera Las capas orgánicas se secaron sobre sulfato de sodio anhidro, el solvente se filtró y evaporó El producto crudo se purificó mediante columna flash (20-40 % EtOAc-Hexano) Rendimiento = 230 mg (38%)

413
415

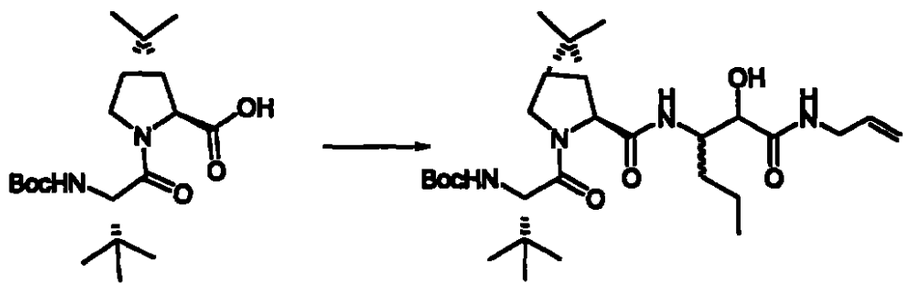
Paso D



13001d 13001e

A la amida 13001d (28 mg, 1 equiv) se le agregó HCl 4M /dioxano (2 mL) a temperatura ambiente Se agitó durante 1 hr La TLC no mostró material de partida alguno El solvente se evaporó y se tomó azeotrópico con hexano y luego con éter Se lavó el material no polar con éter y se mantuvo bajo alto vac. durante el fin de semana Se utilizó la sal sin purificación, El producto fue aislado (sólido amarillo pálido) = 22 mg (100 %)

Paso E

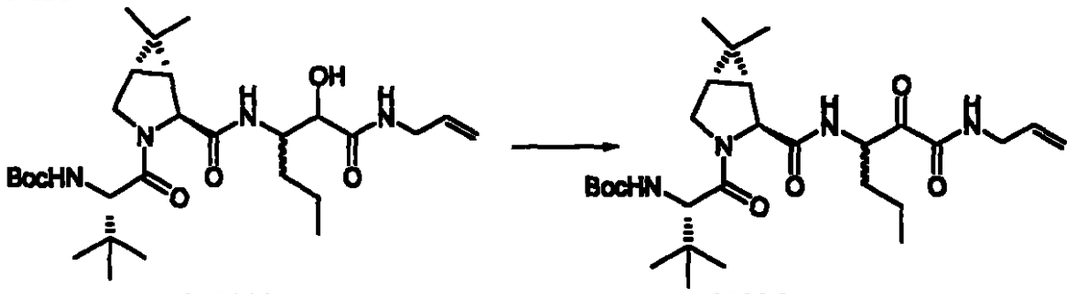


1 17 13001f

A una mezcla de ácido, 1 17 (860 mg, 2,33 mmol, 1 equiv) y clorhidrato de amina 13 01 (570 mg, 2,56 mmol, 1,1 equiv) en DMF (15 mL) a temperatura del hielo se agregó HATU (1,2 equiv , 1,066 g, 2,796 mmol) y DIPEA (8 equiv , 18,69 mmol, 3,26 mL) bajo N_2 y se agitó a 0°C durante la noche La temperatura se dejó subir lentamente hasta temperatura ambiente Se templó con HCl 1N y se extrajo con EtOAc Las capas orgánicas combinadas se lavaron con $NaHCO_3$ ac (sat) y luego con salmuera Se lavó con agua helada (5 x 20 ml) y nuevamente con salmuera Se

secó sobre Na_2SO_4 anhidro, se filtró y evaporó el solvente para proporcionar 1,25 g de 13001f Rendimiento, 100%

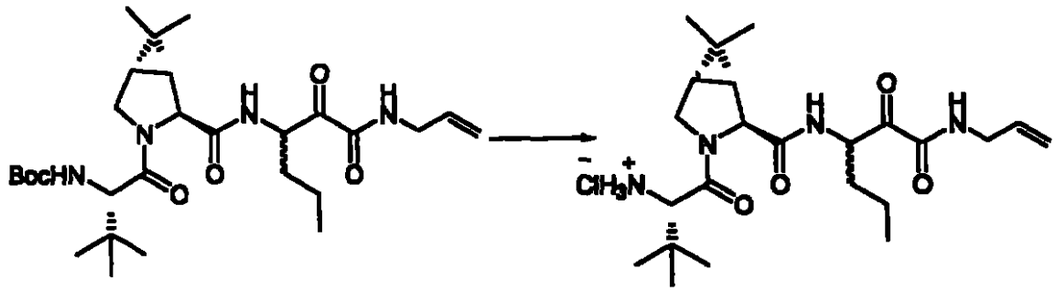
Paso F



13001f 13001g

A la hidroxiamida cruda, 13001f (2,71mmol, 1,45mg, 1 equiv) en DCM (50 mL) a temperatura ambiente, se agregó peryodinano de Dess-Martin (2,30 mg, 5,42 mmol, 2 equiv) y se agitó a temperatura ambiente durante 5 hrs La TLC mostró un completo consumo del material de partida y la aparición del producto Se templó con $NaHCO_3$ sat, solución de tiosulfato ac y se extrajo con EtOAc La capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio anhidro El solvente se filtró y evaporó El producto crudo se purificó mediante columna flash sobre gel de sílice (10-40% acetona-hexano) para proporcionar 860 mg de 13001g, Rendimiento, 62 %

Paso G

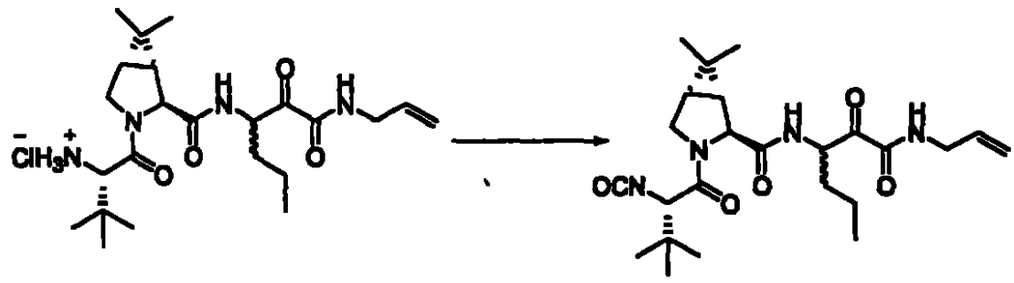


13001g 13001h

Al compuesto amino con Boc 13001g (860 mg, 1 equiv) se agregó HCl 4 M en dioxano (25 mL) a temperatura ambiente Se agitó durante 1 hr La TLC no mostró material de partida alguno El solvente se evaporó y se tornó azeotrópico con hexano

y luego con éter El material no polar se lavó con éter y se mantuvo bajo alto vacío durante el fin de semana Se utilizó la sal sin más purificación, El producto se aisló (sólido amarillo pálido) = 750mg (99%)

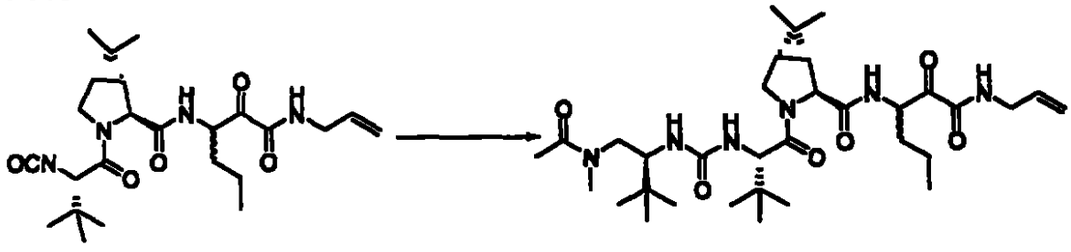
Paso H



13001h 13001l

A la sal de amonio, 13001h, (150 mg, 0,318 mmol, 1 equiv) en DCM (5 ml) se le agregaron 5 ml de $NaHCO_3$ ac sat Se agitó vigorosamente a la temperatura del hielo durante 5 min Se detuvo la agitación y se separó con jeringa el fosgeno (2 equiv 20% en tolueno, 0,318 mL) a la capa inferior y se reanudó la agitación vigorosa de inmediato Se controló la TLC algunas veces y después de 2 horas mostró un completo consumo de material de partida y luego se separaron las capas Se lavó la capa acuosa una vez más con DCM (3 ml) y las capas orgánicas combinadas se secaron sobre sulfato de sodio La capa orgánica se filtró y se concentró in *vacuo* hasta la mitad del volumen Se utilizó 13001l como solución base de 0,01M diluyendo hasta 30 mL de diclorometano

Paso F

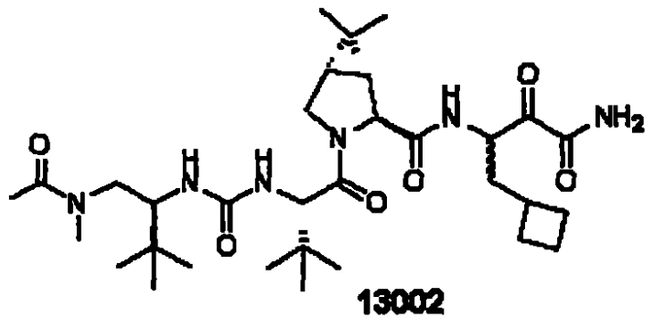


13001l 13001

A la sal de amonio 13001e (22 mg, 0,102 mmol, 1,1 equiv) en DCM (10 ml) se le agregó DIPEA (6 equiv , 135 uL) a temperatura del hielo Se agregó Isocianato 13001l (1 equiv, 9 ml de soluc 0,01M) bajo atmósfera de N_2 y se agitó durante 30 min a la temperatura del hielo y 90 min a temperatura ambiente Se templó con ácido cítrico y se extrajo con EtOAc y se lavó con salmuera Se secó sobre sulfato de sodio anhidro, se filtró y evaporó el solvente El producto crudo se purificó mediante columna flash (SiO_2, 10-50% acetona-hexano) para proporcionar 50 mg de 13001 como un sólido incoloro Rendimiento, (78%)

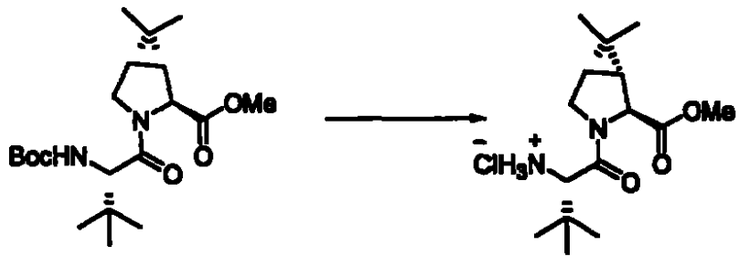
EM (ESI), m/z, 633 (M+1), 312

Ejemplo 13 Síntesis del compuesto de fórmula molecular 13002



13002

Paso A



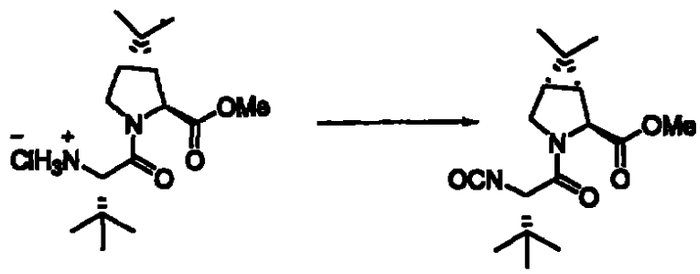
1 03 1.04

Al dipéptido Boc protegido 1 03 (3,6 g, 9,42 mmol, 1 equiv) se agregó HCl 4M/dioxano (60 mL) a temp ambiente Se agitó durante 2 h La TLC no mostró

material de partida alguno El solvente se evaporó y se tomó azeotrópico con hexano y luego con éter Se lavó para separar el material no polar con éter y se mantuvo bajo alto vacío durante la noche Se utilizó la sal, 1 04, sin purificación

Producto aislado = 3g (100%)

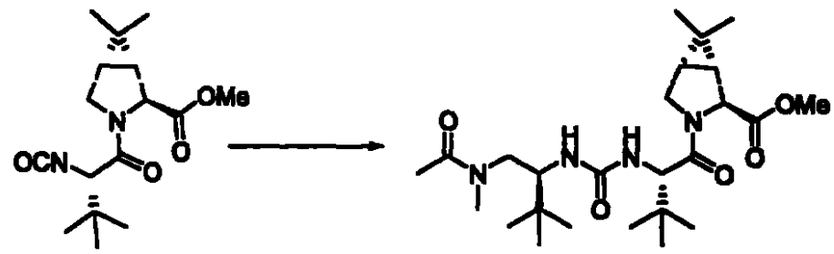
Paso B



1 04 13002a

Al clorhidrato de amina 1 04 (3 g, 9,4 mmol) en diclorometano (50 ml) se agregaron 50 ml de $NaHCO_3$ sat. Se agitó vigorosamente a la temperatura del hielo durante 5 min Se detuvo la agitación y el fosgeno (2 equiv 20% en tolueno, 10 mL) se separó por medio de una jeringa a la capa inferior y se reanudó la agitación vigorosa de inmediato La TLC se controló en ciertos momentos y después de 2 horas mostró un completo consumo de material de partida y luego se separaron las capas Se lavó la capa acuosa una vez más con diclorometano (3 ml) y se secaron sobre sulfato de sodio anhidro El solvente se filtró y se separó por evaporación utilizando un evaporador rotativo bajo presión reducida hasta la mitad del volumen y luego se introdujo N_2 durante 15 minutos Se diluyó hasta 33,5 mL con diclorometano y se utilizó como solución 0,28 M para posteriores acoplamientos

Paso C

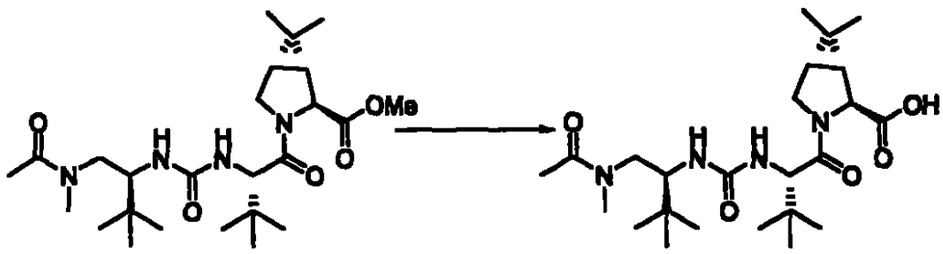


13002a 13002b

A la sal de amina, 13001e, preparada según lo antes descrito (151 mg, 0,73 mmol, 1 equiv) en DCM (10 ml) se le agregó DIPEA (8 equiv , 1,01 mL, 5,84 mmol) a la temperatura del hielo Se agregó isocianato 13002a (1 equiv, 13 ml de soluc 0,02M) bajo atmósfera de N_2 y se agitó durante 30 min a la temperatura del hielo y 90 min a temperatura ambiente Se templó con ácido cítrico 10% y se extrajo con EtOAc y se lavó con salmuera El solvente se secó sobre sulfato de sodio anhidro y se filtró y se separó por evaporación El producto crudo se purificó mediante columna flash (20-80% EtOAC-hexano) para proporcionar 270 mg de 13002b como un sólido blanco Rendimiento (76%)

^{1}H RMN ($CDCl_3$, 300 MHz) δ, 5,8 (bs, N H), 5,4 (bs, NH), 5,2 (d, 1H), 4,4(d, 1H), 4-4,2(m, 2H), 3,8-4(m, 3H), 3,01(s, 3H), 2,01(bs, 6H), 1,6 (m,1H), 1,4(m, 1H), 1,02-0,98 (m, 24 H)

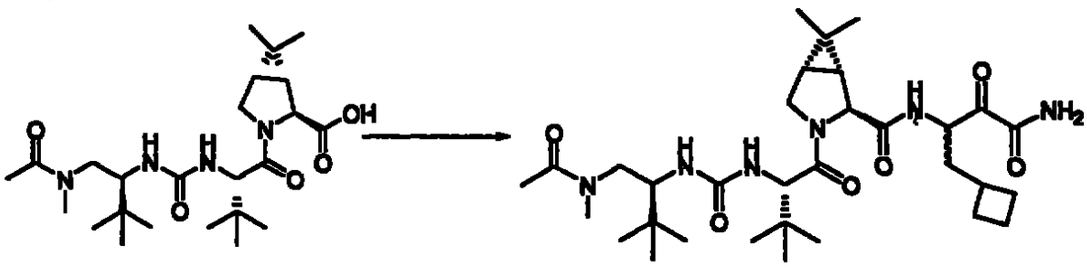
Paso D



13002b 13002c

Al éster metílico, 13002b (270 mg, 0,562 mmol, 1 equiv) en dioxano (10 ml) se le agregó una solución de LIOH (10 equiv , 6 mL de soluc 1N en agua) y se agitó durante la noche Se templó con HCl 1N y se extrajo con EtOAC Se lavó con salmuera y se secó sobre sulfato de sodio anhidro El solvente se filtró y se separó por evaporación Rendimiento crudo 260 mg (99%)

Paso E



13002c 13002

A la sal de amonio, 10 11 (16,06 mg, 0,077mmol, 1,2 equiv) en DCM (10 ml)se le agregó 13002 c (30 mg, 0,064 mmol, 1 equiv) y se enfrió hasta – 20°C y se le agregó HATU (1,2 equiv , 0,077 mmol, 29,37 mg) seguido por DIPEA (8 equiv , 89 94 uL, 0,515 mmol) La mezcla de reacción se agitó durante la noche a esa temperatura Se templó con HCl 1N y se extrajo con EtOAC Se lavó la capa orgánica con bicarbonato de sodio ac saturado y luego con salmuera Se secó sobre sulfato de sodio anhidro, se filtró y el solvente se separó por evaporación Se purificó mediante columna flash (SiO_2, 10-90% EtOAc-Hexano) para proporcionar 40 mg de hidroxiamida Rendimiento, (100%)

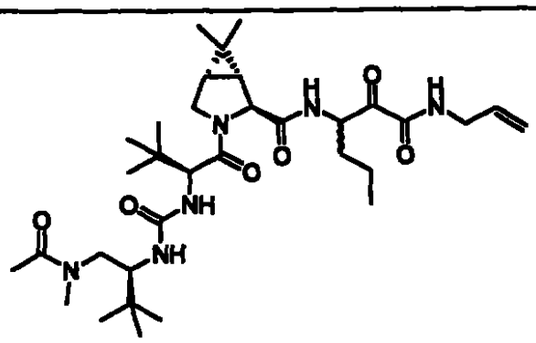
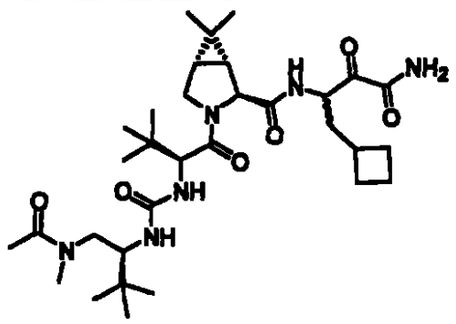
A la hidroxilamida (40 mg, 0,0645 mmol, 1 equiv) en 1 1 de mezcla de DMF/tolueno (6 mL) a la temperatura del hielo se agregó EDCI•HCl (123 mg, 10 equiv , 0,645 mmol) y ácido dicloroacético (27 uL, 5 equiv , 0,322 mmol) y se agitó durante 5 min y temperatura ambiente durante 3 h Se templó con salmuera y se lavó con HCl 1N seguido por $NaHCO_3$ ac. sat. y nuevamente con salmuera Se secó

sobre sulfato de sodio anhidro, se filtró y el solvente se separó por evaporación Se purificó por medio de TLC preparativa sobre gel de sílice (50% acetona-hexano) para proporcionar 30 mg del 13002 Rendimiento (75%)

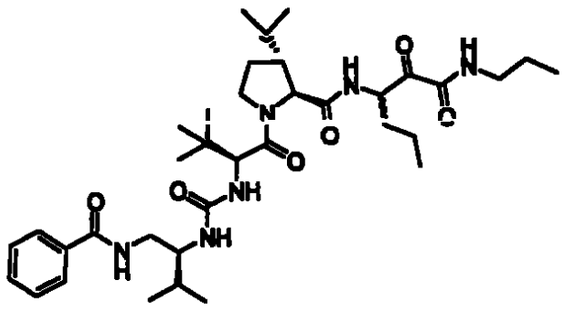
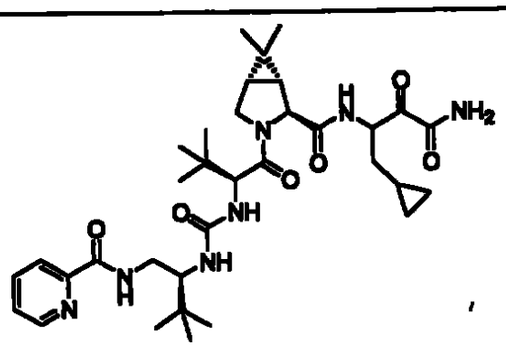
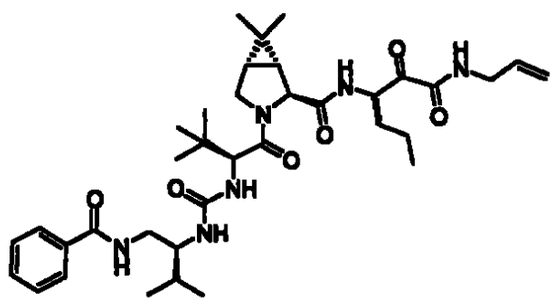
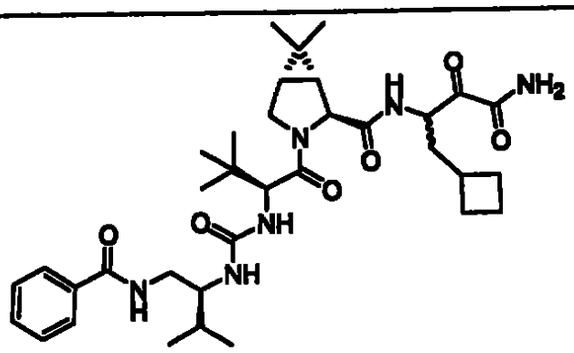
EM (ESI), m/z, 619(M+1), 312

Los compuestos mostrados en la siguiente Tabla 4 fueron sintetizados utilizando reacciones similares a las que se muestran en los Ejemplos anteriores El rango de Ki* indicó A ≤75 nM, 75< B ≤250 nM, C>250 nM

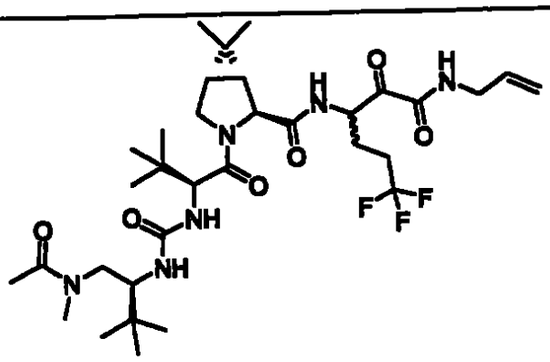
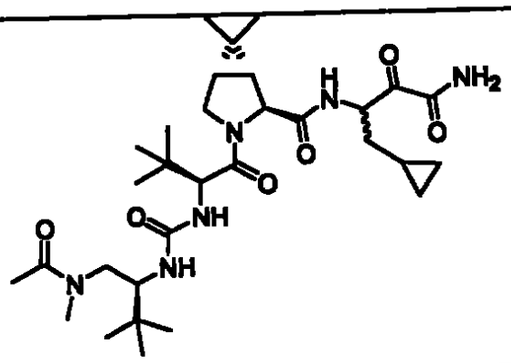
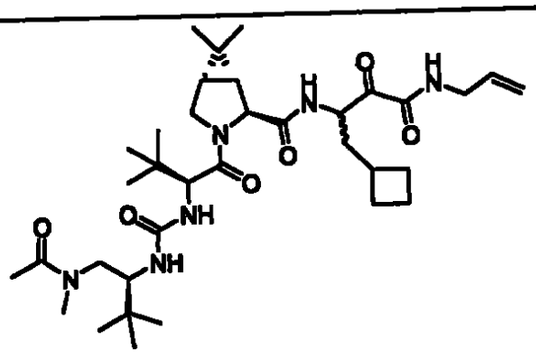
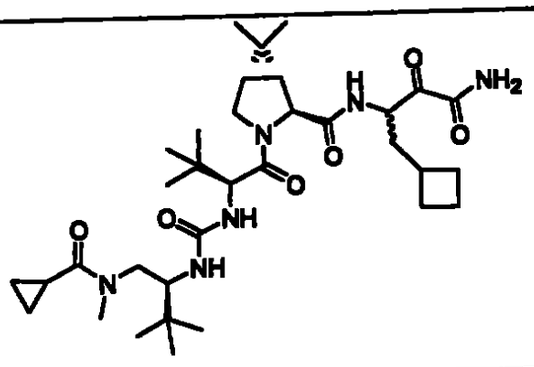
Tabla 4

Item	Estructura	Ki*
13001		A
13002		A

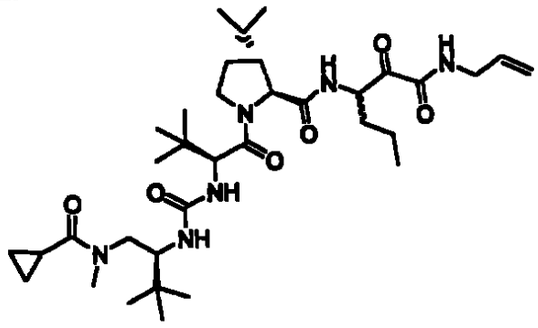
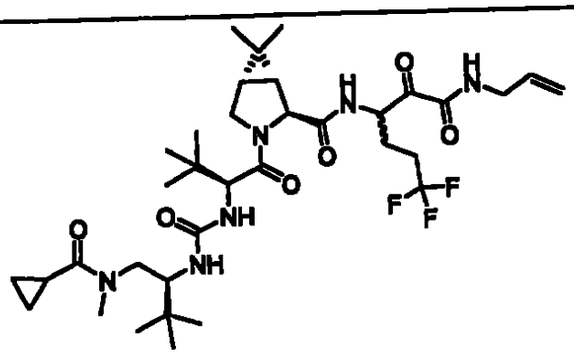
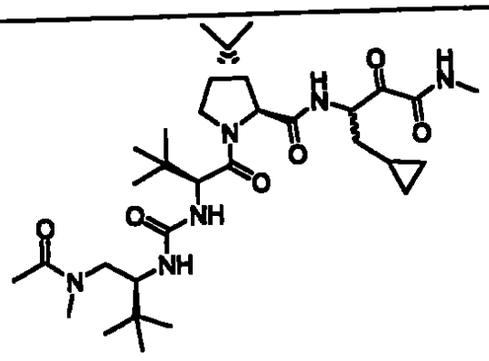
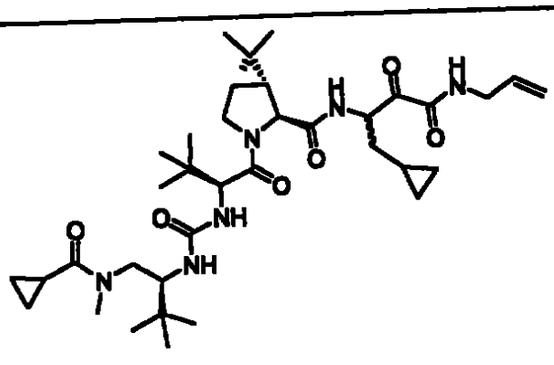
~~427~~
423

13003		B
13004		A
13008		A
13009		A

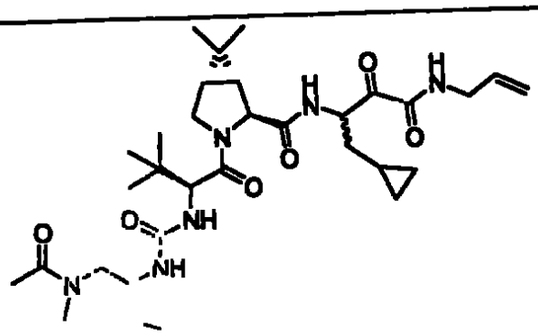
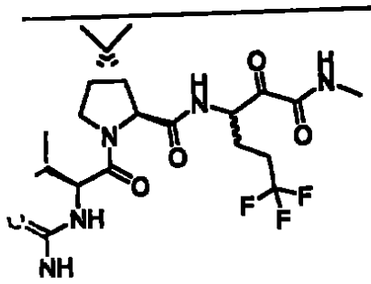
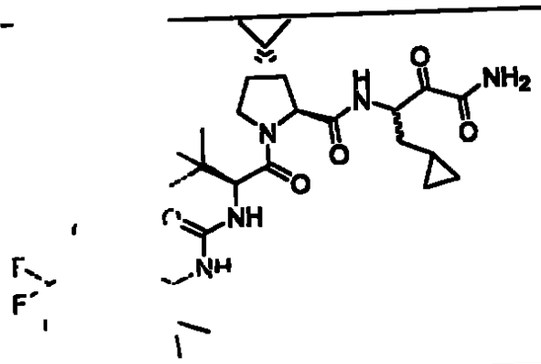
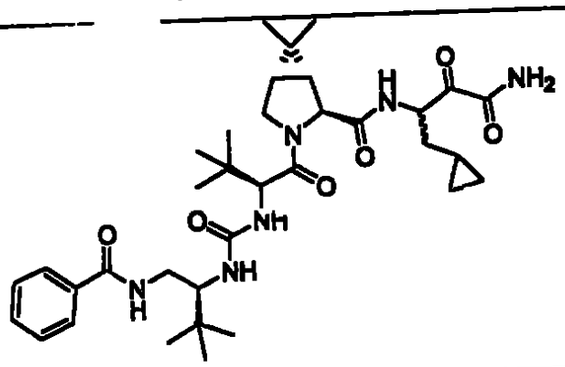
422
424

13010		A
13011		A
13012		B
13013		A

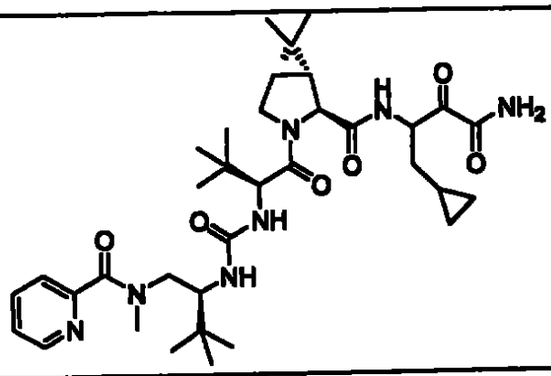
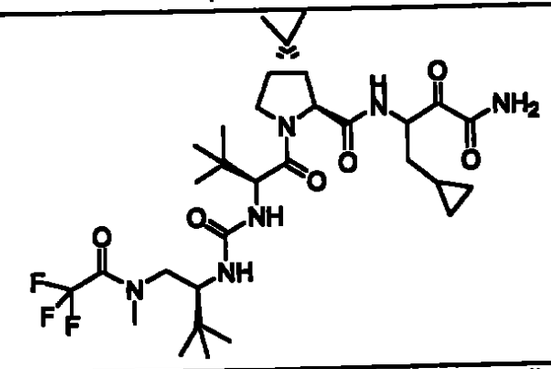
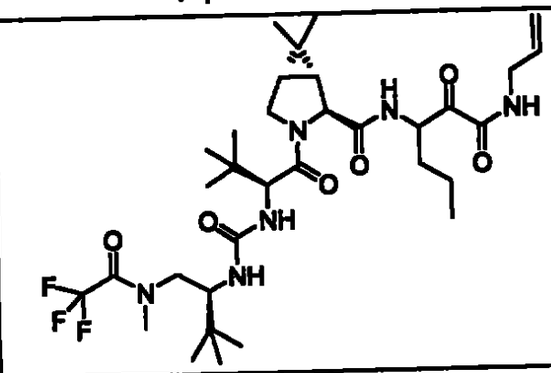
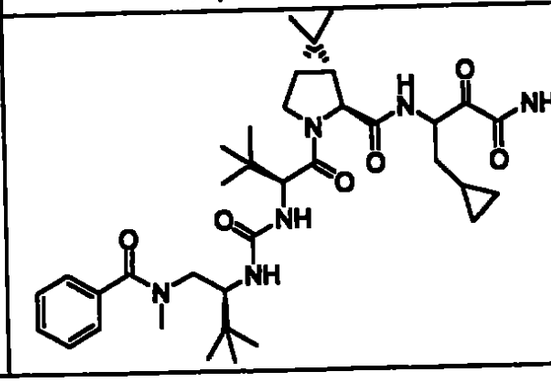
~~423~~
425

13014		B
13015		B
13016		A
13017		C

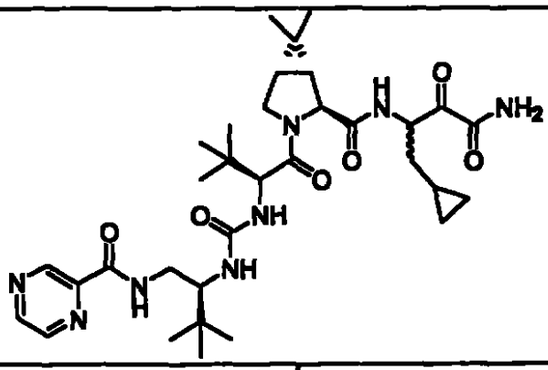
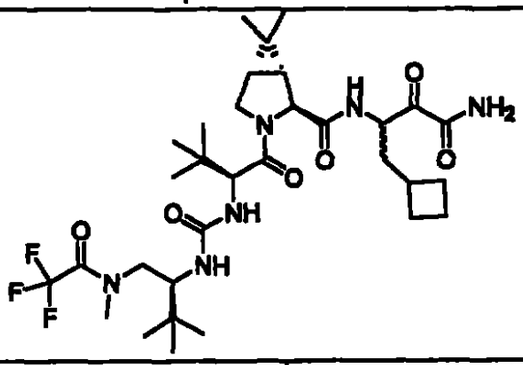
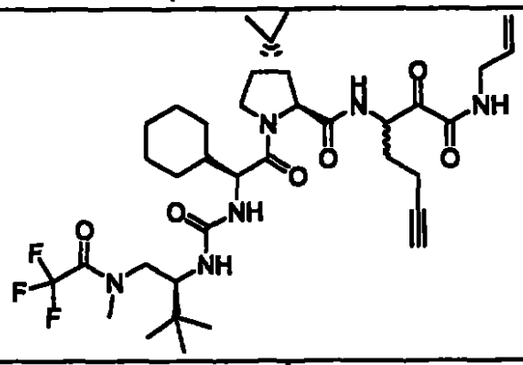
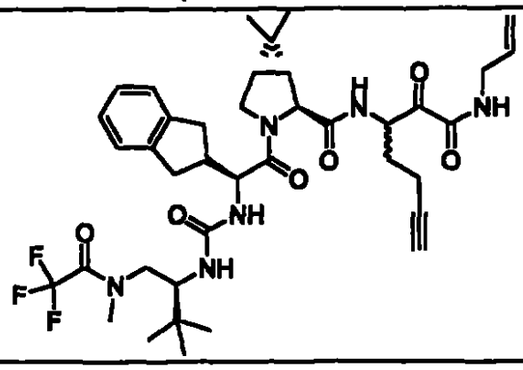
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426

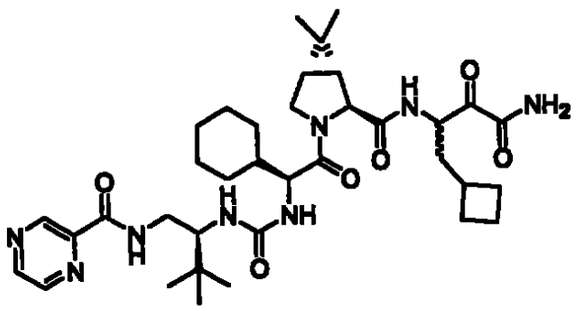
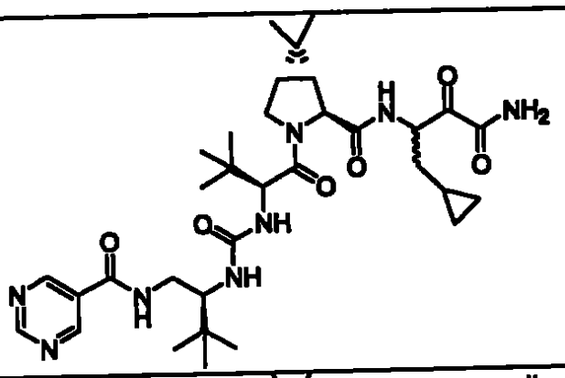
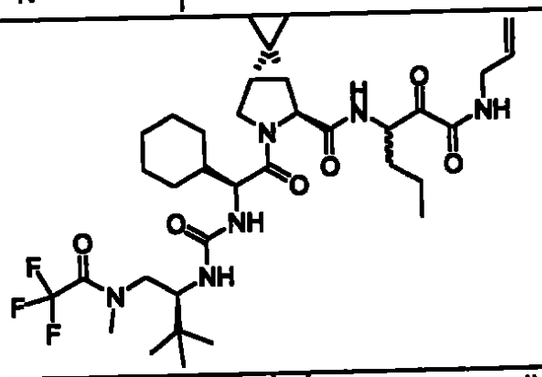
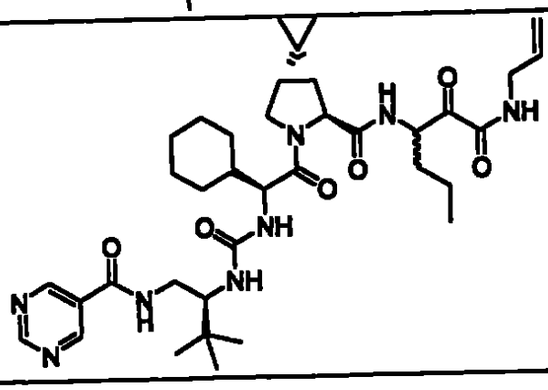
13018		A
13019		A
13020		A
13021		A

427
427

13022		A
13023		A
13024		A
13025		A

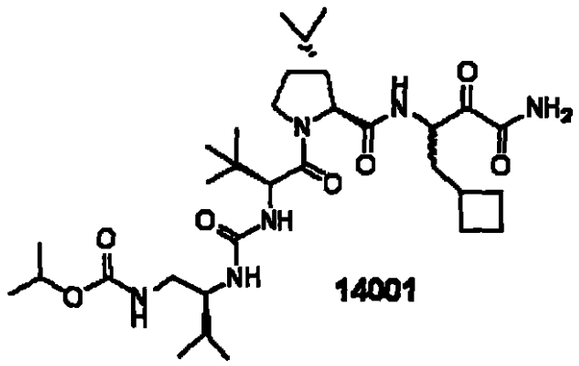
428

13026		A
13027		A
13028		A
13029		A

13030		A
13031		A
13032		A
13033		A

430
430

Ejemplo 14 Síntesis del Compuesto de la Fórmula 14001



14001

Paso A



14001a **14001b**

Una solución de **14001a** (10,0 g, 40,0 mmol químicos Indofine) en tolueno (150 mL) se trató con BH_3•DMS (~ 2 M, 40 mL) y se calentó a 90°C durante la noche La mezcla de reacción se enfrió hasta 0°C y se diluyó con NaOH 2 M ac La mezcla de reacción se calentó a 90°C durante 15 min La capa acuosa se extrajo con CH_2Cl_2 y las capas orgánicas combinadas se secaron ($MgSO_4$) se filtraron y concentraron in *vacuo* para proporcionar 11 g de **14001b**

Paso B



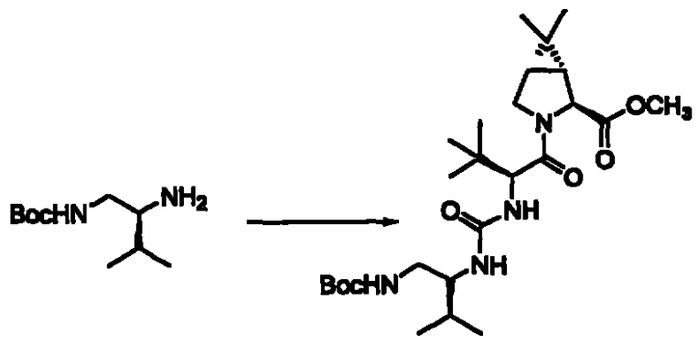
14001b **14001c**

Una solución de la amina **14001b** (10 g, 42,0 mmol) en CH_2Cl_2/DMF (1 5) se enfnó hasta -78 °C y se trató con di-*ter*-butildicarbonato (13,8 g, 63 mmol) La mezcla de reacción se agitó a temperatura ambiente durante 48 h y se diluyó con HCl ac. 1

M y se extrajo con EtOAc La capa orgánica combinada se lavó con $NaHCO_3$ ac , salmuera, se secó, se filtró y se concentró In *vacuo* El residuo se purificó mediante cromatografía (SiO_2, EtOAc/Hexanos 1 3) para proporcionar 4 g del compuesto Boc protegido

Una solución de compuesto Boc (6 g, 17,8 mmol) en metanol se trató con $Pd(OH)_2/C$ (1,89 g, 20% sobre C) y se hidrogenó durante 1h La mezcla de reacción se filtró a través de un tapón de célite y se concentró In *vacuo* El residuo 14001c se utilizó en otra reacción sin purificación

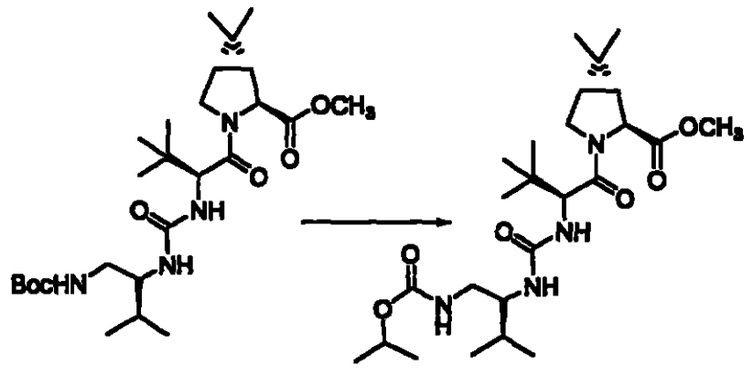
Paso C



14001c 14001d

Una solución de la amina desprotegida 14001c (3,6 g, 17,8 mmol) en CH_2Cl_2/DMF (1 1, 20 mL) se trató con 4-nitrofenilcarbamato 1.16 (7,97 g, 17,8 mmol), NMM (4 g, 14,0 mmol) y se agitó a temperatura ambiente durante la noche La mezcla de reacción se concentró In *vacuo* y se diluyó con EtOAc y se lavó con HCl ac , $NaHCO_3$ saturado ac , salmuera, se secó ($MgSO_4$), se filtró, y se purificó mediante cromatografía (SiO_2, Hexanos/EtOAc 3 7) para proporcionar 14001d

Paso D

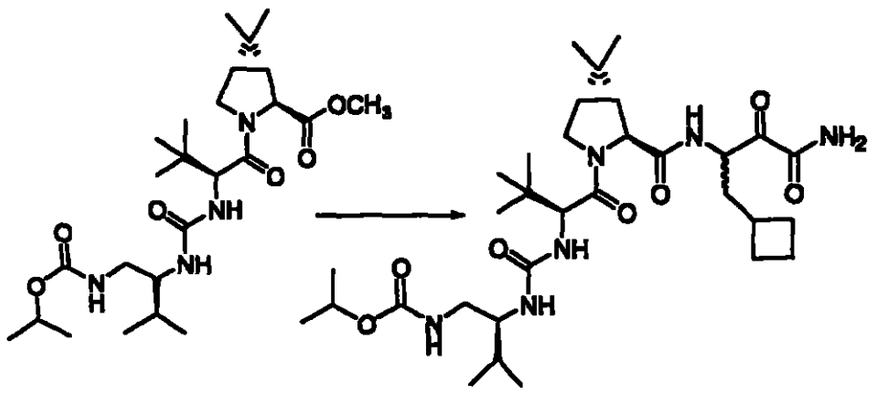


14001d 14001e

Una solución de 14001d se disolvió en HCl 4 M en dioxano y se agitó a ta durante 2 h La mezcla de reacción se concentró in *vacuo* y se utilizó en reacciones posteriores sin purificación

La sal de amonio (100 mg, 0,224 mmol) disuelta en DMF/CH_2Cl_2 (1 1) se trató con isopropilcloroformato (54 mg, 0,448 mmol) y Et_3N (45 mg, 0,448 mmol) a 0°C y se agitó a temperatura ambiente durante la noche La mezcla de reacción se diluyó con EtOAc y la capa orgánica se lavó con HCl ac 1 M, $NaHCO_3$ saturado ac , y salmuera Se secó ($MgSO_4$) se filtró, se concentró in *vacuo* y se utilizó como estaba en la siguiente reacción

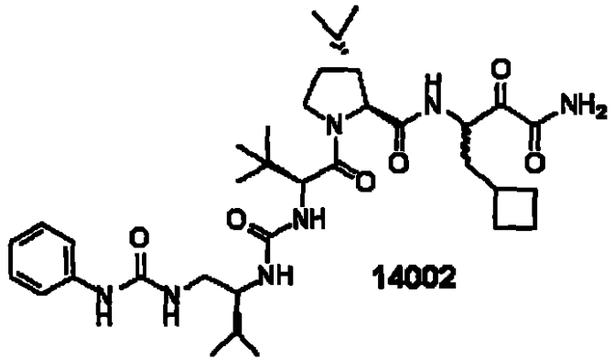
Paso E



14001e 14001

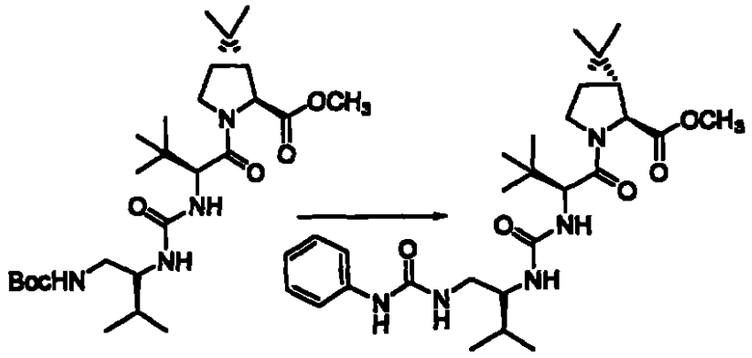
El intermediano 14001e se convirtió en 14001 mediante acoplamiento al intermediano 10 11 seguido por oxidación de Moffett idéntica a los procedimientos descritos en el ejemplo preparativo 6 de síntesis de 11001, Paso D y Paso E

Ejemplo 15 Síntesis del Compuesto de la Fórmula 14002



14002

Paso A

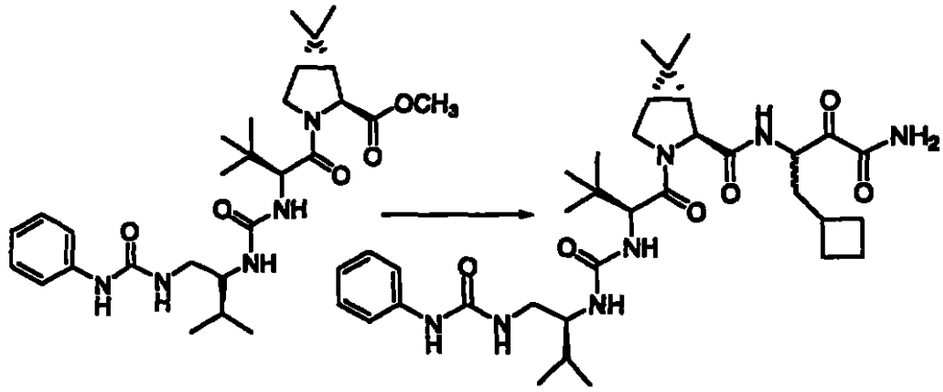


14001d **14002a**

Una solución de 14001d se disolvió en 4 M HCl en dioxano y se agitó a temperatura ambiente durnte 2 h La mezcla de reacción se concentró in *vacuo* y se usó en reacciones adicionales sin purificación

La sal de amonio (100 mg, 0 224 mmol) disuelta en DMF/CH_2Cl_2 (1 1) se trató con fenilisocianato (53 mg, 0 448 mmol) y Et_3N (45 mg, 0 448 mmol) a 0°C y se agitó a temperatura ambiente durante la noche La mezcla de reacción se diluyó con EtOAc y la capa orgánica se lavó con HCl 1M acuoso, $NaHCO_3$ saturado acuoso y salmuera Se secó ($MgSO_4$), se filtró, concentró in *vacuo* y purificó mediante cromatografía (SiO_2, EtOAc/Hex 2 3) para proporcionar 14002a

Paso B

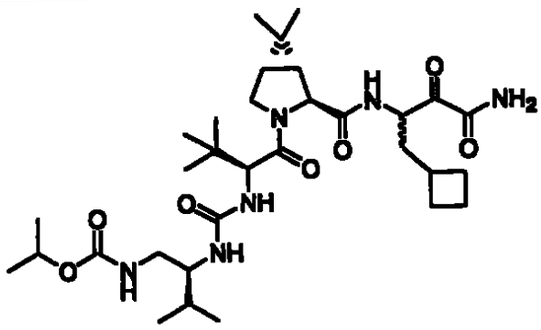
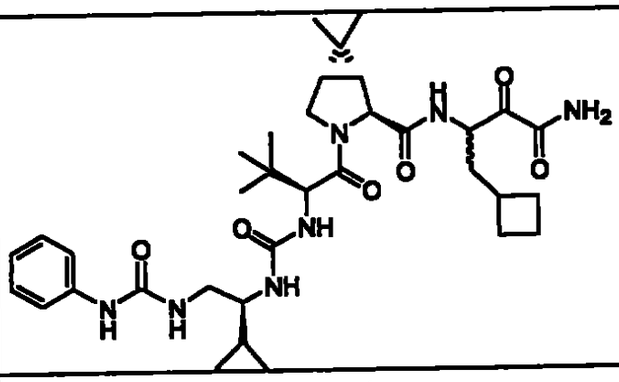
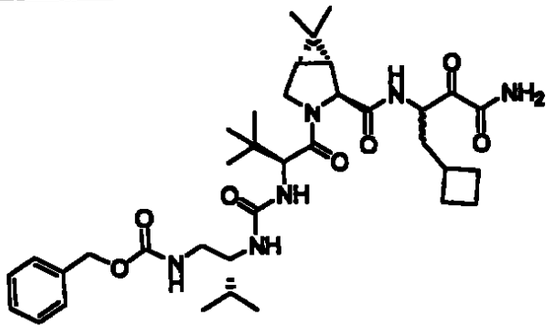


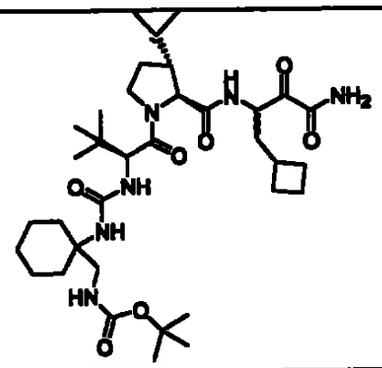
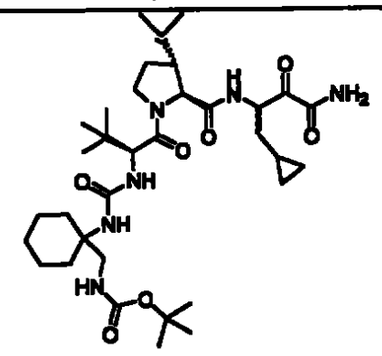
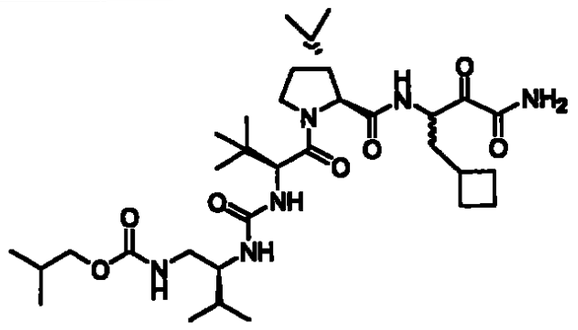
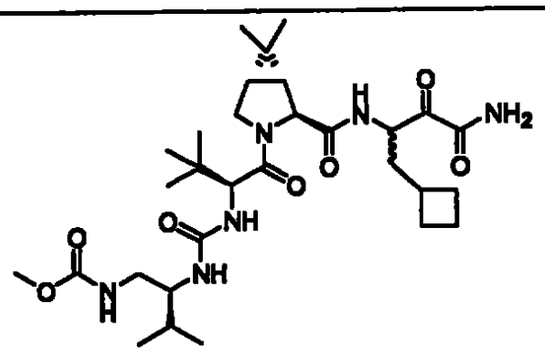
14002a 14002

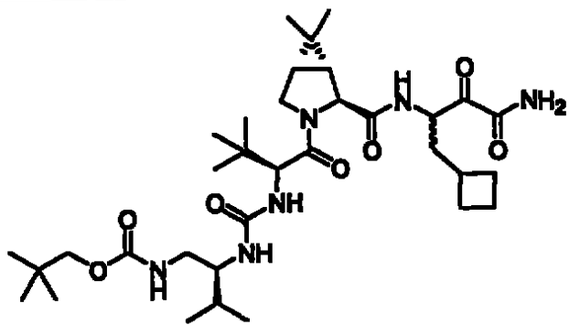
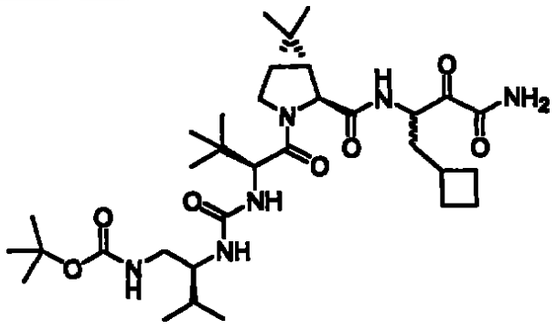
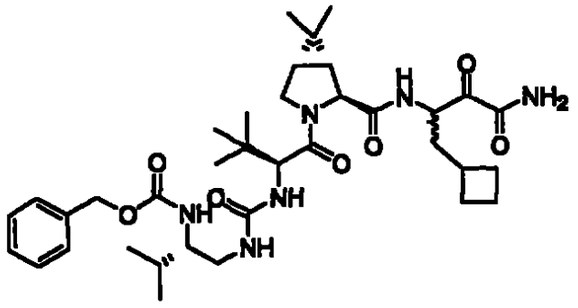
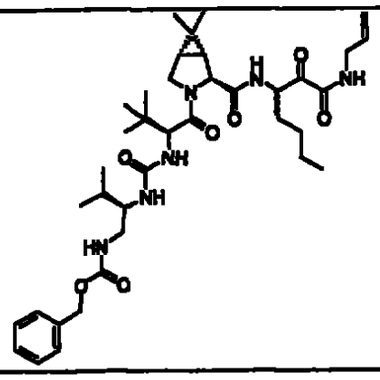
El intermediario 14002a se convirtió en 14002 mediante acoplamiento al intermediario 10 11 seguido por oxidación de Moffett idéntica a los procedimientos descritos en el ejemplo preparativo 6 de síntesis de 11001, Paso D y Paso E

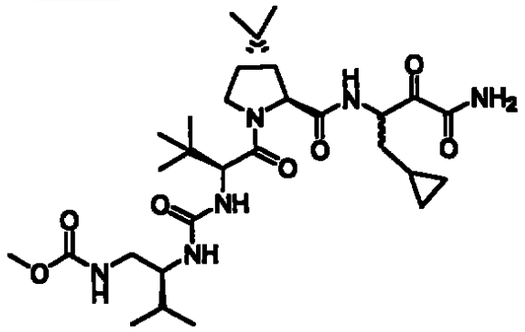
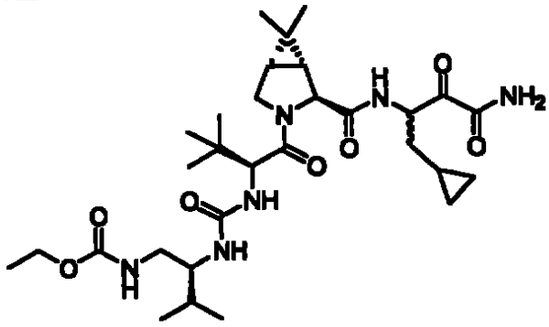
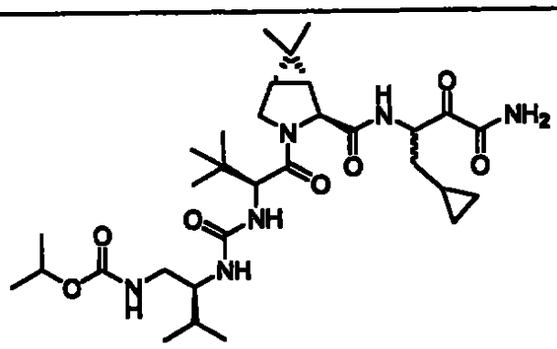
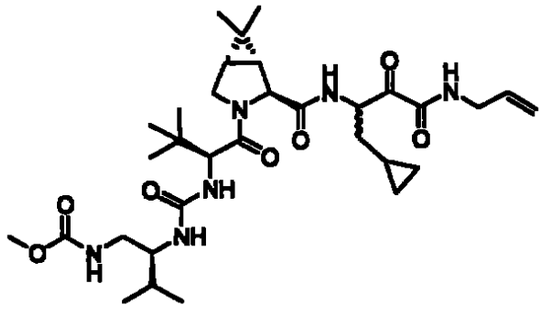
Los compuestos que se muestran en la siguiente Tabla 5 fueron sintetizados utilizando reacciones similares a las mostradas en los Ejemplos anteriores El rango de Ki* indicó que A≤75 nM, 75<B≤250 nM, C>250 nM

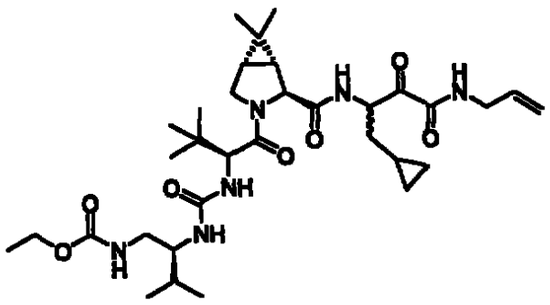
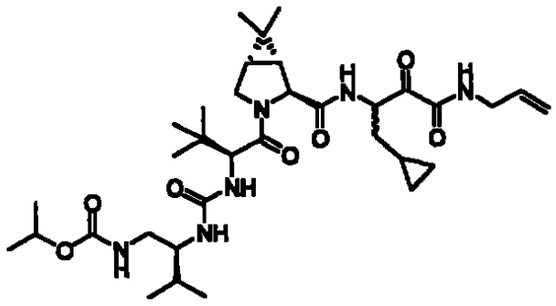
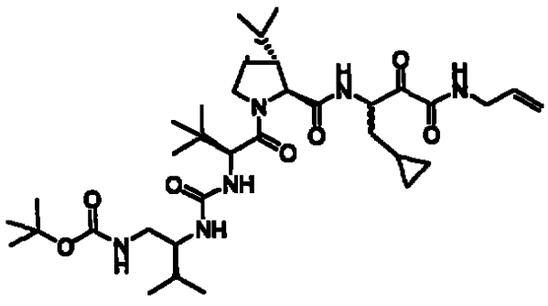
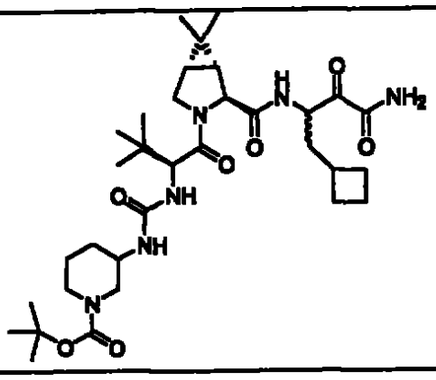
Tabla 5

Item	Estructura	K_i*
14001		A
14002		A
14003		B

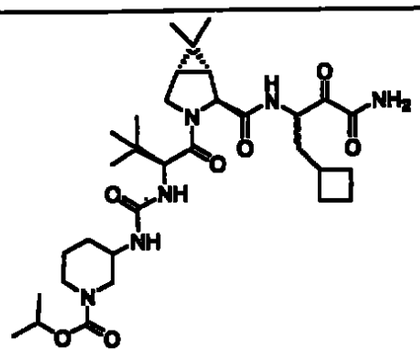
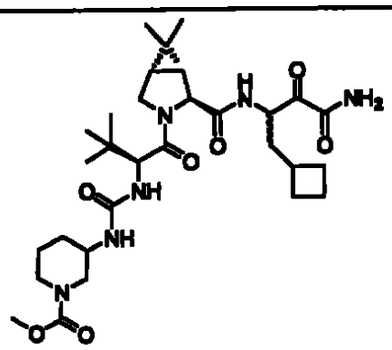
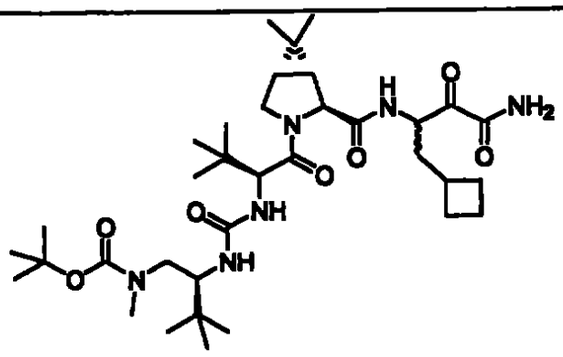
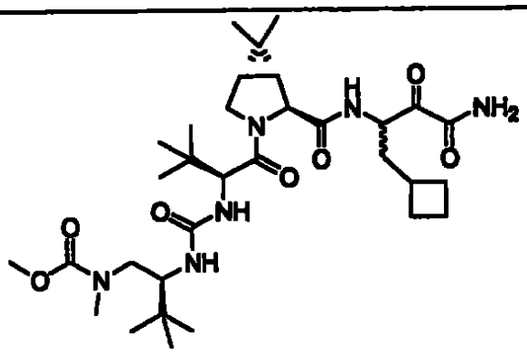
14004		A
14005		A
14009		A
14010		A

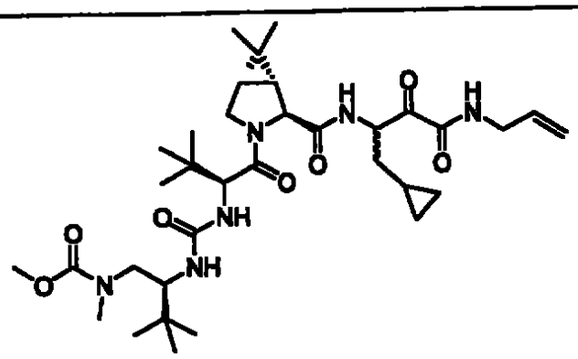
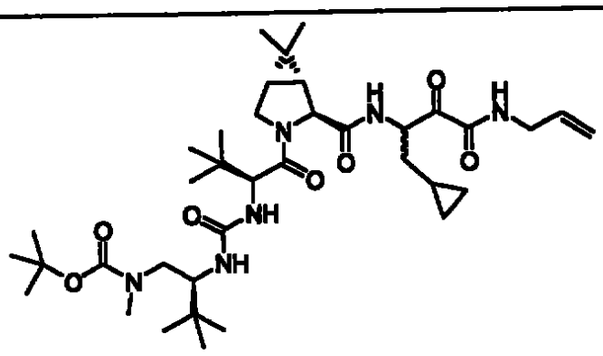
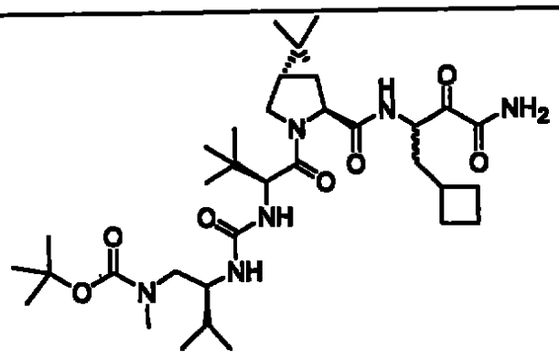
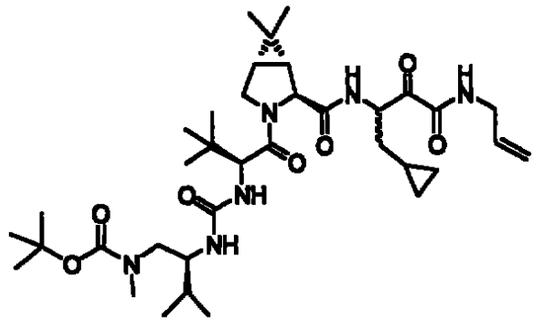
14011		A
14012		B
14016		B
14017		B

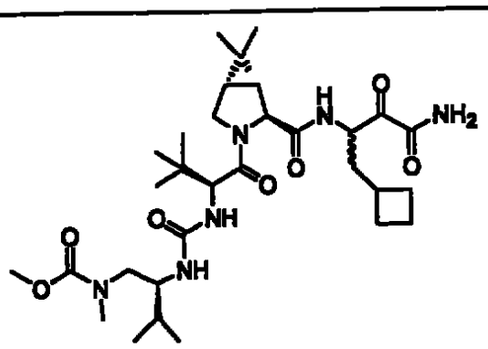
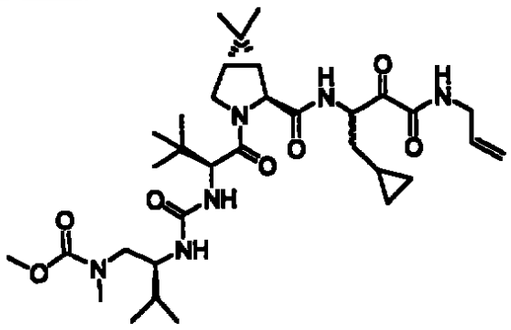
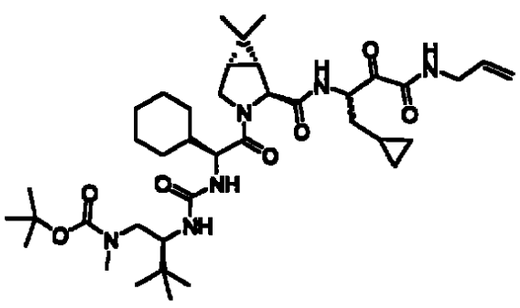
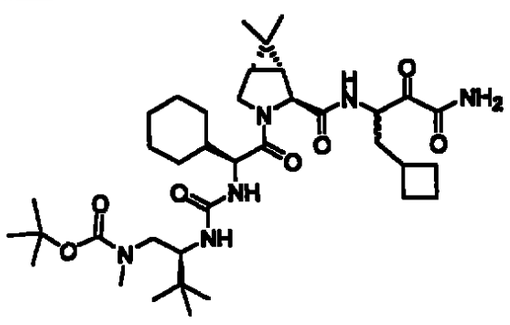
14019		A
14020		A
14021		A
14022		A

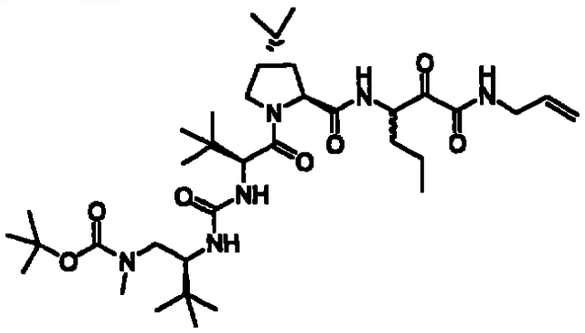
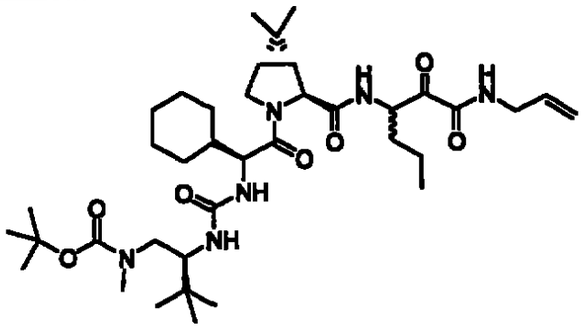
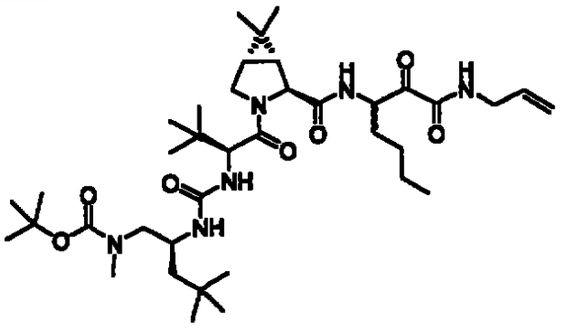
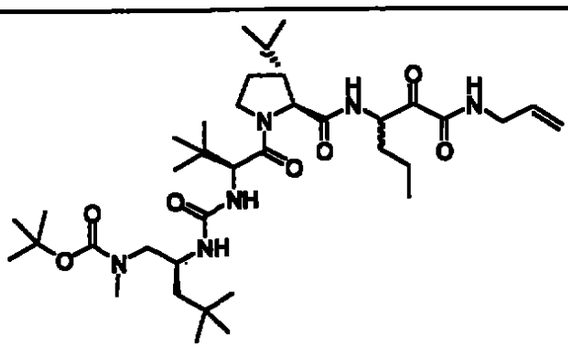
14023		B
14024		B
14025		C
14026		C

440
440

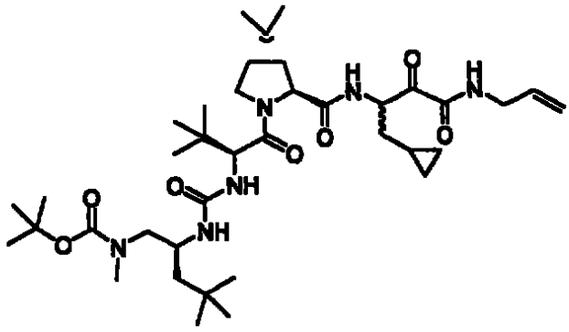
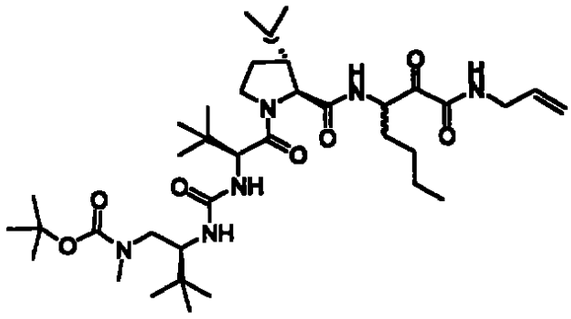
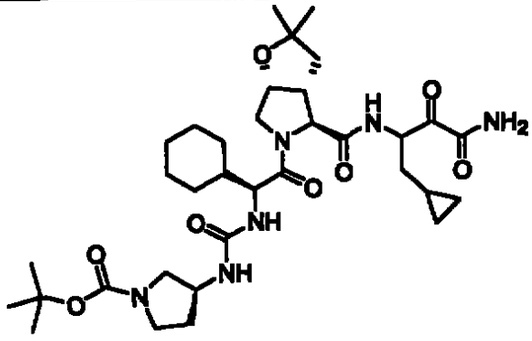
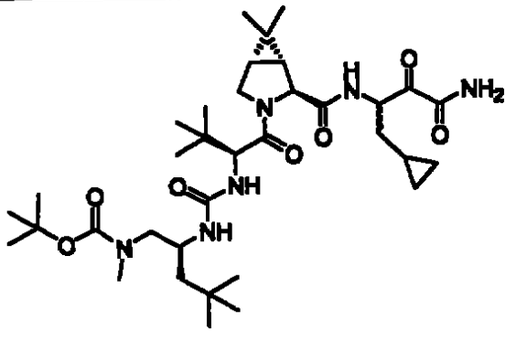
14027		B
14028		B
14029		C
14030		A

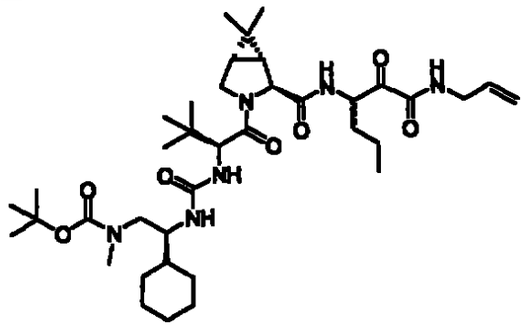
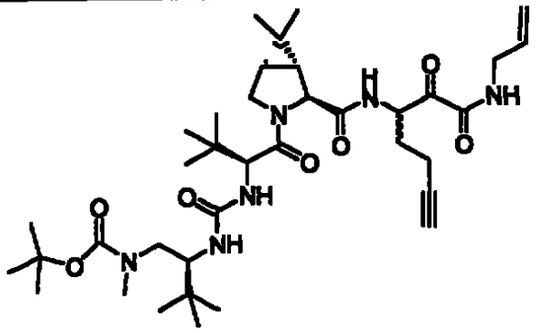
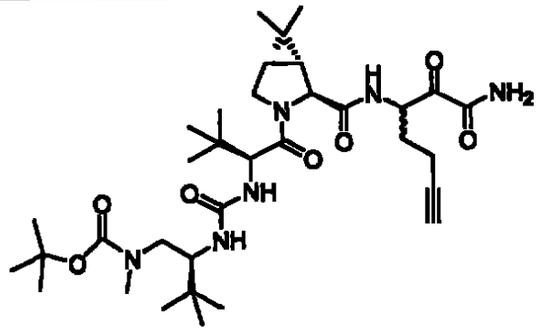
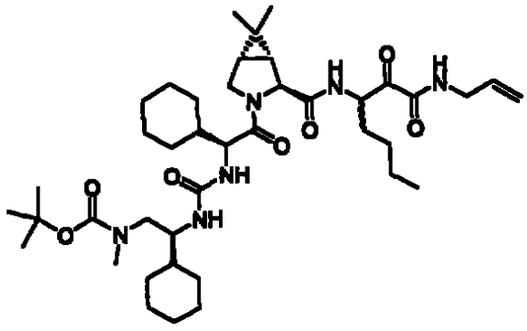
14031		B
14032		C
14033		B
14034		C

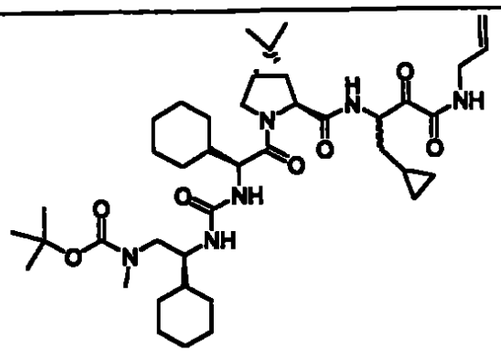
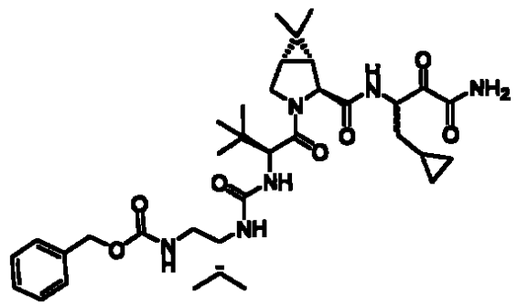
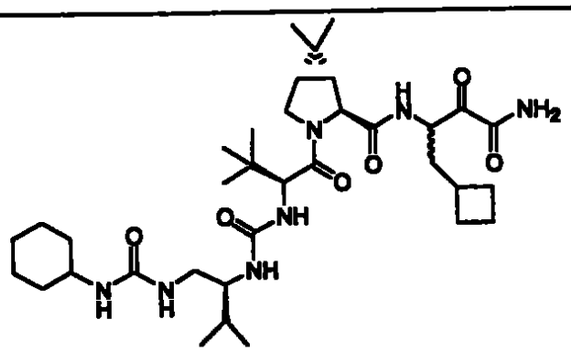
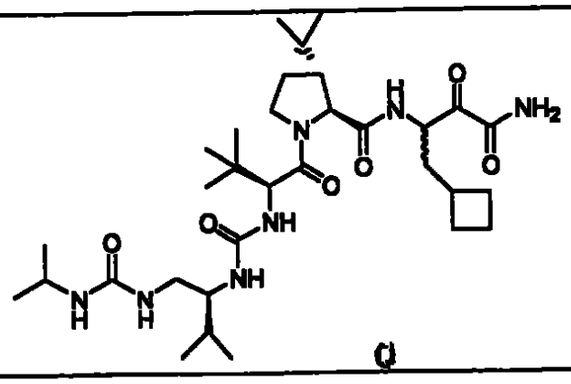
14035		A
14036		B
14037		C
14038		B

14039		C
14040		C
14041		C
14042		C

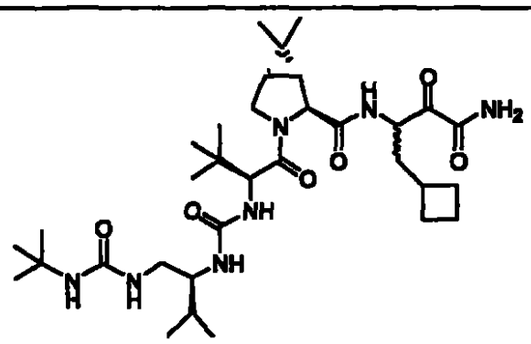
444
444

14043		C
14044		C
14045		C
14046		C

14051		C
14052		C
14053		C
14054		C

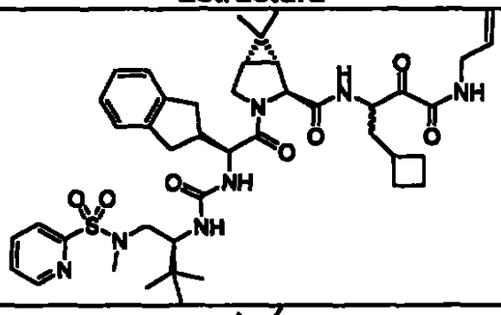
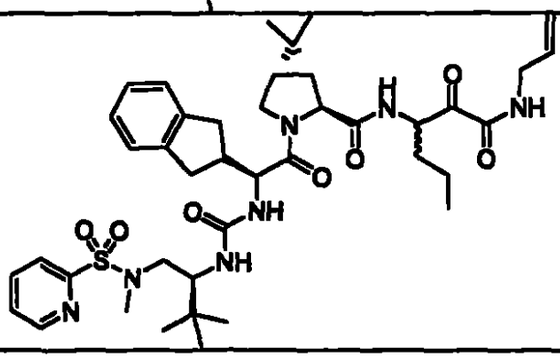
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14057		A
14058		A

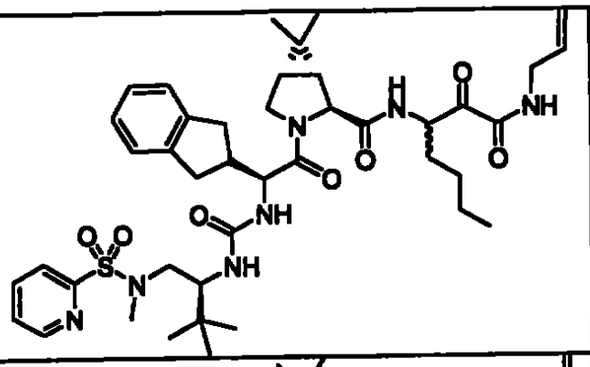
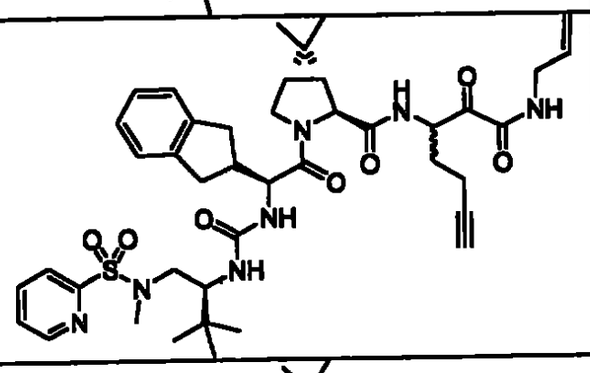
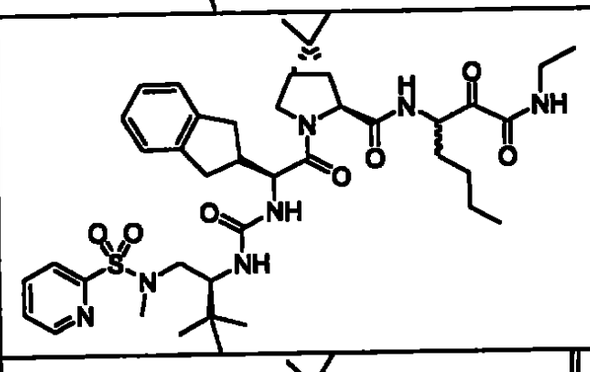
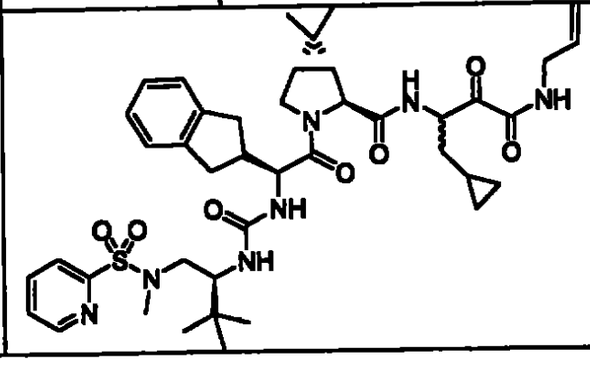
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448

14059		A

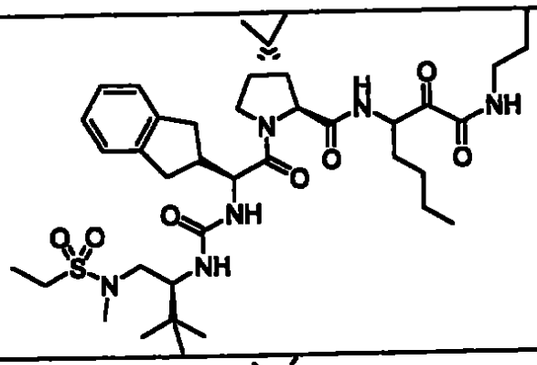
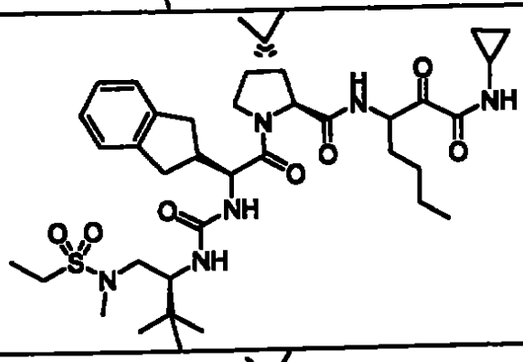
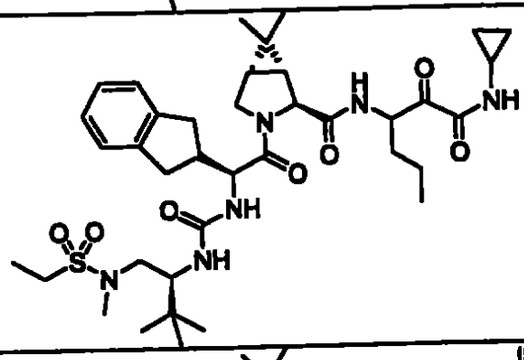
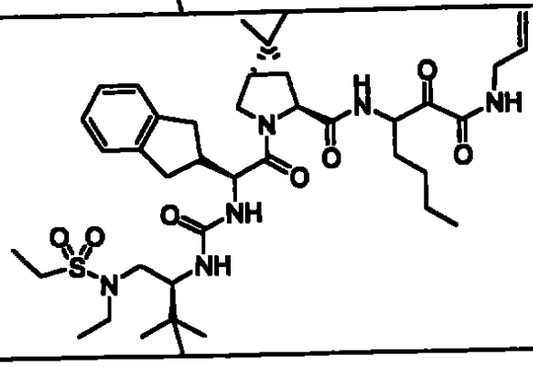
En la Tabla 5A se muestran compuestos adicionales de la presente invención

Tabla 5A

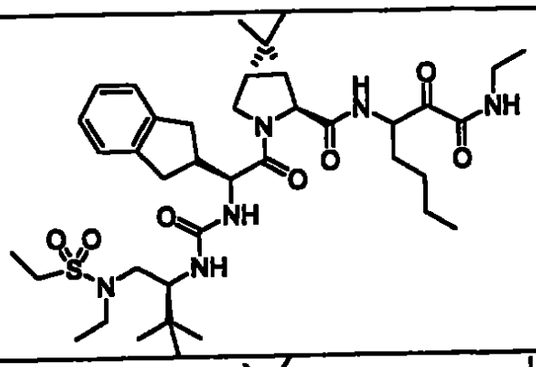
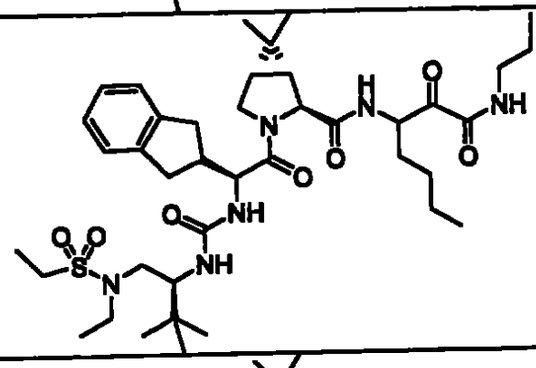
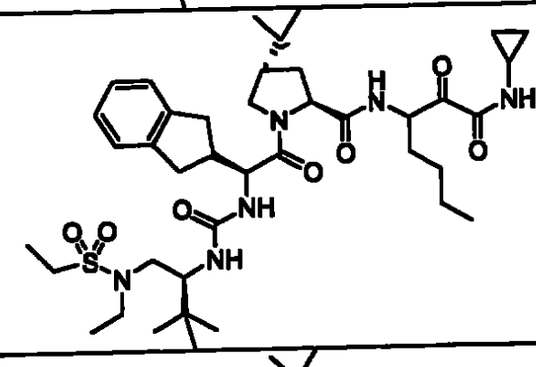
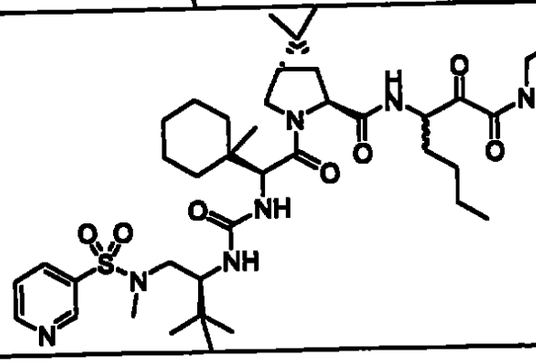
Item	Estructura	K_i*
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11393		A

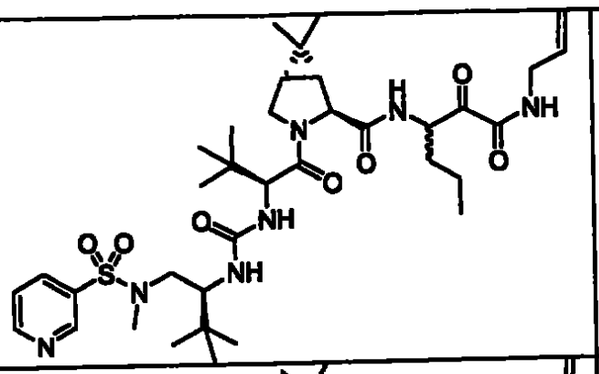
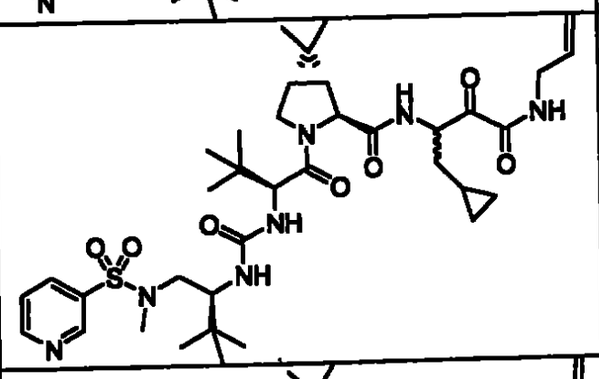
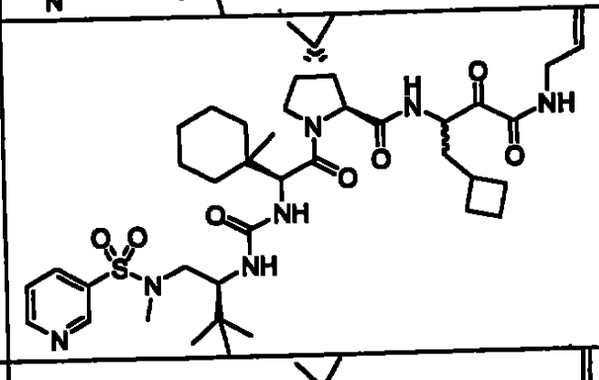
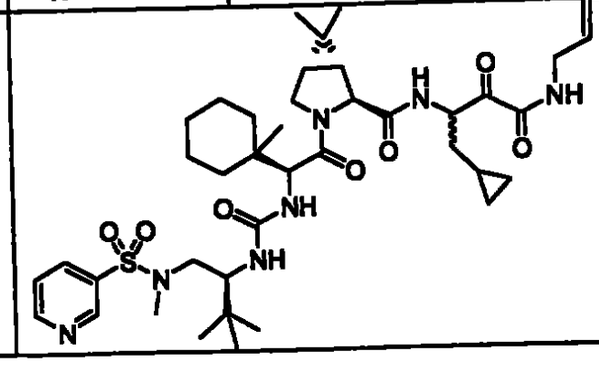
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11395		A
11396		A
11397		B

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450

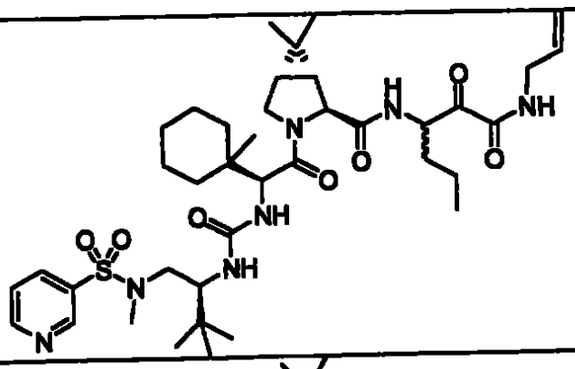
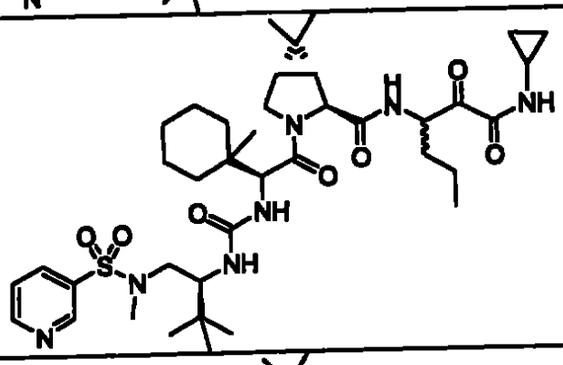
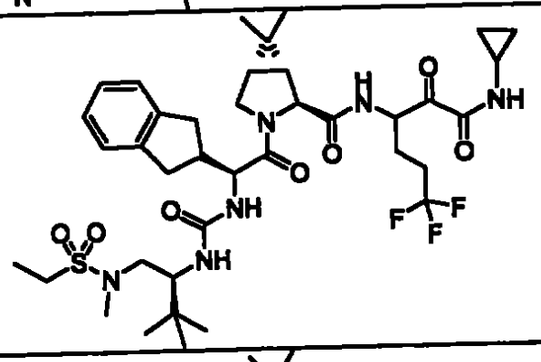
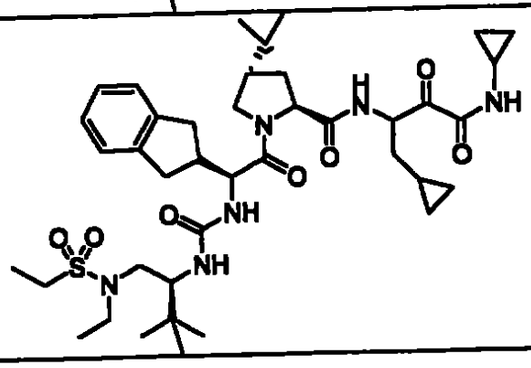
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11401		A

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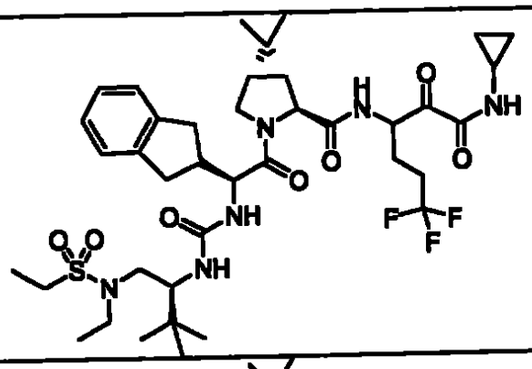
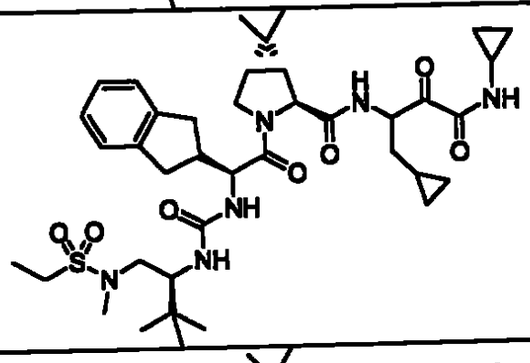
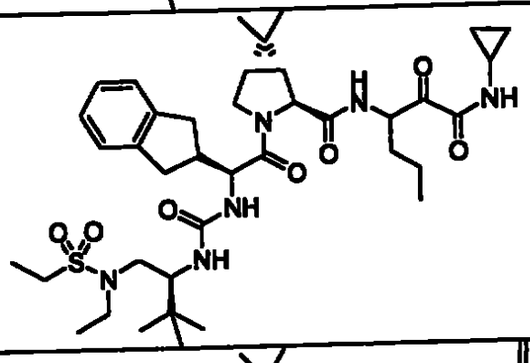
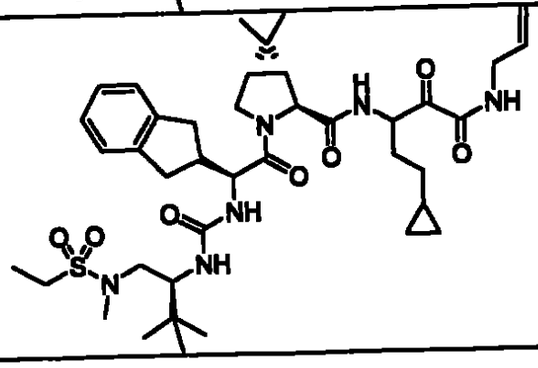
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11407		A
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11409		A

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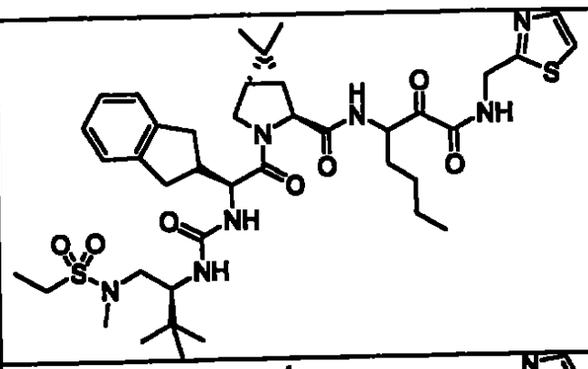
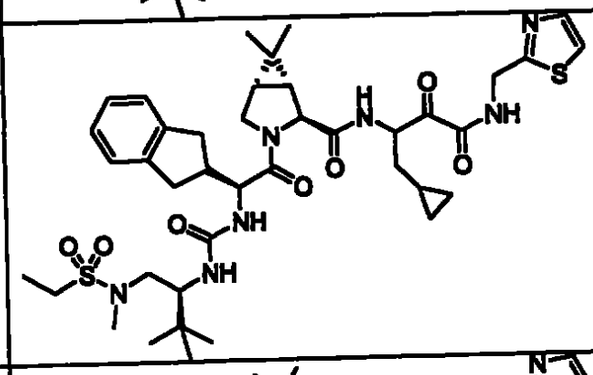
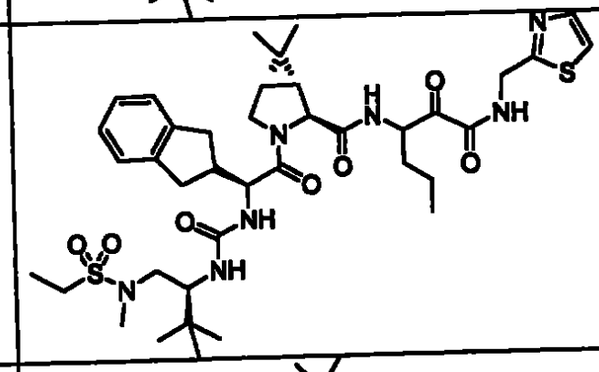
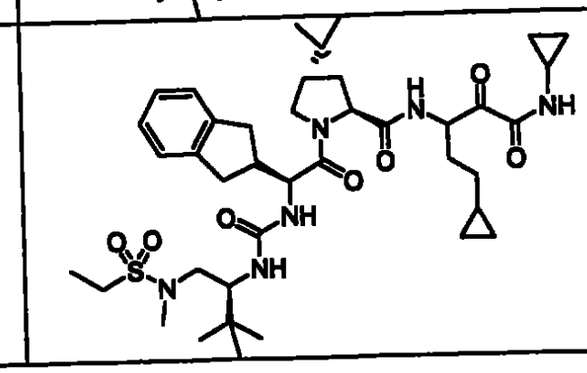
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11413		A

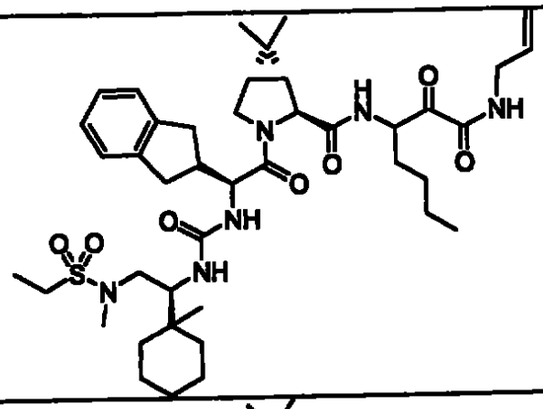
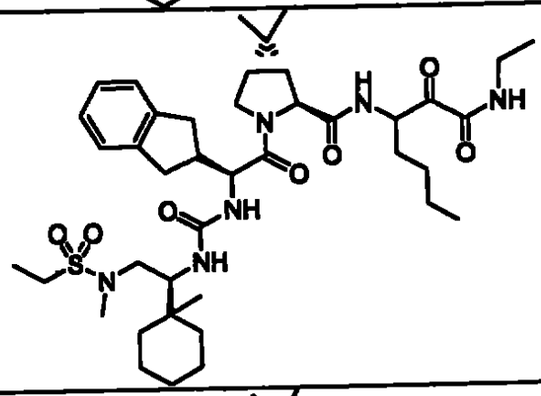
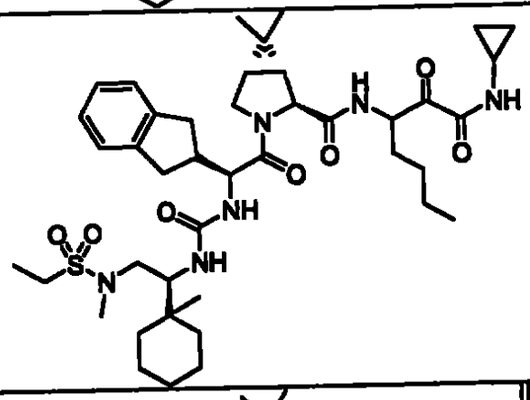
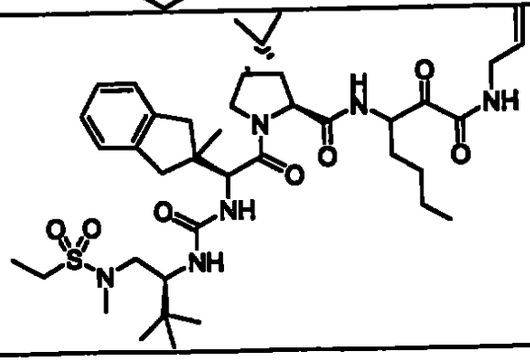
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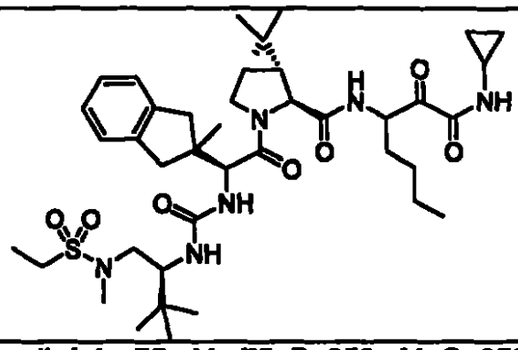
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11417		A

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455

11418		A
11419		A
11420		A
11421		A

11422		A
11423		A
11424		A
11425		A

11426		A

Rango de KI* indicó A≤75 nM, 75<B≤250 nM, C>250 nM

La presente invención se refiere a novedosos inhibidores de proteasa de VHC Esta utilidad puede manifestarse en su capacidad de inhibir a la serina proteasa NS2/NS4a del VHC Un procedimiento general para tal demostración es ilustrado por el siguiente ensayo *in vitro*

Ensayo para Determinar la Actividad Inhibitoria de Proteasa de VHC.

Ensayo espectrofotométrico Puede realizarse un ensayo espectrofotométrico para determinar la serina proteasa de VHC en los compuestos de la invención siguiendo el procedimiento descrito por R Zhang *et al*, *Analytical Biochemistry*, 270 (1999) 268-275, cuya descripción se incorpora en la presente memoria descriptiva como referencia El ensayo basado en la proteólisis de sustratos de éster cromogénicos es adecuado para el monitoreo continuo de la actividad de proteasa NS3 de VHC Los sustratos son derivados del lado P de la secuencia de unión NS5A-NS5B (Ac-DTEDVVX(Nva), donde X = A o P) cuyos grupos carboxilo de terminal C son esterificados con uno de cuatro alcoholes cromofóricos diferentes (3- o 4-nitrofenol, 7-hidroxi-4-metil-cumarina, o 4-fenilazofenol) Más adelante se ilustran la síntesis, caracterización y aplicación de estos novedosos sustratos de éster espectrofotométricos a screening de alto rendimiento y evaluación cinética detallada de los inhibidores de proteasa NS3 de VHC

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Materiales y Métodos

Materiales Los reactivos químicos para los buffers relacionados con el ensayo son obtenidos de Sigma Chemical Company (St Louis, Missouri) Los reactivos para la síntesis peptídica eran de Aldrich Chemicals, Novabiochem (San Diego, California), Applied Biosystems (Foster City, California) y Perseptive Biosystems (Framingham, Massachusetts) Los péptidos son sintetizados manualmente o en un sintetizador ABI modelo 431A automático (de Applied Biosystems) El espectrómetro UV/VIS modelo LAMBDA 12 era de Perkin Elmer (Norwalk, Connecticut) y las placas de UV de 96 pocillos fueron obtenidas de Corning (Corning, Nueva York) El bloque de precalentamiento puede ser de USA Scientific (Ocala, Florida) y el aparato para vórtice de placas de 96 pocillos es de Labline Instruments (Melrose Park, Illinois) Un lector de placas de microtítulo Spectramax Plus con medidor monocromático es obtenido de Molecular Devices (Sunnyvale, California)

Preparación Enzimática La proteasa NS3/NS4A del VHC heterodimérica recombinante (cepa 1a) es preparada utilizando los procedimientos publicados previamente (D L Sali *et al*, *Biochemistry*, 37 (1998) 3392-3401) Las concentraciones de proteína son determinadas mediante el método de tinte Biorad utilizando patrones de proteasa de VHC recombinante previamente cuantificados por análisis de aminoácidos Con anterioridad a la iniciación del ensayo, el buffer de almacenamiento de enzima (fosfato de sodio 50 mM, pH 8 0, NaCl 300 mM, 10% glicerol, 0,05% maltosida de laurilo y DTT 10 mM) es intercambiado por el buffer de ensayo (MOPS 25 mM pH 6,5, NaCl 300 mM, 10% glicerol, 0,05% maltosida de laurilo, 5 µM EDTA y 5 µM DTT) utilizando una columna preempaquetada Bio-Spin P-6 de Biorad

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Síntesis y Purificación de Sustratos La síntesis de los sustratos es realizada segun lo reportado por R Zhang *et al*, (*ibid*) y es iniciada mediante anclaje de Fmoc-Nva-OH a resina de cloruro de 2-clorotritilo utilizando un protocolo estándar (K Barlos *et al*, *Int J Pept Protein Res*, 37 (1991), 513-520) Los péptidos son posteriormente ensamblados, utilizando química de Fmoc, ya sea manualmente o en un sintetizador de péptidos ABI modelo 431 automático Los fragmentos peptídicos N-acetilados y completamente protegidos son disociados de la resina ya sea mediante ácido acético al 10% (HOAc) y trifluoretanol al 10% (TFE) en diclorometano (DCM) durante 30 min, o mediante ácido trifluoracético al 2% (TFA) en DCM durante 10 min El filtrado combinado y el lavado con DCM es evaporado azeotrópicamente (o extraído repetidamente mediante solución de Na_2CO_3 acuoso) para eliminar el ácido utilizado en la disociación La fase de DCM es secada sobre Na_2SO_4 y evaporada

Los sustratos de éster son ensamblados utilizando procedimientos de acoplamiento de ácido- alcohol estándares (K Holmber *et al*, *Acta Chem Scand*, B33 (1979) 410-412) Los fragmentos peptídicos son disueltos 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 diciclohexilcarbodiimida (DCC, 3 eq) para iniciar las reacciones de acoplamiento La formación del producto es monitoreada mediante HPLC y puede encontrarse completa luego de 12-72 horas de reacción a temperatura ambiente El solvente de piridina es evaporado bajo vacío y luego eliminado adicionalmente por evaporación azeotrópica con tolueno El éster peptídico es desprotegido con TFA al 95% en DCM durante dos horas y extraído tres veces con éter etílico anhidro para eliminar el cromóforo en exceso El sustrato desprotegido es purificado mediante HPLC de fase

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inversa en una columna C3 o C8 con un gradiente 30% a 60% de acetonitrilo (utilizando volumenes de seis columnas) El rendimiento total luego de la purificación por HPLC puede ser de aproximadamente 20-30% La masa molecular puede ser confirmada mediante espectroscopía de masas y ionización por electropulverización Los sustratos son almacenados en forma de polvo seco bajo desecación

Espectros de Sustratos y Productos. Los espectros de sustratos y los productos de cromóforos correspondientes son obtenidos en el buffer de ensayo de pH 6,5 Los coeficientes de extinción son determinados a la longitud de onda fuera de pico óptima en cubetas de 1 cm (340 nm para 3-Np y HMC, 370 nm para PAP y 400 nm para 4-Np) utilizando múltiples diluciones La longitud de onda fuera de pico óptima es definida como aquella longitud de onda la cual proporciona la diferencia fraccional máxima en absorbancia entre el sustrato y el producto (DO del producto – DO del sustrato)/DO del sustrato)

Ensayo de Proteasa Se llevan a cabo ensayos de proteasa de VHC a 30°C utilizando una mezcla de reacción de 200 µl en una placa de microtítulo de 96 pocillos Las condiciones del buffer de ensayo (MOPS 25 mM, pH 6,5, NaCl 300 mM, 10% glicerol, 0,05% laurilmaltosida, 5 µM EDTA y 5 µM DTT) son optimizadas para el heterodímero NS3/NS4A (D L Sali *et al*, *ibid*)) Típicamente, se colocan 150 µl de mezclas de buffer, sustrato e inhibidor en pocillos (concentración final de DMSO ≤4 % v/v) y se dejan preincubar a 30°C durante aproximadamente 3 minutos 50 ul de proteasa precalentada (12 nM, 30°C) en buffer de ensayo, se utiliza luego para iniciar la reacción (volumen final 200 µl) Las placas son controladas durante toda la duración del ensayo (60 minutos) para detectar un cambio en la absorbancia en la longitud de onda apropiada (340 nm para 3-Np y HMC, 370 nm para PAP, y 400 nm para 4-Np) utilizando un lector de placas de microtítulo Spectromax Plus equipado

con un medidor monocromático (pueden obtenerse resultados aceptables con lectores de placas que utilizan filtros de corte) La disociación proteolítica de la ligación de éster entre el Nva y el cromóforo es controlada a la longitud de onda apropiada contra un testigo no enzimático como control para la hidrólisis no enzimática La evaluación de los parámetros cinéticos de los sustratos se lleva a cabo sobre un rango de concentración de sustrato de 30 veces (~6-200 μM) Las velocidades iniciales son determinadas utilizando regresión lineal y las constantes cinéticas son obtenidas mediante ajuste de los datos a la ecuación Michaelis-Menten utilizando análisis de regresión no lineal (Mac Curve Fit 1 1, K Raner) Los números de productividad (k_{cat}) son calculados suponiendo que la enzima es completamente activa

Evaluación de los inhibidores e inactivadores. Las constantes de inhibición (K_i) para los inhibidores competitivos Ac-D-(D-Gla)-L-I-(Cha)-C-OH (27), Ac-DTEDVVA(Nva)-OH y Ac-DTEDVVP(Nva)-OH se determinan experimentalmente a concentraciones fijas de enzima y sustrato trazando v_o/v_i vs concentración de inhibidor ($[I]_o$) de acuerdo con la ecuación Michaelis-Menten reordenada para la cinética de inhibición competitiva $v_o/v_i = 1 + [I]_o /(K_i (1 + [S]_o /K_m))$, donde v_o es la velocidad inicial no inhibida, v_i es la velocidad inicial en presencia de inhibidor a cualquier concentración de inhibidor determinada ($[I]_o$) y $[S]_o$ es la concentración de sustrato utilizada Los datos resultantes son ajustados utilizando regresión lineal y la inclinación resultante, $1/(K_i(1+[S]_o/K_m)$, es utilizada para calcular el valor K_i Los valores K_i^* para algunos de los compuestos de la invención fueron proporcionados anteriormente en la Tabla 6

Si bien la presente invención ha sido descrita juntamente con las realizaciones específicas expuestas anteriormente, muchas alternativas, modificaciones y otras

variaciones de las mismas serán evidentes para los expertos en la técnica Todas esas alternativas, modificaciones y variaciones tienen el propósito de caer dentro del espíntu y alcance de la presente invención

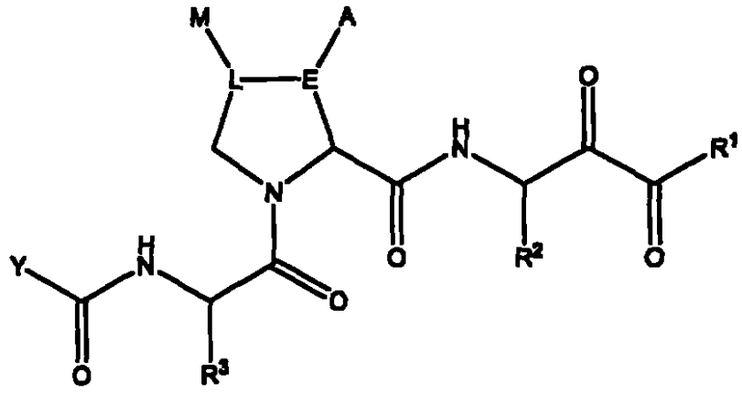
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REIVINDICACIONES

Habiendo así especialmente descrito y determinado la naturaleza de la presente invención y la forma cómo la misma ha de ser llevada a la práctica se declara reivindicar como de propiedad y derecho exclusivo

1 Un compuesto o enantiómeros, estereoisómeros, rotámeros, tautómeros, diastereómeros y racematos de dicho compuesto, o una sal, solvato o éster de dicho compuesto farmacéuticamente aceptable, teniendo dicho compuesto la estructura general mostrada en la Fórmula I

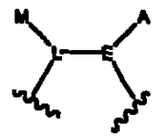


Fórmula I

en la cual

R^1 es H, OR^8, NR^9R^{10}, o CHR^9R^{10}, en la cual R^8, R^9 y R^{10} pueden ser iguales o diferentes, siendo cada uno seleccionado independientemente del grupo formado por H, alquil-, alquenil-, alquinil-, aril-, heteroalquil-, heteroaril-, cicloalquil-, heterociclil-, arilalquil-, y heteroarilalquilo,

A y M pueden ser iguales o diferentes, siendo cada uno seleccionado independientemente entre R, NR^9R^{10}, SR, SO_2R, y halo, o A y M están conectados entre sí (en otras palabras, A-E-L-M tomados en forma conjunta) de modo que la porción



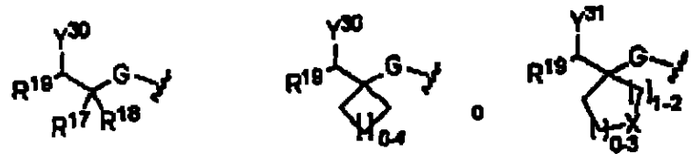
que se muestra más arriba en la Fórmula I forma ya sea un cicloalquilo de tres, cuatro, seis, siete u ocho miembros, un heterociclilo de cuatro a ocho miembros, un arilo de seis a diez miembros o un heteroarilo de cinco a diez miembros,

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

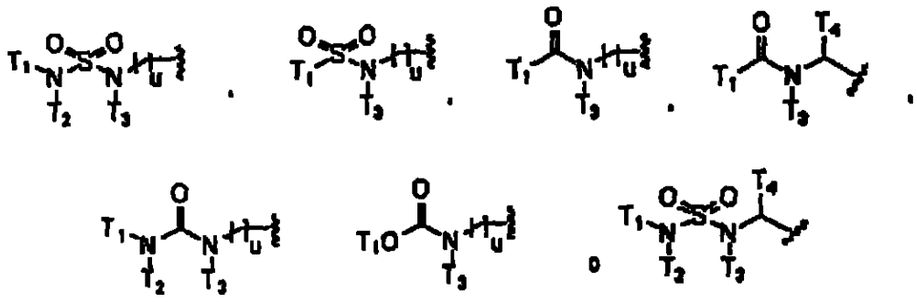
L es C(H), C(R), $CH_2C(R)$, o $C(R)CH_2$,

R, R', R^2, y R^3 pueden ser iguales o diferentes, siendo cada uno seleccionado independientemente del grupo formado por H, alquil-, alquenil-, alquinil-, cicloalquil-, heteroalquil-, heterociclil-, aril-, heteroaril-, (cicloalquil)alquil-, (heterociclil)alquil-, aril-alquil-, y heteroaril-alquil-, o alternativamente R y R' en NRR' están conectados entre sí de modo que NR^9R^{10} forma un heterociclilo de cuatro a ocho miembros,

Y se selecciona de las siguientes porciones



donde Y^{30} e Y^{31} se seleccionan entre



donde u es un Nº 0-6

X se selecciona entre O, NR^{15}, $NC(O)R^{15}$, S, S(O) y SO_2,

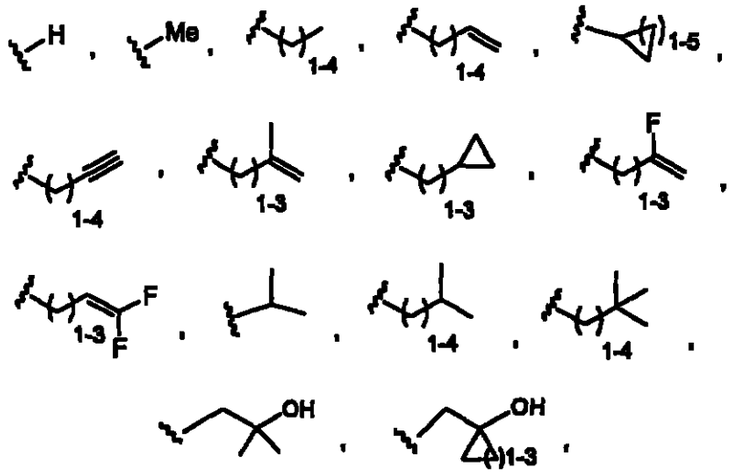
G es NH o O, y

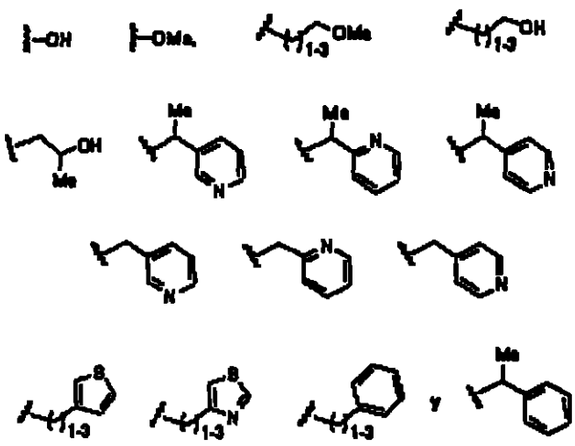
R^{15}, R^{16}, R^{17} , R^{18}, R^{19}, T_1, T_2, T_3 y T_4 pueden ser iguales o diferentes, siendo cada uno seleccionado independientemente del grupo formado por H, alquilo, heteroalquilo, alquenilo, heteroalquenilo, alquinilo, heteroalquinilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroarilo, y heteroarilalquilo, o alternativamente, R^{17} y R^{18} están conectados entre sí para formar un cicloalquilo o heterociclilo de tres a ocho miembros,

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

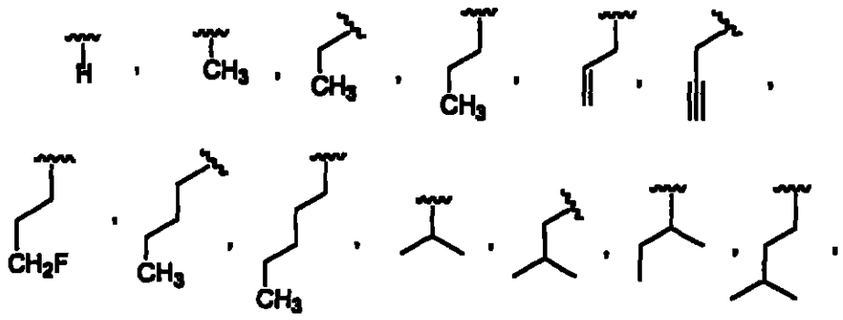
2 El compuesto de acuerdo con la reivindicación 1, donde R^1 es NR^9R^{10}, y R^9 es H, R^{10} es H, o R^{14} donde R^{14} es H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, alquil-arilo, alquil-heteroarilo, aril-alquilo, alquenilo, alquinilo o heteroaril-alquilo

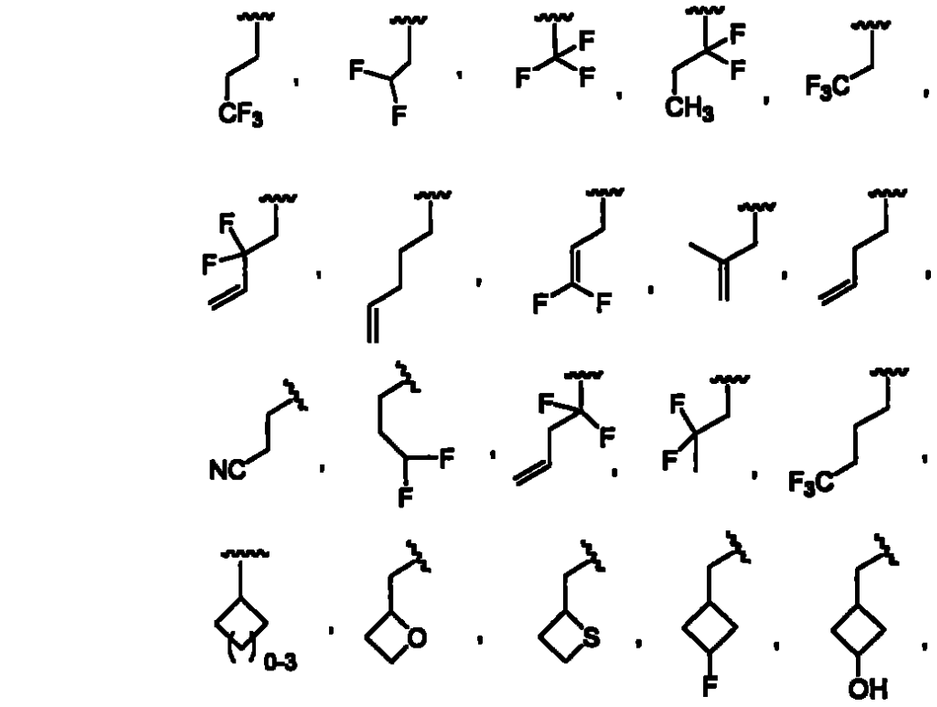
3 El compuesto de acuerdo con la reivindicación 2, donde R^{14} se selecciona entre el grupo que consiste en

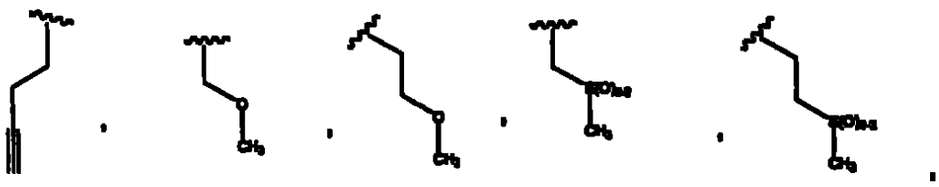


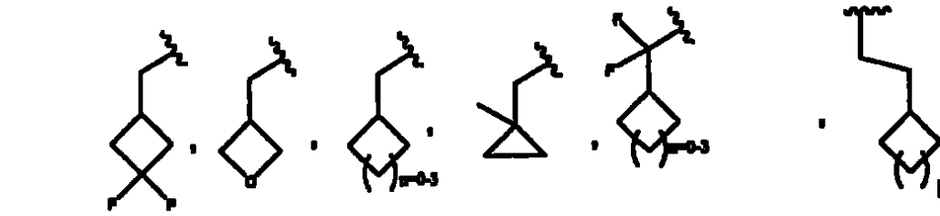


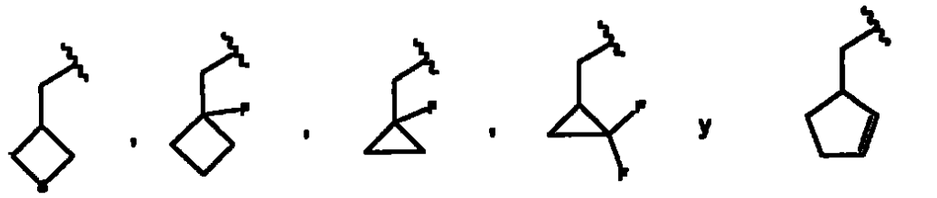
4 El compuesto de acuerdo con la reivindicación 1, donde R^2 se selecciona entre el grupo que consiste en las siguientes porciones



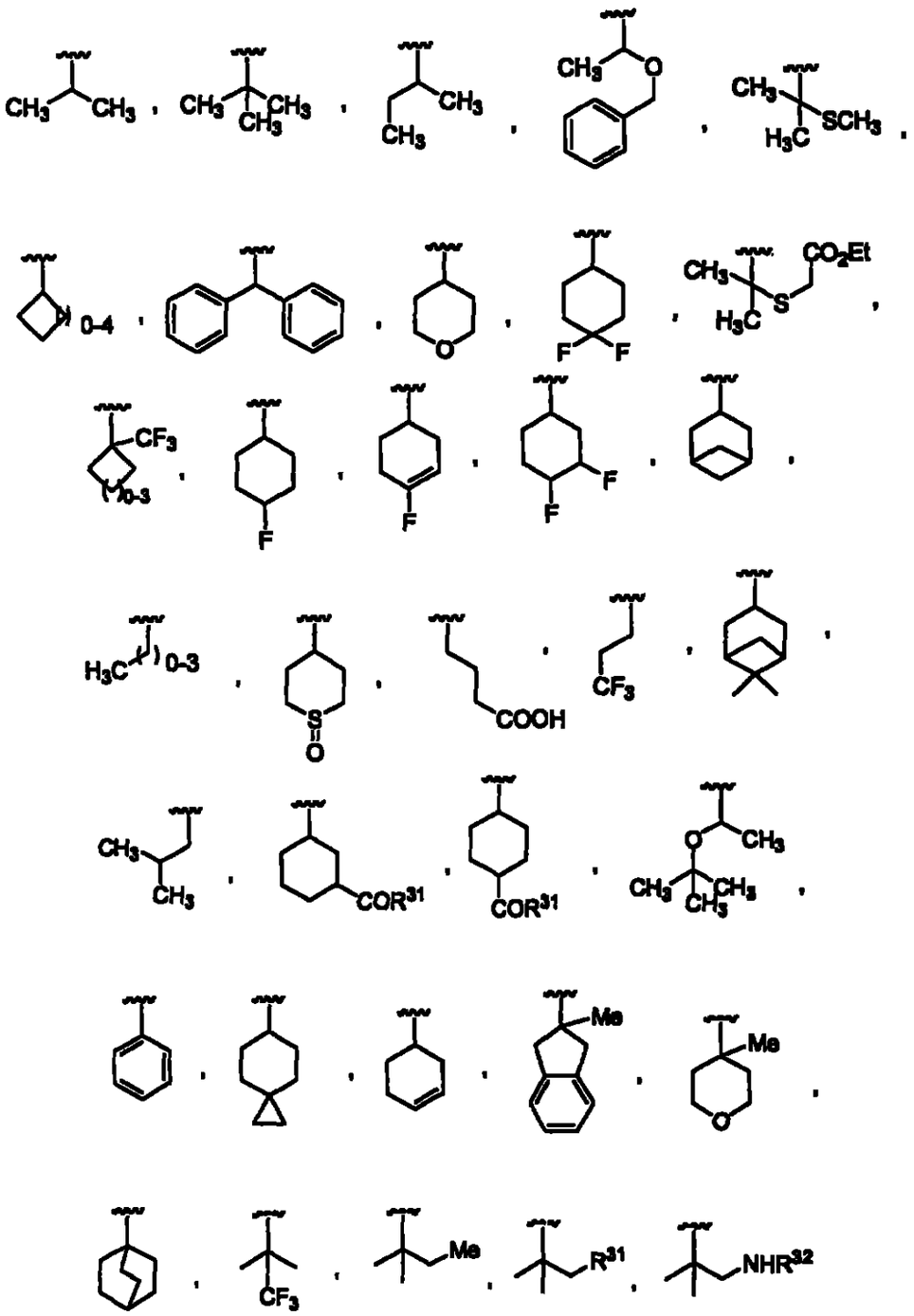


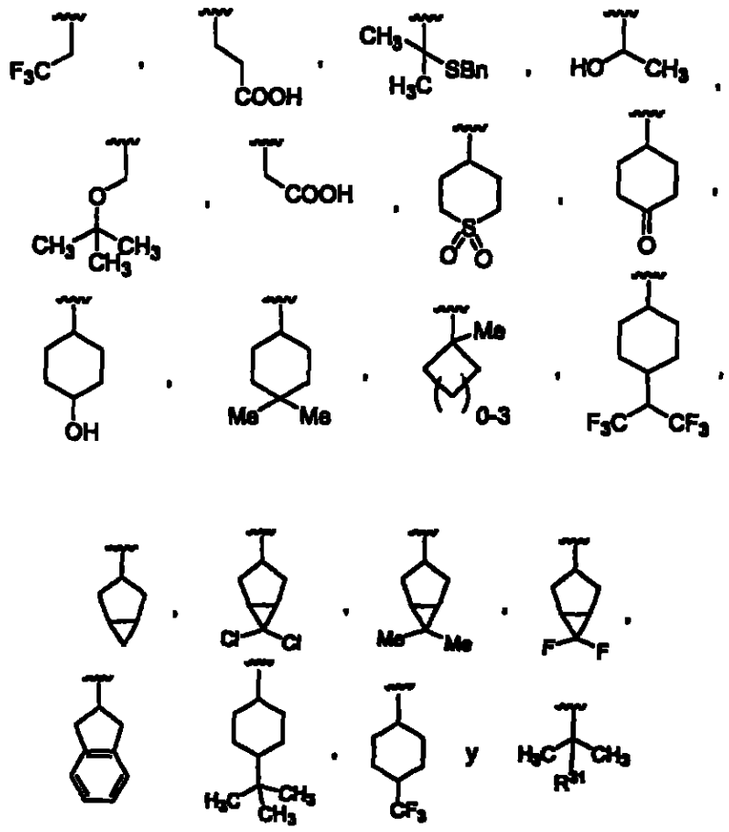






5 El compuesto de acuerdo con la reivindicación 1, donde R^3 se selecciona entre el grupo que consiste en

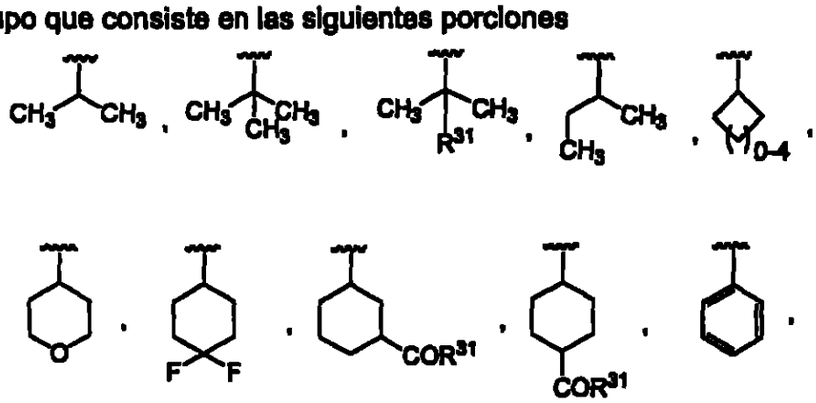


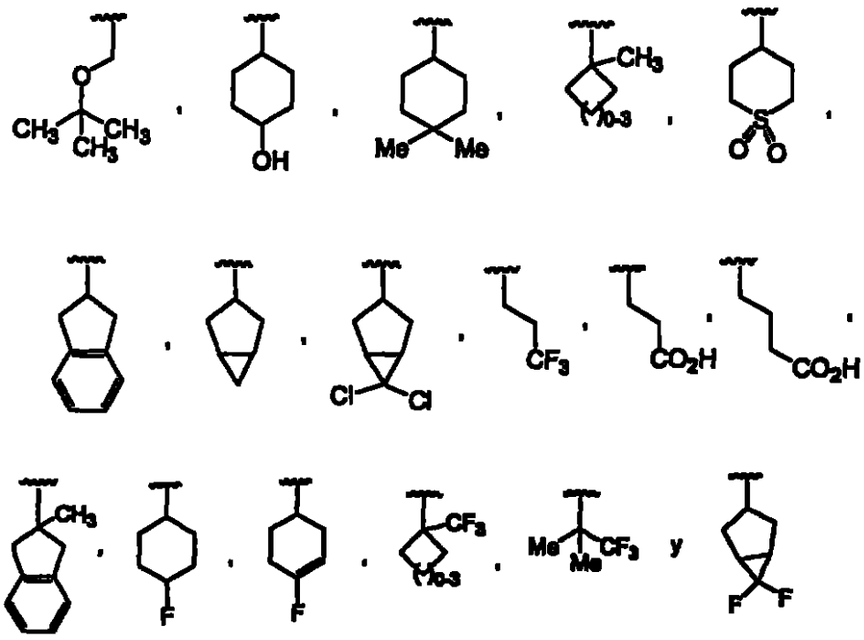


donde R^{31} es OH o O-alquilo, y

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

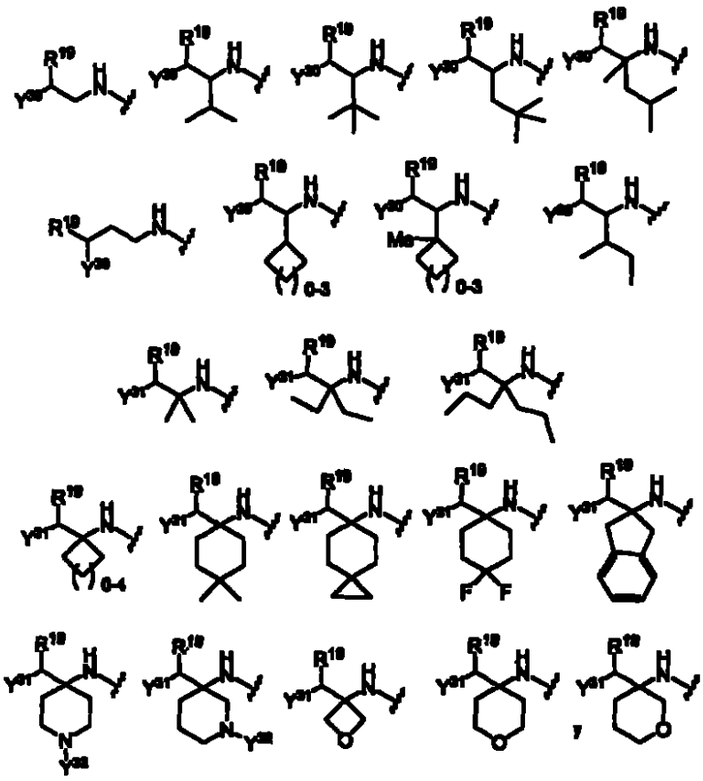
6 El compuesto de acuerdo con la reivindicación 5, donde R^3 se selecciona entre el grupo que consiste en las siguientes porciones



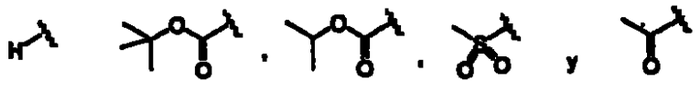


7 El compuesto de acuerdo con la reivindicación 1, donde G es NH

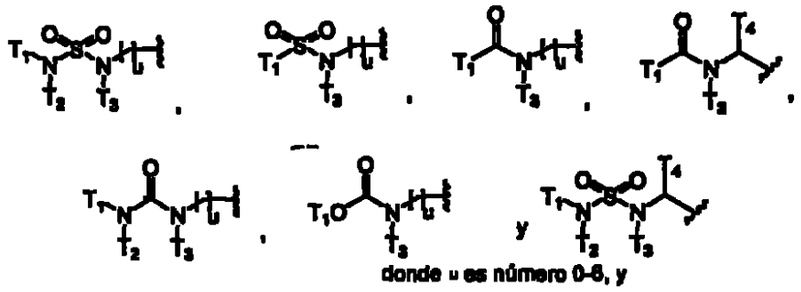
8 El compuesto de acuerdo con la reivindicación 7, donde Y se selecciona entre las siguientes porciones



donde Y^{32} se selecciona entre el grupo que consiste en

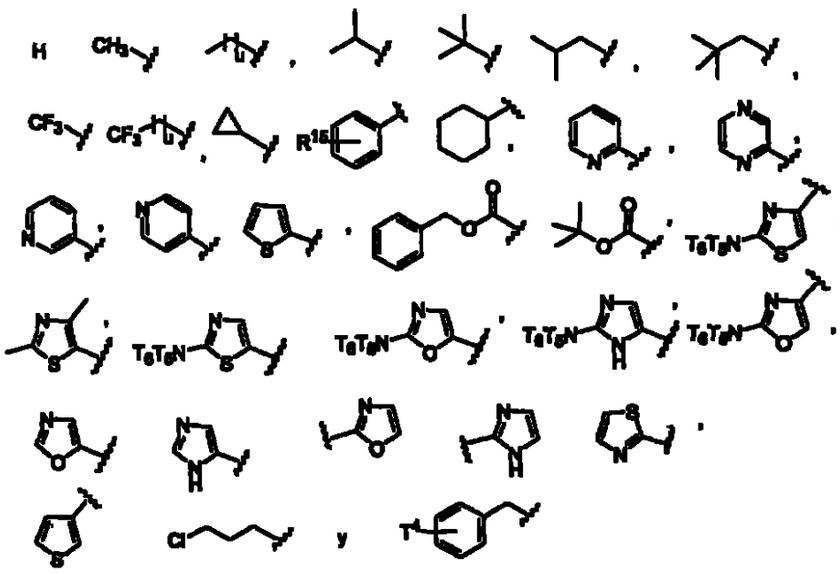


Y^{30} y Y^{31} se selecciona entre



donde u es número 0-6, y

R^{19} se selecciona entre H, alquilo, fenilo o bencilo 9 El compuesto de acuerdo con la reivindicación 8, donde T_1 y T_2 pueden ser iguales o diferentes, siendo cada uno seleccionado independientemente entre el grupo que consiste en

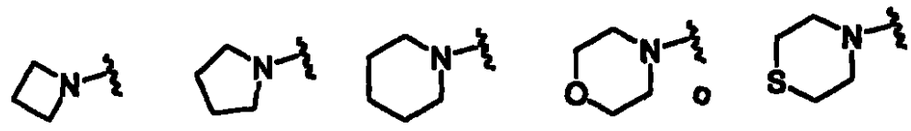


donde T_5 y T_6 pueden ser iguales o diferentes, siendo cada uno seleccionado en forma independiente entre el grupo que consiste en alquilo, arilo, cicloalquilo, heteroarilo y heterociclilo,

o la porción

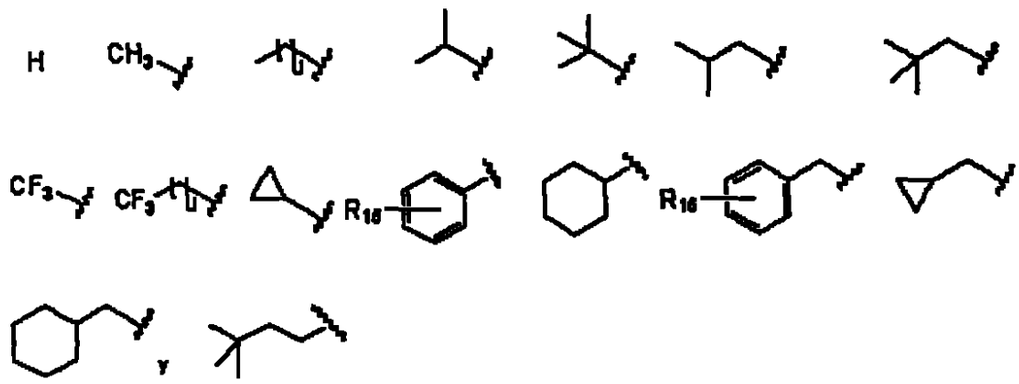


en forma conjunta representan



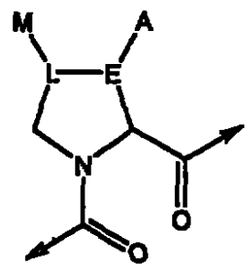
y

T_3 y T_4 pueden ser iguales o diferentes , siendo cada uno seleccionado en forma independientemente entre

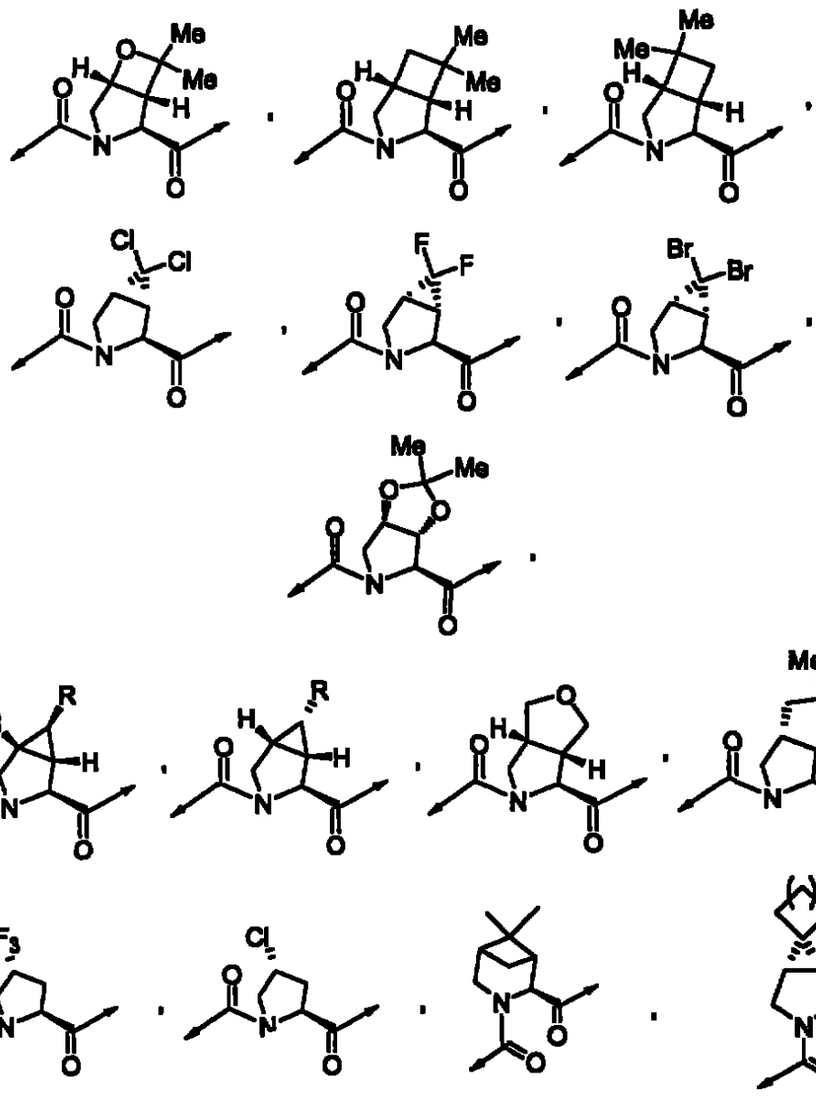


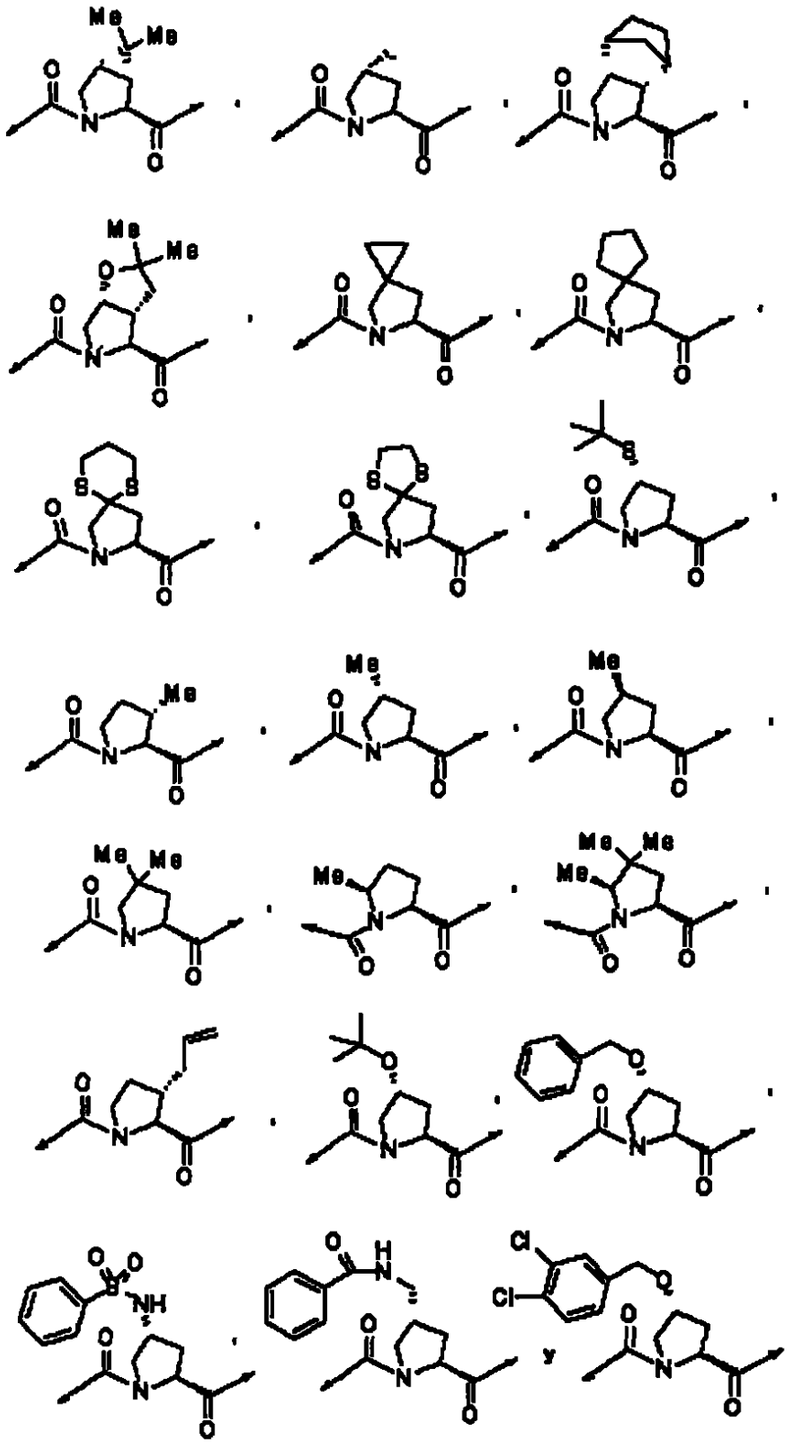
o T_3 y T_4 tomados en forma conjunta pueden formar parte de un anillo heterocíclico de cuatro a siete miembros

9 El compuesto de acuerdo con la reivindicación 1, donde la porción

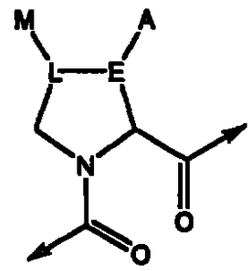


se selecciona entre las siguientes estructuras

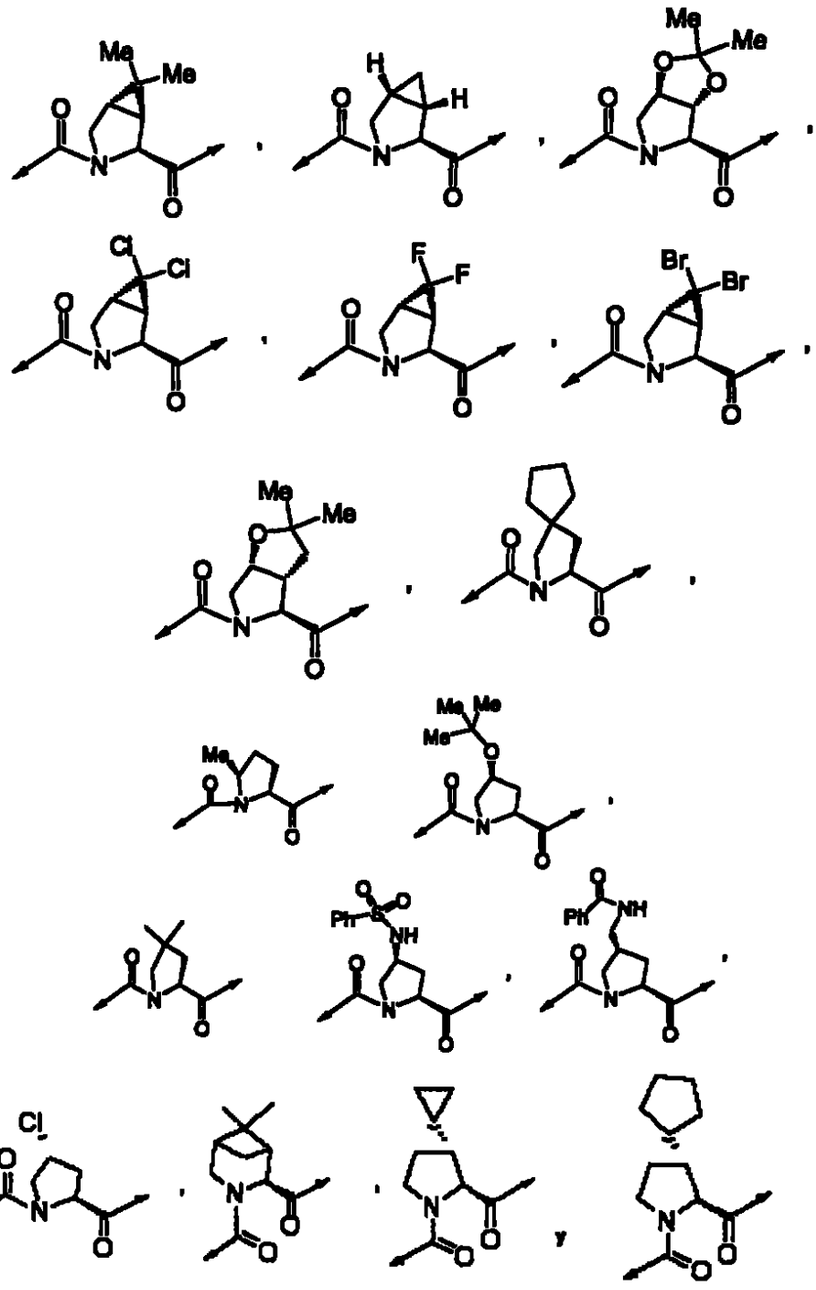




10 El compuesto de acuerdo con la reivindicación 9, donde la porción

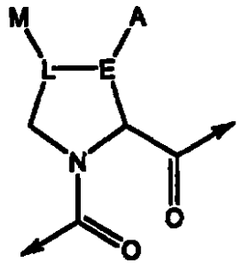


se selecciona entre las siguientes estructuras

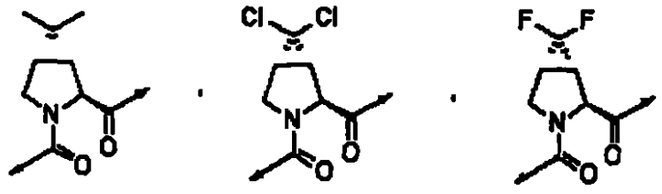


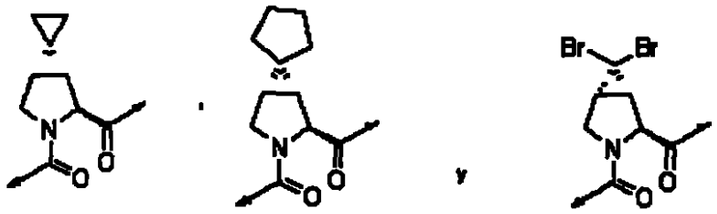
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11 El compuesto de acuerdo con la reivindicación 10, donde la porción

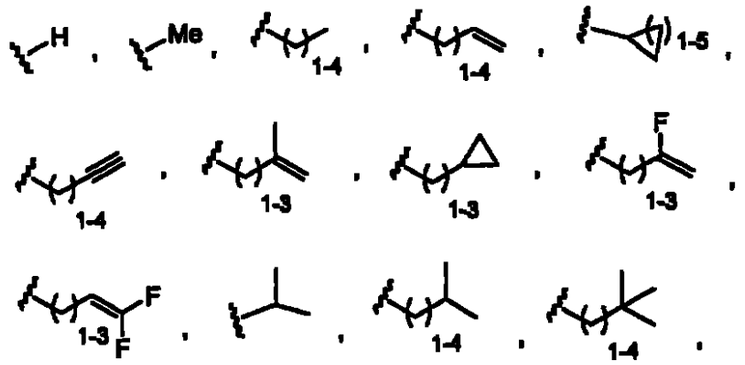


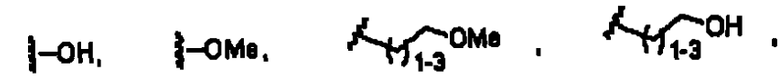
se selecciona entre las siguientes estructuras

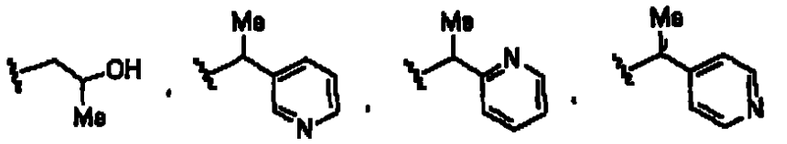


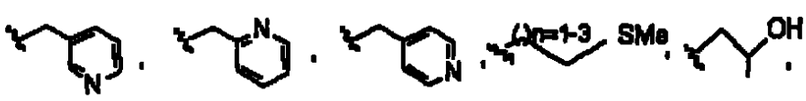


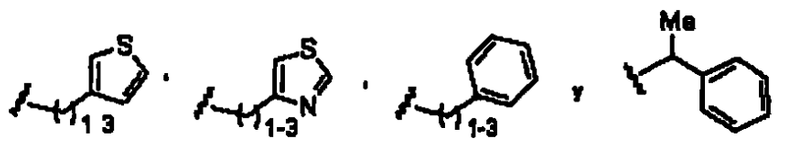
12 El compuesto de acuerdo con la reivindicación 1, donde R^1 es NHR^{14}, donde R^{14} se selecciona entre el grupo que consiste en



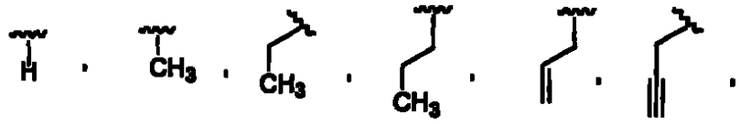


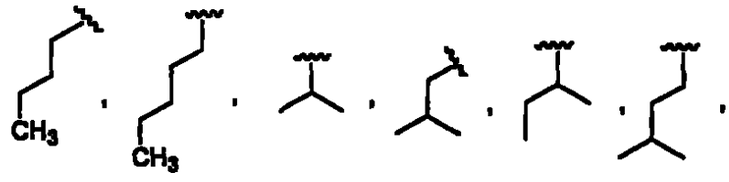


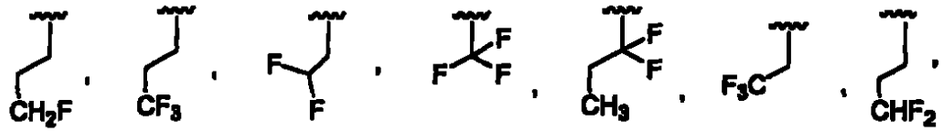


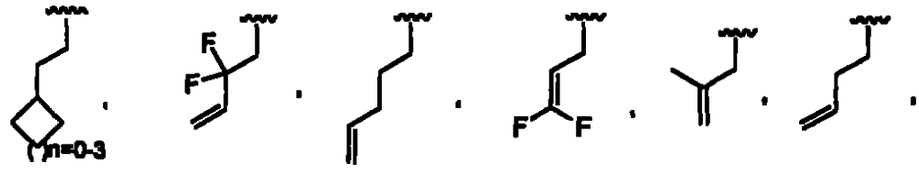


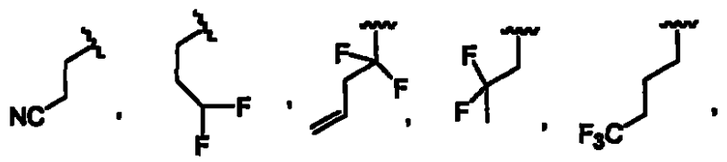
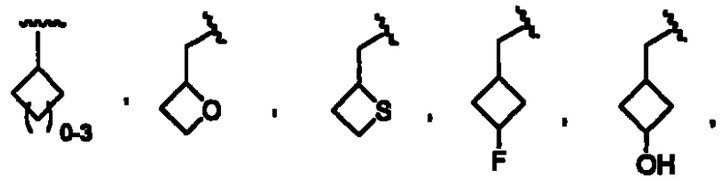
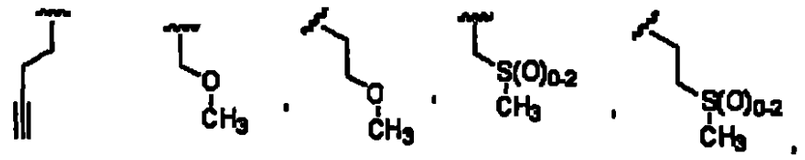
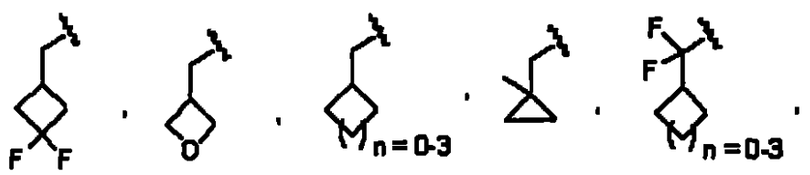
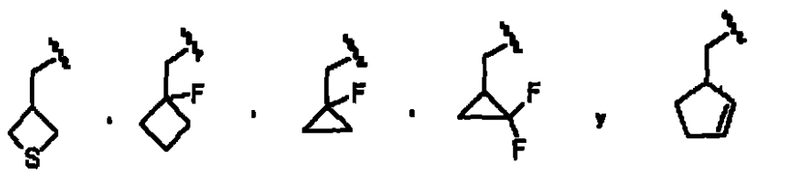
R^2 se selecciona entre el grupo que consiste en las siguientes porciones



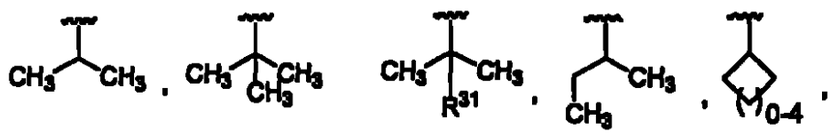
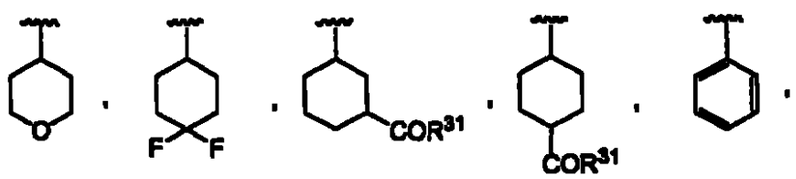


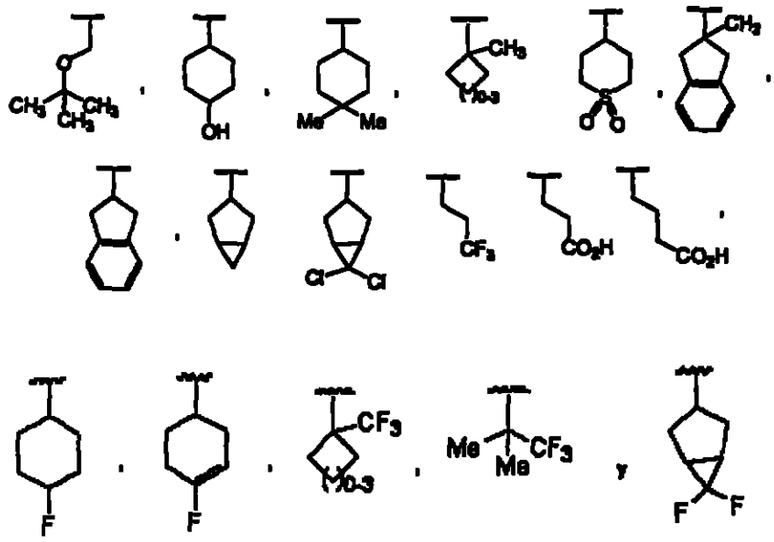




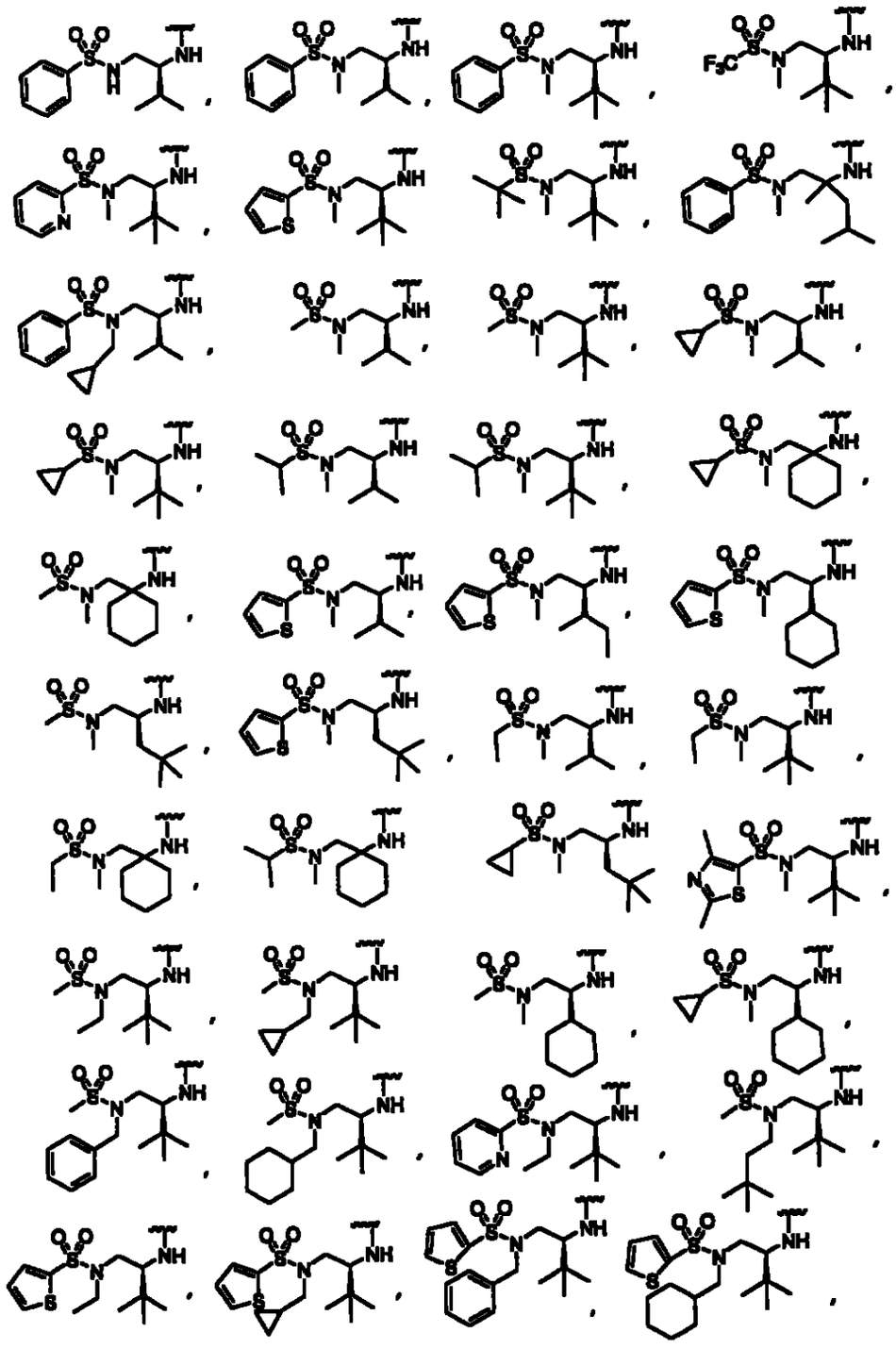






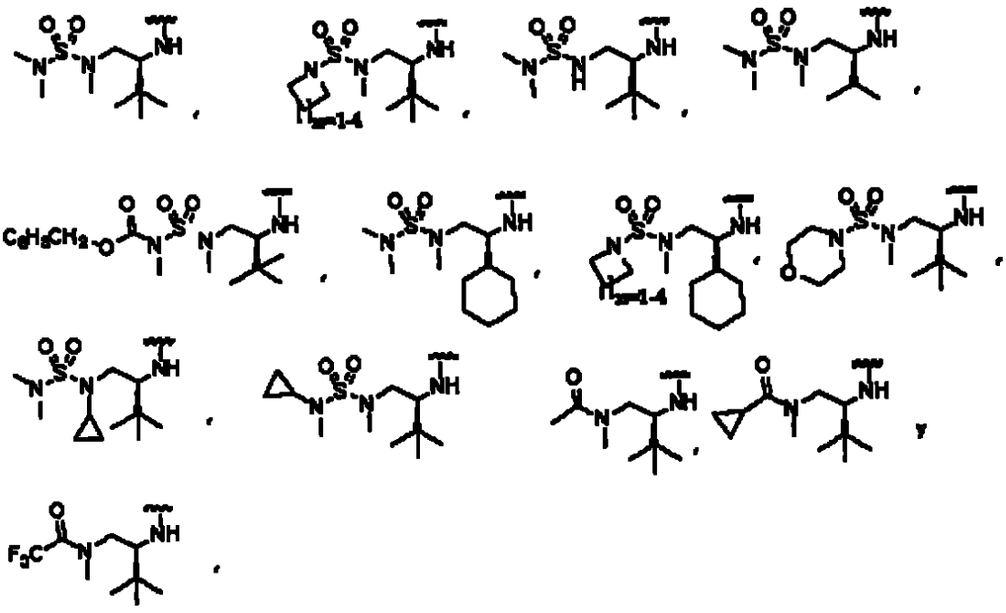
R^3 se selecciona entre el grupo que consiste en las siguientes porciones

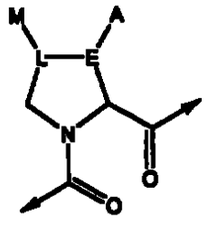


Y se selecciona entre el grupo que consiste en

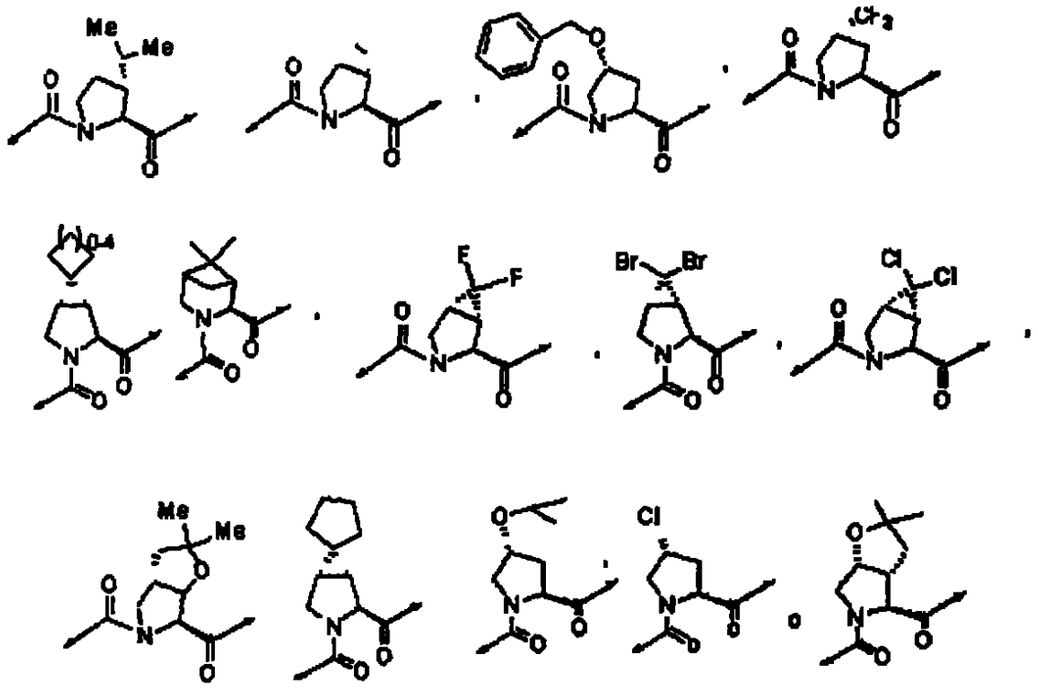




y la porción



es



13 Una composición farmacéutica que comprende como ingrediente activo por lo menos un compuesto de acuerdo con la reivindicación 1

14 La composición farmacéutica de acuerdo con la reivindicación 13 para uso en el tratamiento de trastornos asociados con el Virus de la Hepatitis C ("VHC")

15 La composición farmacéutica de acuerdo con la reivindicación 14 que comprende adicionalmente por lo menos un portador farmacéuticamente aceptable

16 La composición farmacéutica de acuerdo con la reivindicación 15, que contiene adicionalmente por lo menos un agente antiviral

17 La composición farmacéutica de acuerdo con la reivindicación 16, que contiene adicionalmente por lo menos un interferón

18 La composición farmacéutica de acuerdo con la reivindicación 17, donde dicho por lo menos un agente antiviral es ribavirina y dicho por lo menos un interferón es α-interferón o interferón pegilado

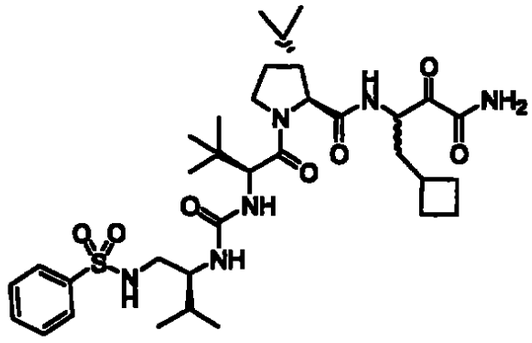
19 Un método para tratar trastornos asociados con el VHC, comprendiendo dicho método administrar a un paciente que necesita de dicho tratamiento una composición farmacéutica la cual comprende cantidades terapéuticamente eficaces de por lo menos un compuesto de acuerdo con la reivindicación 1

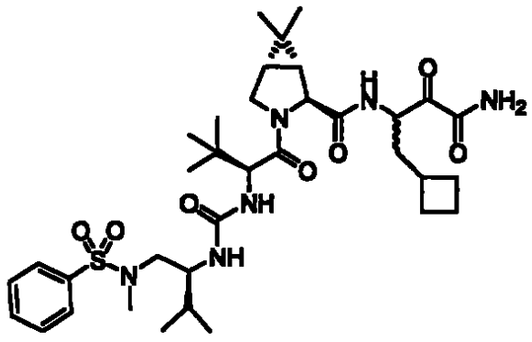
20 El método de acuerdo con la reivindicación 19, donde dicha administración es oral o subcutánea

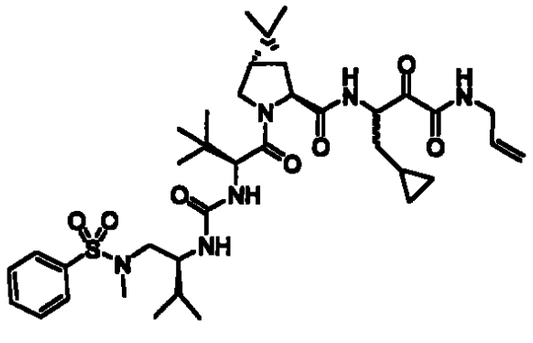
21 El uso de un compuesto de acuerdo con la reivindicación 1 para la manufactura de un medicamento para tratar trastornos asociados con el VHC

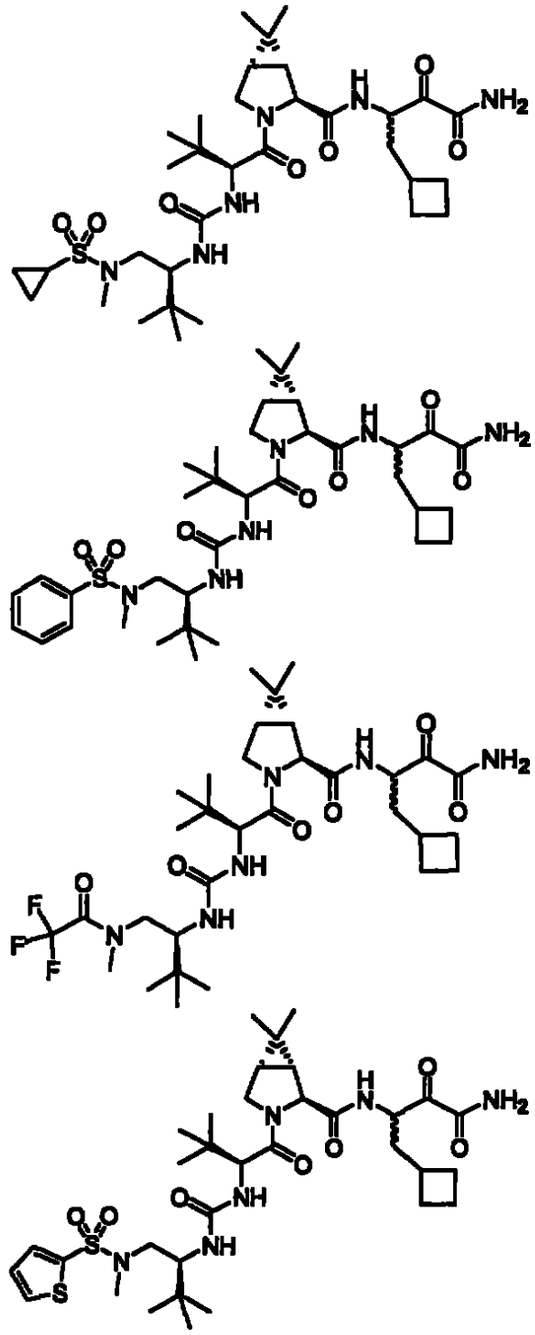
22 Un método para preparar una composición farmacéutica para tratar los trastornos asociados con el VHC, comprendiendo dicho método poner en contacto físico íntimo al menos un compuesto de acuerdo con la reivindicación 1 y por lo menos un portador farmacéuticamente aceptable

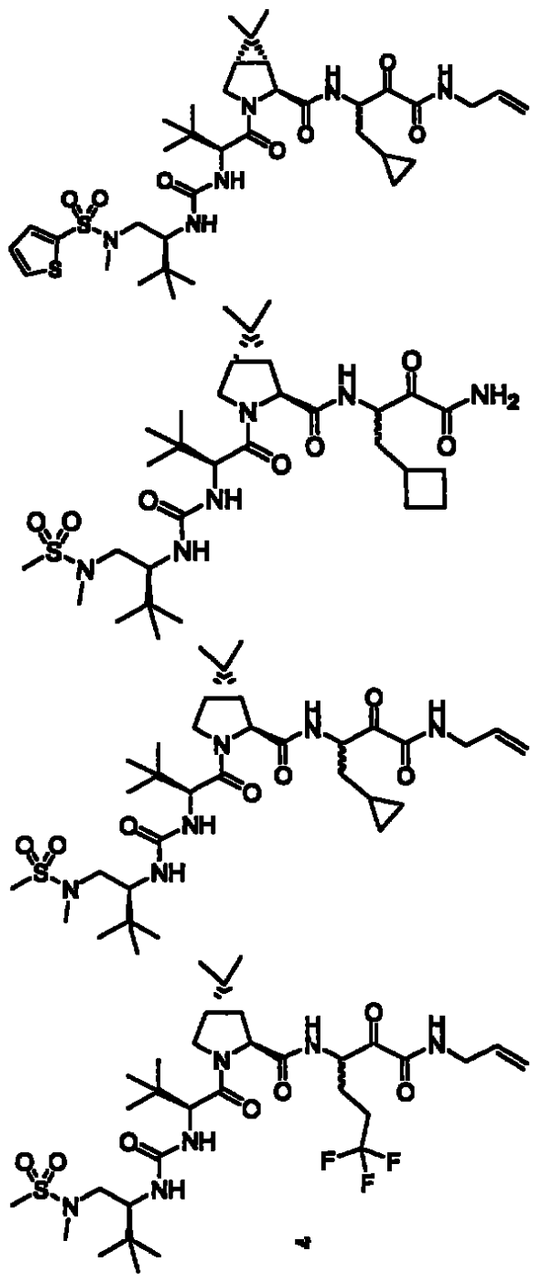
23 Un compuesto que exhibe actividad inhibitoria de la proteasa de VHC, o enantiómeros, estereoisómeros, rotámeros, tautómeros, diastereómeros, y racematos de dicho compuesto, o una sal, solvato o éster de dicho compuesto farmacéuticamente aceptable, siendo dicho compuesto seleccionado entre los compuestos de las estructuras mostradas a continuación

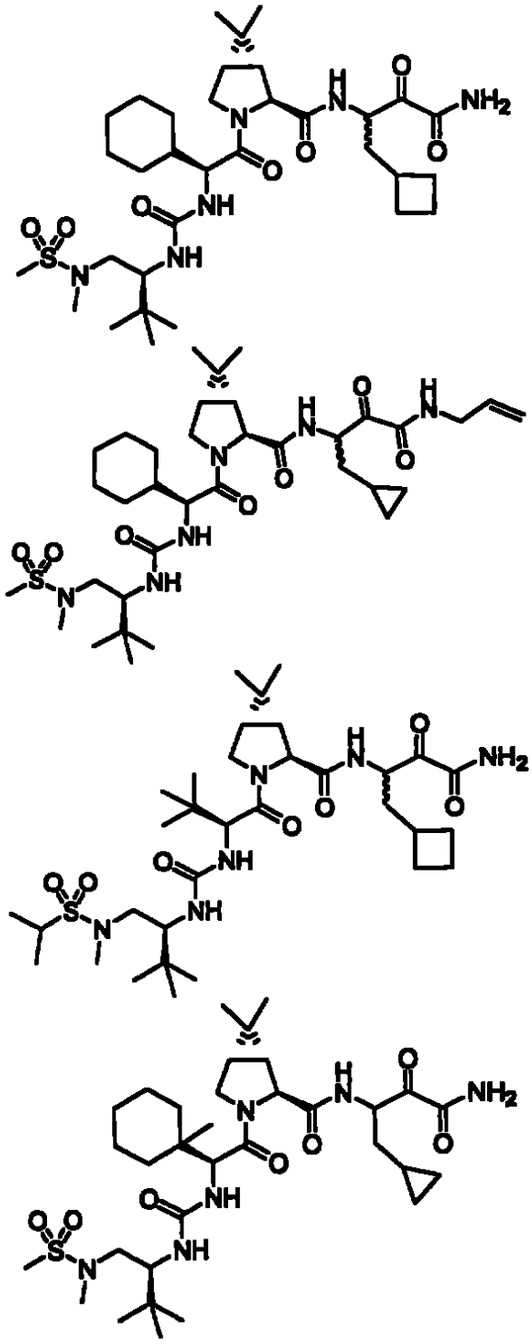


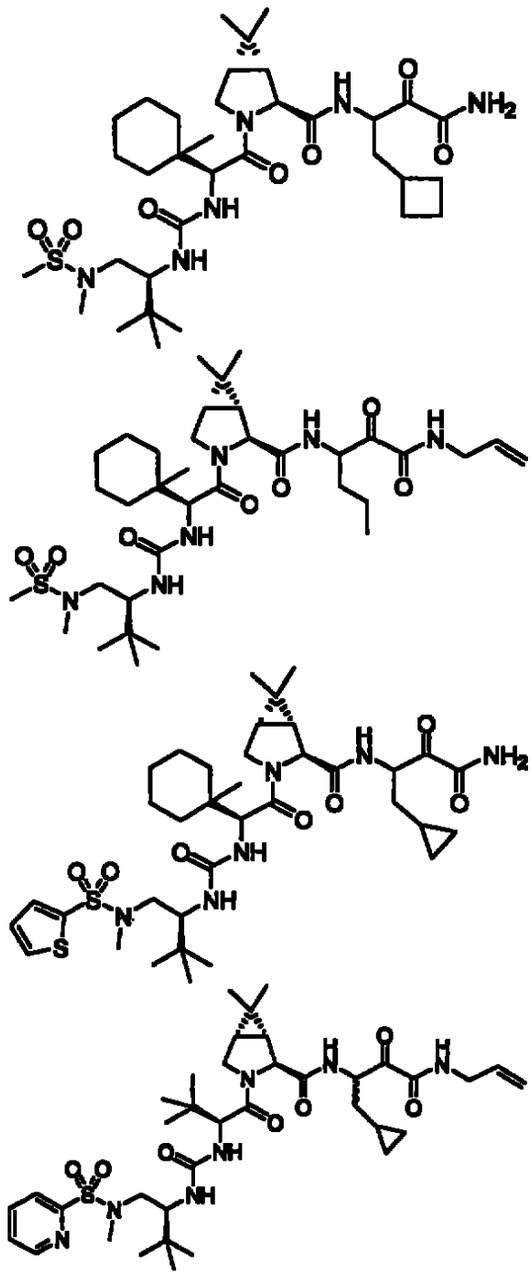


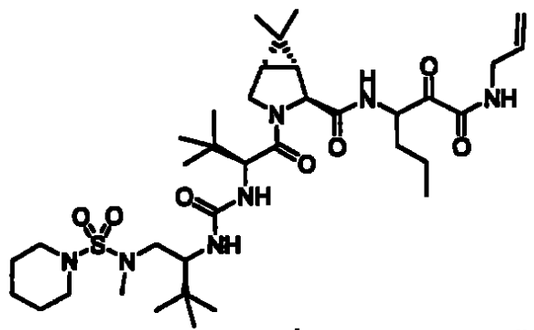


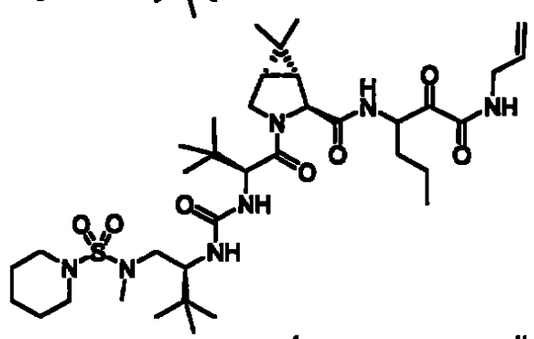


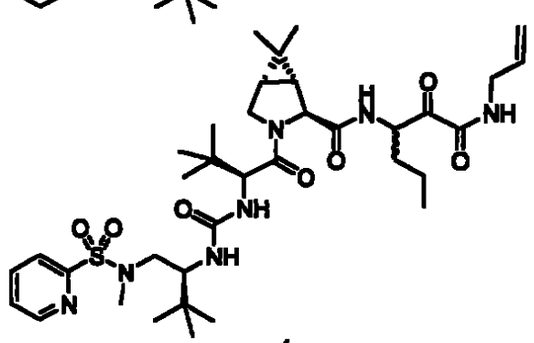


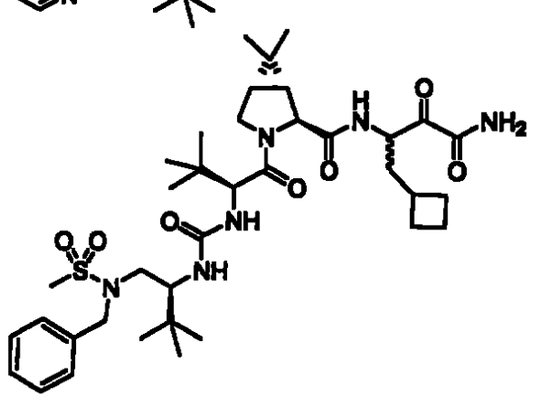


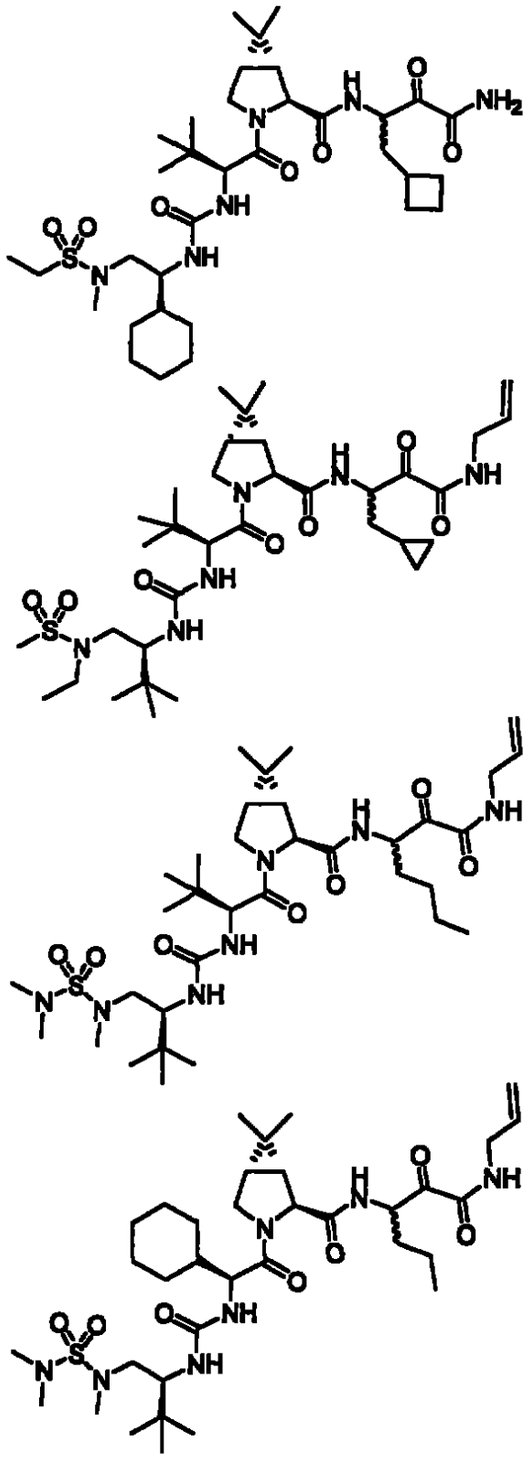


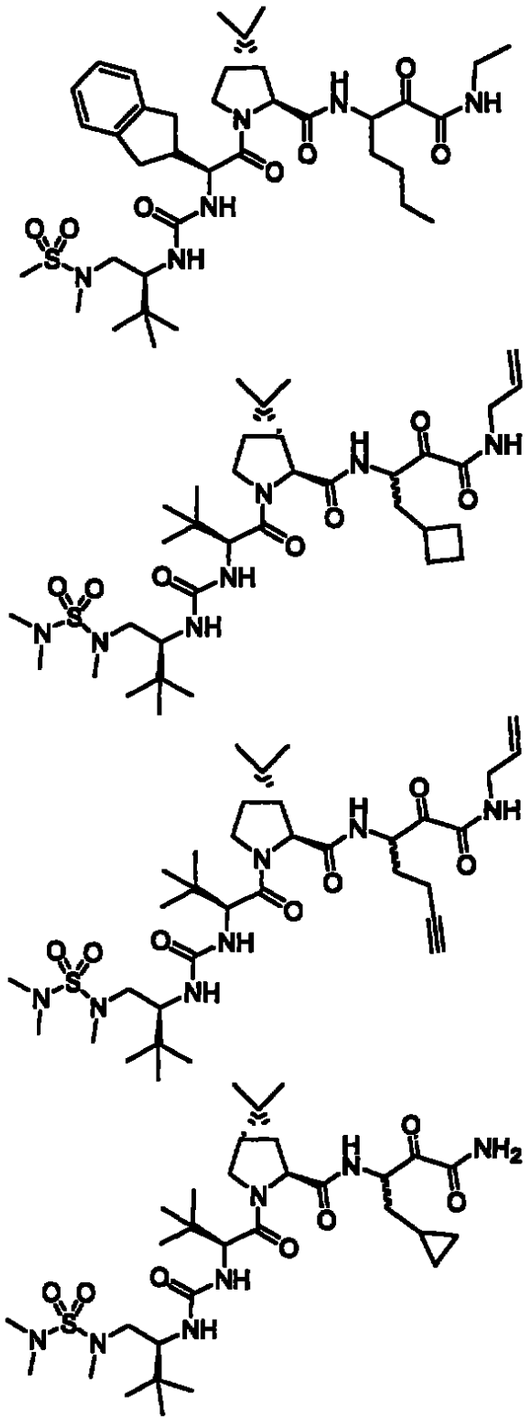


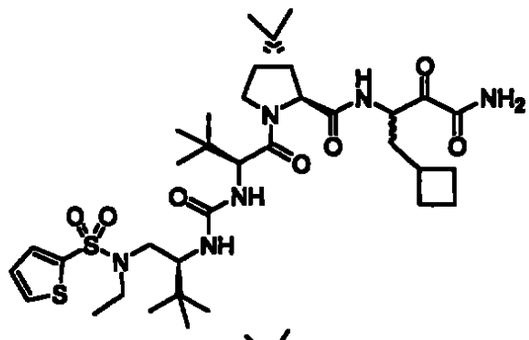


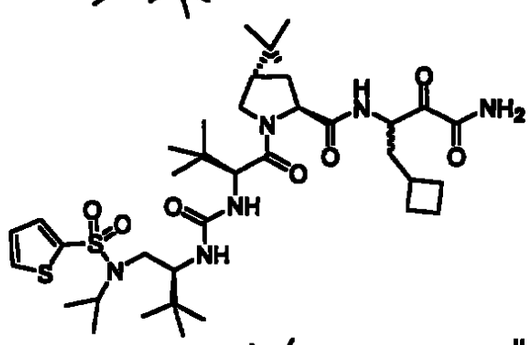


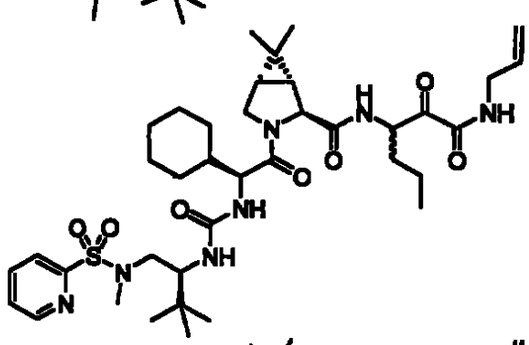


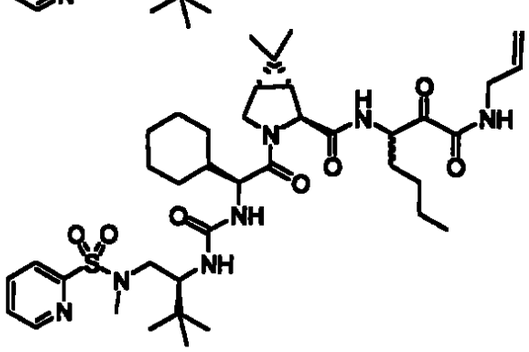


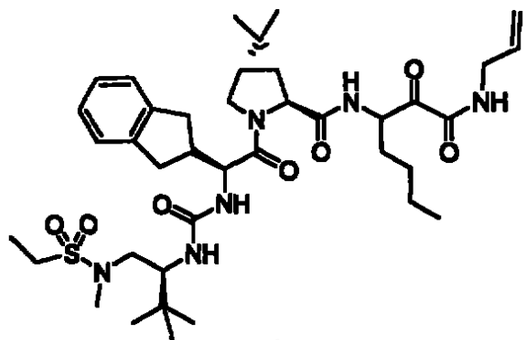


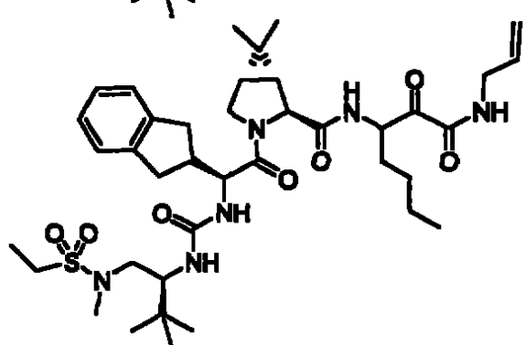


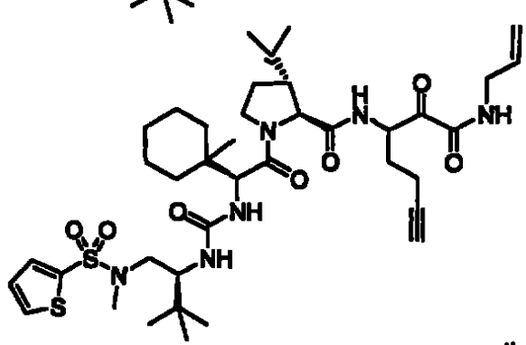


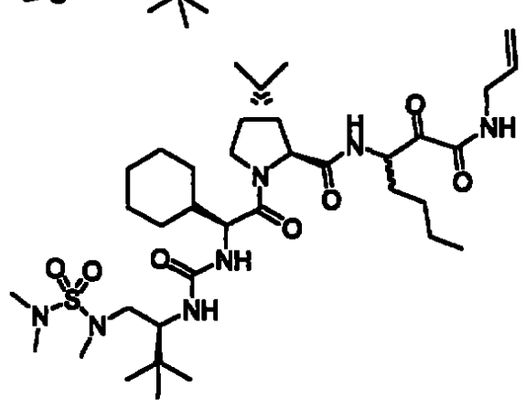


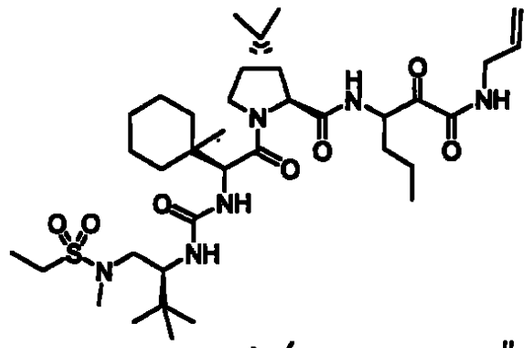


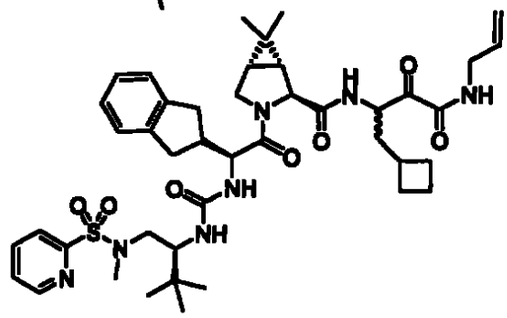


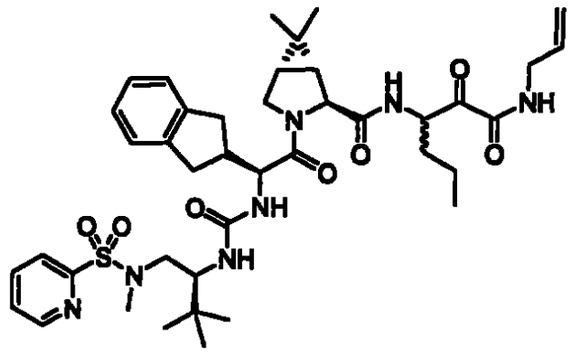


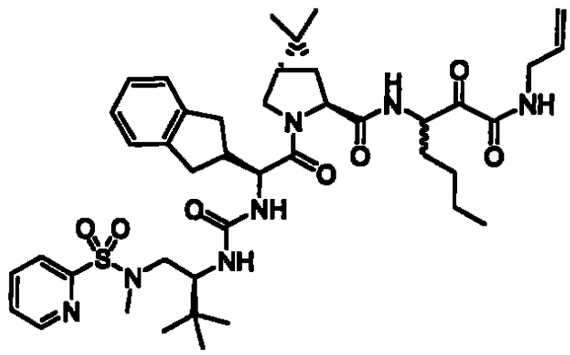


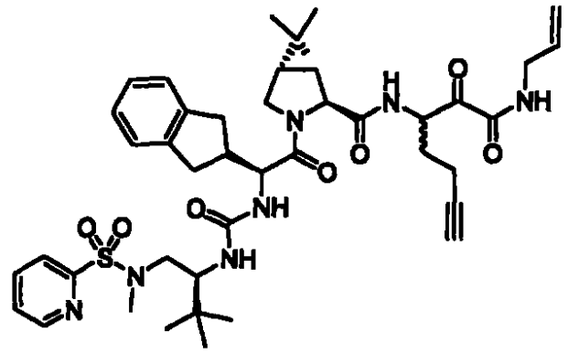


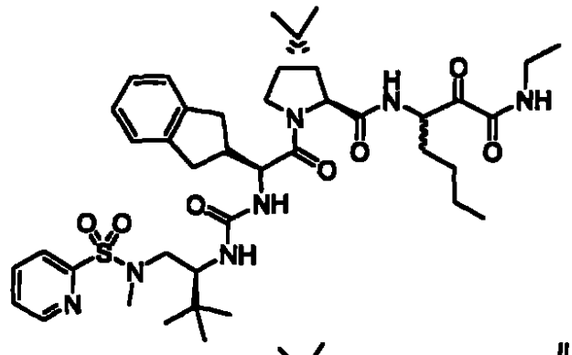


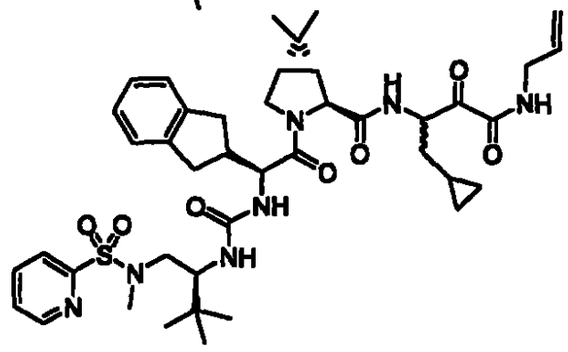












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24 Una composición farmacéutica para tratar trastornos asociados con el VHC, comprendiendo dicha composición una cantidad terapéuticamente eficaz de uno o más compuestos en las reivindicación 23 y un portador farmacéuticamente aceptable

25 La composición farmacéutica de acuerdo con la reivindicación 24, que contiene adicionalmente por lo menos un agente antiviral

498
497

26 La composición farmacéutica de acuerdo con la reivindicación 25, que contiene adicionalmente por lo menos un interferón o conjugado de PEG-interferón alfa ("interferón pegilado")

27 La composición farmacéutica de acuerdo con la reivindicación 26, donde dicho por lo menos un agente antiviral es ribavirina y dicho al menos un interferón es α-interferón o interferón pegilado

28 Un método para el tratamiento de un trastorno asociados con el virus de hepatitis C, que comprende administrar una cantidad eficaz de uno o más compuestos de acuerdo con la reivindicación 23

29 Un método para la modulación de la actividad de la proteasa del virus de la hepatitis C (VHC), que comprende poner en contacto a la proteasa del VHC con uno o más compuestos de acuerdo con la reivindicación 23

30 Un método para tratar, prevenir o aliviar uno o más síntomas de la hepatitis C, el cual comprende administrar una cantidad terapéuticamente eficaz de uno o más compuestos de acuerdo con la reivindicación 23

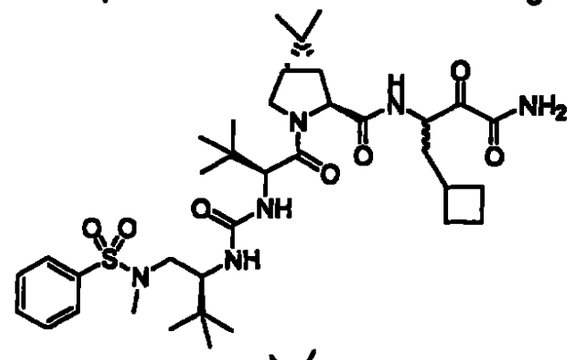
31 El método de acuerdo con la reivindicación 30, donde la proteasa del HCV es la proteasa NS3/NS4a

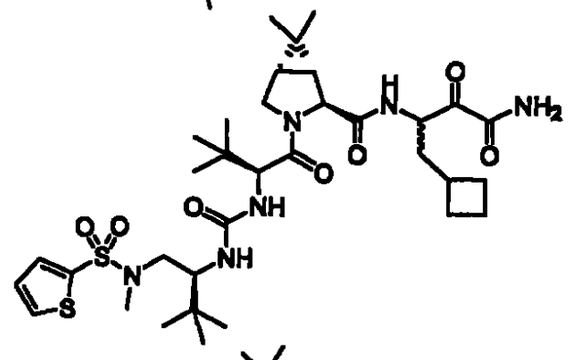
32 El método de acuerdo con la reivindicación 31, donde el compuesto o los compuestos inhiben la proteasa NS3/NS4a del VHC

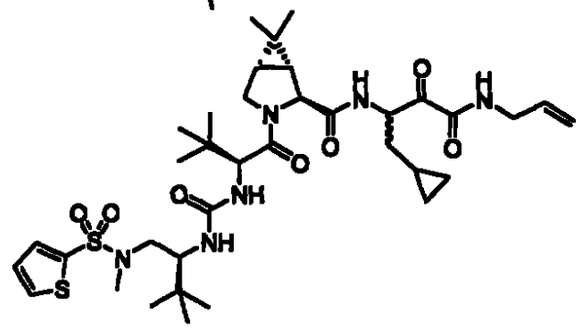
33 Un método para modular el procesamiento del polipéptido del virus de la hepatitis C (VHC), que comprende poner en contacto una composición que contiene el polipéptido del VHC bajo condiciones en las que dicho polipéptido es procesado con uno o más compuestos de acuerdo con la reivindicación 23

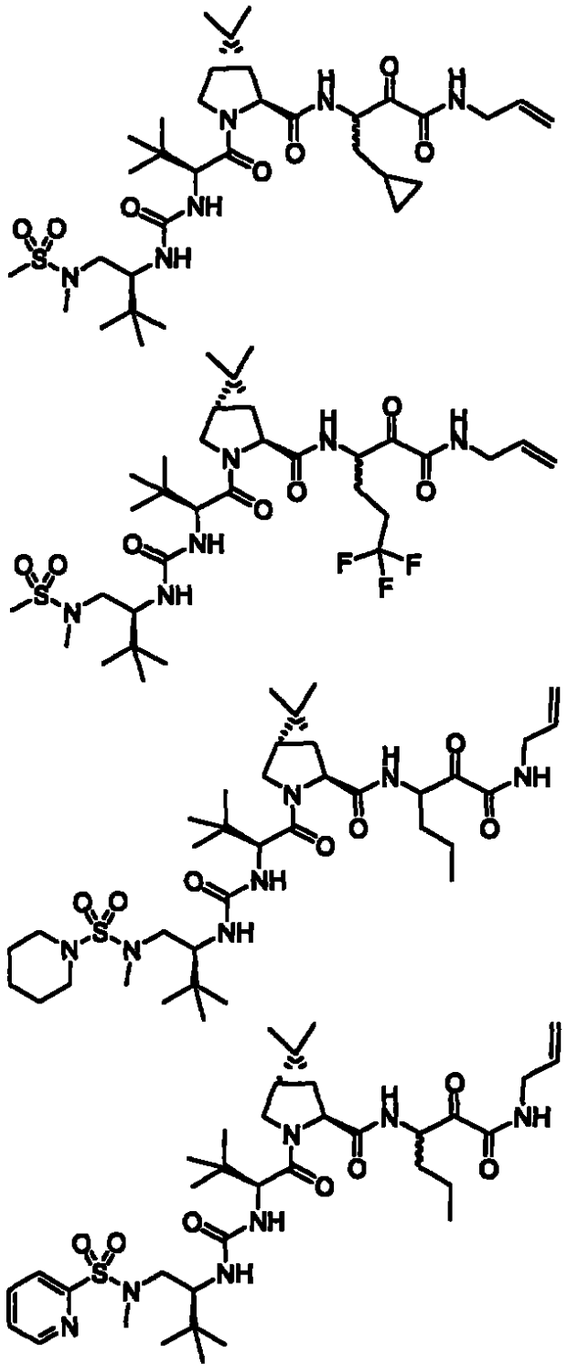
34 Un método para el tratamiento de trastornos asociados con el VHC, comprendiendo dicho método administrar a un paciente que necesita de dicho

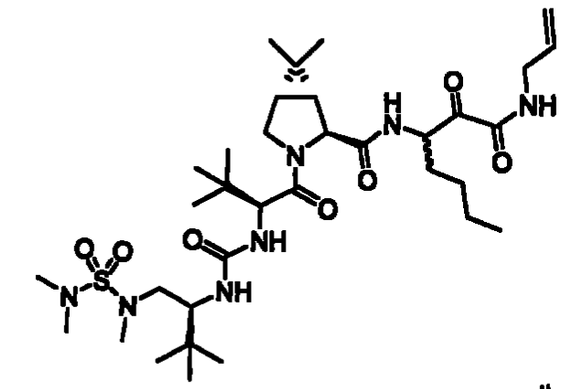
tratamiento, una composición farmacéutica la cual comprende cantidades terapéuticamente eficaces de por lo menos un compuesto, o enantiómeros, estereoisómeros, rotámeros, tautómeros, diastereómeros y racematos de dicho compuesto, o una sal, solvato o éster de dicho compuesto farmacéuticamente aceptable, siendo dicho compuesto seleccionado entre los siguientes

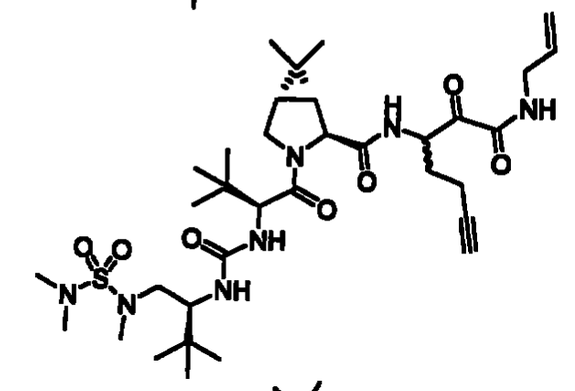


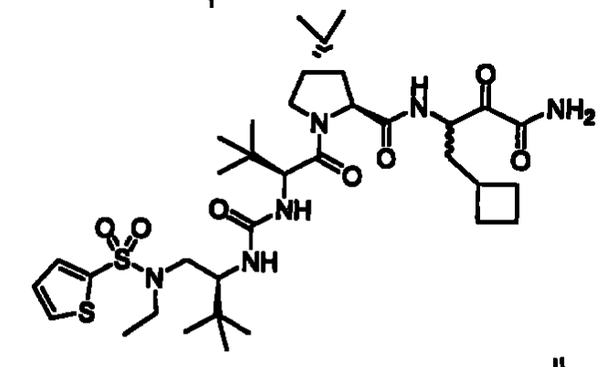


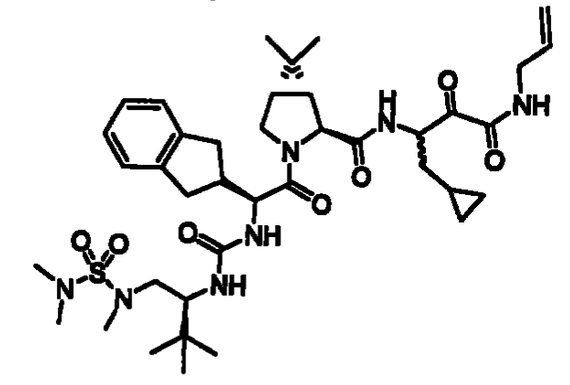


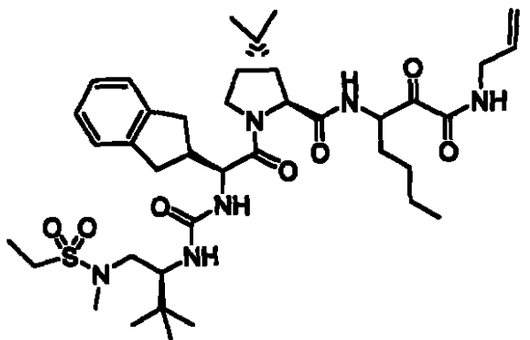


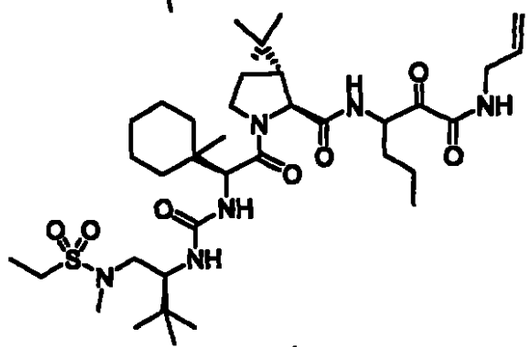


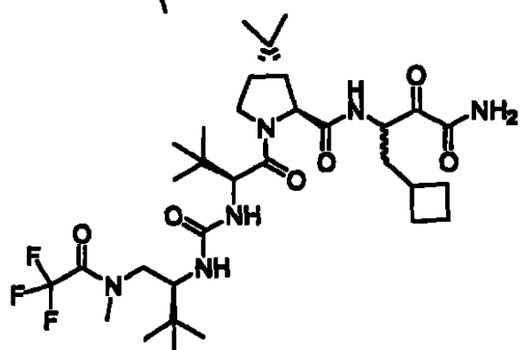


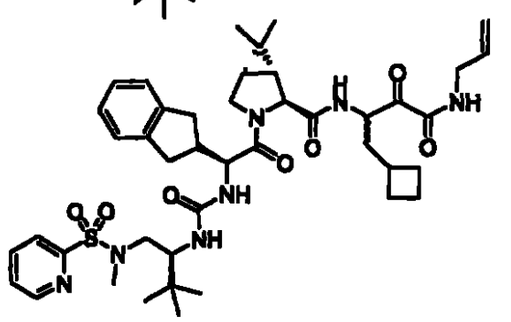


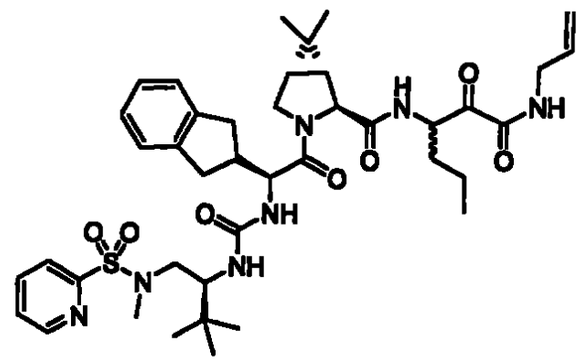


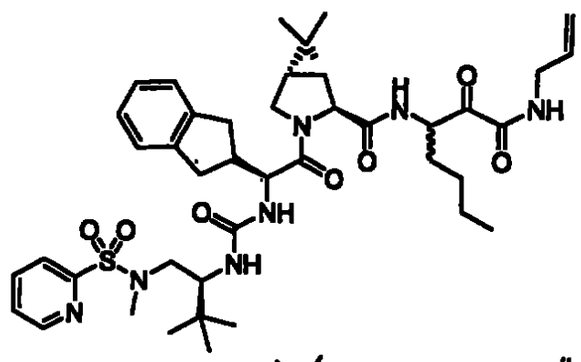


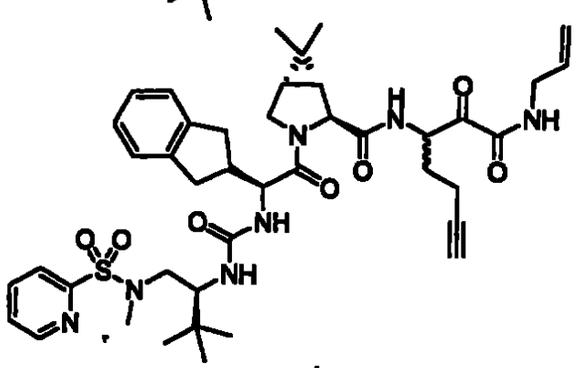


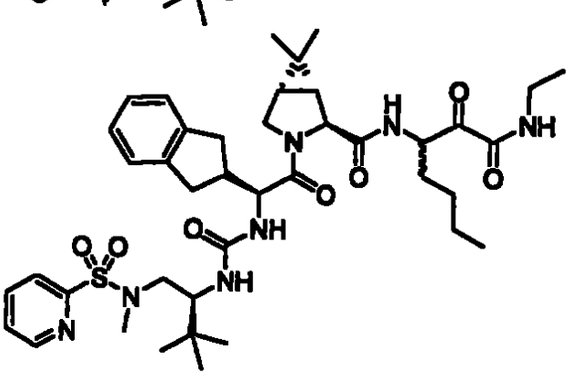


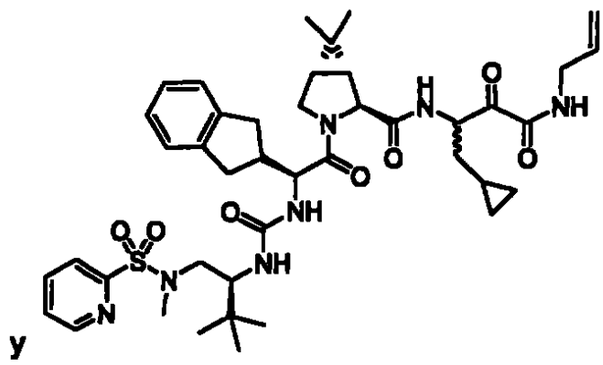












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Un compuesto de acuerdo con la reivindicación 1 en forma purificada

p SCHERING CORPORATION

RESUMEN DE LA INVENCIÓN

La presente invención describe novedosos compuestos los cuales tienen actividad inhibitoria de la proteasa del VHC así como también métodos para preparar ese tipo de compuestos En otra realización, la invención describe composiciones farmacéuticas que comprende ese tipo de compuestos así como también métodos para su utilización para tratar trastornos asociados con la proteasa del VHC

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TRATADO DE COOPERACIÓN DE PATENTES
PCT
NOTIFICACIÓN DE TRANSMISIÓN DEL REPORTE PRELIMINAR INTERNACIONAL DE PATENTABILIDAD
(PCT Regla 71 1)
De AUTORIDAD DE REVISION PRELIMINAR INTERNACIONAL

Para
KALYANARAMAN, Palaiyur S
SCHERING CORPORATION
Departamento de Patente K-6-1 1990
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530
Estados Unidos de América

Fecha de expedición 04 04 2006
Referencia del expediente del solicitante o mandatario IN06132
Solicitud Internacional No PCT/US2005/005772
Fecha de presentación internacional 24 02 2005
Fecha de prioridad 27 02 2004
Solicitante SCHERING CORPORATION ET AL

1 Se notifica al solicitante que la Administración Encargada del Examen Preliminar Internacional ha emitido el informe de examen preliminar internacional para la solicitud internacional y se lo transmite adjunto, acompañado, si procede, de sus anexos

2 Se transmite una copia del presente informe y, si procede, de sus anexos, a la Oficina Internacional para comunicacion a todas las Oficinas elegidas

3 Si alguna Oficina elegida lo exige, la Oficina Internacional realizará una traduccion en ingles del informe (con exclusion de sus anexos) y la transmitirá a las Oficinas interesadas

4 **RECORDATORIO**

Para iniciar la fase nacional ante cada Oficina elegida, el solicitante debe cumplir ciertos actos (presentacion de la traduccion y pago de las tasas nacionales) en el plazo de 30 meses desde la fecha de prioridad (o mas tarde por lo que respecta a ciertas oficinas) (Articulo 39 (1)) (véase también el recordatorio enviado por la Oficina Internacional en el formulario PCT/IB/301)

Cuando deba entregarse una traducción de la solicitud internacional o una oficina elegida, se incluirá la traduccion de cualquier anexo de informe de Examen Preliminar Internacional Corresponde al solicitante preparar la traduccion en cuestion y entregarla directamente a cada Oficina elegida interesada

Para más amplios detalles en lo relativo a los plazos aplicables y las exigencias de las oficinas elegidas, véase el Volumen II de la guia del solicitante PCT

Se llama la atención del solicitante sobre el Articulo 33(5) que preve que los criterios de novedad, actividad inventiva y de aplicación industrial definidos en el Articulo 33(2) a (4) solo servirán a los efectos del examen preliminar internacional, y que "todo Estado contratante puede aplicar criterios adicionales o diferentes al objeto de decidir, en ese Estado, si la invencion es patentable o no" (véase tambien el Articulo 27(5)) Tales criterios adicionales pueden afectar, por ejemplo, a las excepciones de patentabilidad, requisitos especificos relativos a la divulgación, la claridad de las reivindicaciones

Nombre y dirección postal de la Administracion encargada del Examen Preliminar Internacional

Oficina de Patentes Europea - Gitschiner Str 103
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TRATADO DE CO PERACIÓN DE PATENTES
PCT
INFORME PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD
(Capítulo II del Tratado de Cooperacion en materia de Patentes)
(PCT Articulo 36 y Regla 70)

Referencia del expediente del solicitante o mandatario IN06132
Solicitud Internacional No PCT/US2005/005772
Fecha de presentacion internacional. 24 02 2005
Fecha de prioridad 27 02 2004
Clasificacion Internacional de Patentes (IPC) o la vez clasificacion nacional e IPC INV C07D 209/52, C07D 403/12, C07D 401/12, C07D 409/12, C07D 417/12, C07K 5/08, A61K 31/40, A61K 31/4025, A61K 38/06, A61P 31/12
Solicitante SCHERING CORPORATION ET AL

1 El reporte de examen preliminar internacional ha sido preparado por esta Autoridad de Revisión Preliminar Internacional bajo el Articulo 35 y es transmitido al solicitante segun el Articulo 36

2 Este REPORTE consta de un total de 8 hojas, incluida la presente hoja de portada

3 Este informe también contiene ANEXOS, que comprenden

a ☐ (*remitido al solicitante y a la oficina internacional*) un total de hojas, descritas a continuacion

☐ hojas de la descripción, las reivindicaciones y/o los dibujos que han sido modificadas y que sirven de base al presente informe, y/o de hojas que contienen rectificaciones autorizadas por esta Administracion (vease la Regla 70 16 y la Instrucción Administrativa 607 del PCT)

☐ hojas que reemplazan a otras hojas anteriores, pero que esta Administración considera que contienen modificaciones que se extienden más allá de la divulgación de la invención tal como fue originalmente presentada, segun se indica en el punto 4 del Reglamento I y en el Recuadro Suplementario

b ☐ (remitido unicamente a la Oficina Internacional) un total de (indicar tipo y soporte(s) electrónico(s)) , que contienen una lista de secuencias y/o tabla(s) relativa(s), solo en formato legible por ordenador, como se indica en el Recuadro Suplementario relativo a Listas de Secuencias (ver Instrucción Administrativa 802)

4 El presente informe contiene indicaciones relativas a los siguientes puntos

☒	Recuadro I	Base de este informe
☐	Recuadro II	Prioridad
☒	Recuadro III	Ninguna formulación de opinion sobre la novedad, la actividad inventiva y la aplicación industrial
☐	Recuadro IV	Falta de unidad de Invencion
☒	Recuadro V	Declaración motivada según el Articulo 35(2) sobre la novedad, la actividad inventiva y la aplicación industrial, citas y explicaciones en apoyo de esta declaración
☐	Recuadro VI	Ciertos documentos citados
☐	Recuadro VII	Defectos en la Solicitud Internacional
☒	Recuadro VIII	Observaciones relativas a la solicitud internacional

Fecha de radicación de la demanda 12 09 2005
Fecha de elaboración de este reporte 04 04 2006

Nombre y direccion postal de la Administración encargada del Examen Preliminar Internacional

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Recuadro I Base de este informe

1 Por lo que respecta al **idioma**, este informe se ha establecido sobre la base de la solicitud internacional en el idioma en el cual se depositó, salvo indicación en contra señalada a continuacion

☐ Este informe esta basado en una traducción del idioma original al siguiente idioma , que es el de una traducción proporcionada a los fines de

- ☐ busqueda internacional (según Reglas 12 3 y 23 1 (b))
- ☐ publicación de la solicitud internacional (segun Regla 12 4)
- ☐ examen preliminar internacional (según Reglas 55 2 y/o 55 3)

2 Por lo que respecta a los **elementos*** de la solicitud internacional, esta opinion se ha establecido sobre la base de (*las hojas de reemplazo que hayan sido enviadas a la Oficina receptora en respuesta a un requerimiento según el Artículo 14 se las denomina en este informe como "inicialmente presentadas" y no se anexan al informe)*

Descripción, Páginas

1 – 266 tal como se presentaron inicialmente

Reivindicaciones, Números

1 – 36 tal como se presentaron inicialmente

☐ una lista de secuencias y/o tabla(s) relativa(s) – ver Recuadro Suplementario relativo a Listas de Secuencias

3 ☐ Las modificaciones ha ocasionado la cancelación de

- ☐ la descripción, paginas
- ☐ las reivindicaciones, Nos
- ☐ los dibujos, hojas/fig.
- ☐ la lista de secuencias (especificar)
- ☐ tabla(s) relativa(s) a la lista de secuencias (especificar)

4 ☐ El presente informe ha sido establecido como si no se hubiesen presentado (algunas de) las modificaciones anexadas a este informe y listadas abajo, ya que se ha considerado que iban más alla de la divulgación de la invencion tal como fue presentada, como se indica en el Recuadro Suplementario (Regla 70 2(c))

- ☐ la descripción, paginas

☐ las reivindicaciones, Nos
☐ los dibujos, hojas/fig
☐ la lista de secuencias (especificar)
☐ tabla(s) relativa(s) a la lista de secuencias (especificar)

* Si se utiliza el punto 4, algunas o todas estas páginas pueden llevar el sello de "sustituida"

Recuadro No III Ninguna formulación de opinión sobre la novedad, la actividad inventiva y la aplicación industrial

1 Las preguntas con respecto a si el invento reivindicado parece ser novedoso, implica una actividad inventiva (no ser evidente), o ser susceptible de aplicación industrial, por lo que respecta

☐ al conjunto de la solicitud internacional,
☒ a las reivindicaciones Nos 20, 21, 29-35 (en relación con la aplicación industrial)

debido a que

☐ la solicitud internacional, o las reivindicaciones Nos en cuestión se refieren al objeto, respecto del cual no requiere examen preliminar internacional (especifique)

☐ a descripción, reivindicaciones, o los dibujos (indíquese cuales a continuación) o tales reivindicaciones Nos en cuestión no son claras, de manera que no es posible formular una opinion significativa (especifique)

☐ las reivindicaciones, o las reivindicaciones Nos en cuestión no son claras, de manera que no es posible formular una opinión significativa

☒ no se ha emitido informe de busqueda internacional para dichas reivindicaciones Nos 20, 21, 29-35 (en relación con la aplicación industrial)

☐ la lista de de secuencias nucleótidas y/o de aminoacidos no cumplen la norma estándar prevista en el Anexo C de las Instrucciones Administrativas por que

La lista en papel ☐ no se presentó

☐ no cumple con la norma estándar

La lista en formato legible por ordenador

☐ no se presento

☐ no cumple con la norma estandar

☐ las tablas relativas a las listas de secuencias de nucleótidas y/o de aminoácidos, si únicamente se han presentado en formato legible por ordenador, no cumplen con los requisitos tecnicos previstos en el Anexo C-*bis* de las Instrucciones Administrativas

☒ Ver recuadro suplementario para mas detalles

Recuadro No V Declaración razonada según el Artículo 35 (2) con respecto a la novedad, nivel inventivo o aplicación industrial. anterioridades y explicaciones que soportan tal declaración

1 Declaración

Novedad (N)	Si	Reivindicaciones 1-36
	No	Reivindicaciones
Nivel Inventivo (NI)	Si	Reivindicaciones
	No	Reivindicaciones 1-36
Aplicacion Industrial (AI)	Si	Reivindicaciones 1-19, 22-28, 36
	No	Reivindicaciones

2 Citas y explicaciones (Regla 70 7)

ver hoja separada

Recuadro No VIII Observaciones relativas a la solicitud internacional

Se formulan las observaciones siguientes sobre la claridad de las reivindicaciones, de la descripción y de los dibujos o sobre si las reivindicaciones se fundan totalmente en la descripcion

ver hoja adjunta

S13
S12

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL – HOJA ANEXA
Solicitud Internacional No PCT/US2005/005772

Ítem III
No formulación de concepto con respecto a la novedad, nivel inventivo y aplicación industrial

Las reivindicaciones 20, 21, 29-35 se relacionan con materia considerada por esta Autoridad cubierta por las provisiones de la Regla 67 1(iv) del PCT De manera que no se formulará concepto alguno con respecto a la aplicación industrial de la materia de estas reivindicaciones (Artículo 34(4)(a)(I) del PCT)

Ítem V
Declaración razonada con respecto a la novedad, nivel inventivo o aplicación industrial, citas y explicaciones que soporten dicha declaración

V 1 Documentos citados

D1 US 2003/216325 A1 (SAKSENA ANIL K ET AL) 20 de noviembre de 2003

D2 WO 02/08244 A (SCHERING CORPORATION, CORVAS INTERNATIONAL, INC) 31 de enero de 2002

D3 WO 02/48172 A (SCHERING CORPORATION) 20 de junio de 2002

D4 WO 03/062228 A (SCHERING CORPORATION) 31 de julio de 2003

D5 J LAMAR ET AL "Tropeptidilo alfa-cetoamidas P4 truncadas novedosas útiles como inhibidores de la proteasa" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol 14, no 1, 5 de enero de 2004, páginas 263-266, XP002343374

D6 WO 03/035060 A (VERTEX PHARMACUETICALS INCORPORATED, PERNIE, ROBERT, B, PITLIK, JANOS,) 1 de mayo de 2003

Los señalamientos indicados serán utilizados en todo el procedimiento de evaluación

V 2 Novedad

V 2 1 Los documentos D1 a D5 divulgan compuestos que difieren de los compuestos de la presente reivindicación 1 en cuanto a que su fracción que corresponde a Y no comprende las fracciones Y^{30} o Y^{31} tal como se define en la presente reivindicación 1 (ver los pasajes relevantes citados en el reporte de búsqueda internacional), o si la fracción correspondiente a Y de hecho si comprende una fracción Y^{30} o Y^{31}, no existe un grupo que corresponda a G (en Y, ver por ejemplo, D1, páginas 408 y 528)

V 2 2 El documento D6 divulga compuestos en donde la fracción que corresponde a G no es NH u O, pero si es $C(R_1)$

V 2 3 Por lo tanto, la materia de la reivindicación 1 y también la de las reivindicaciones 2 a 36 se considera novedosa

V 3 Nivel Inventivo

V 3 1 Según la descripción detallada, el problema que enfrenta la presente solicitud es intentar proporcionar compuestos adicionales que sean activos como inhibidores de proteasa del HCV

V 3 2 Todos los documentos D1 a D6 divulgan compuestos con actividad inhibidora de proteasas del HCV

V 3 3 Los presentes compuestos difieren de los compuestos encontrados en D1 a D5 en que la mayoría de estos compuestos del estado de la técnica anterior no contienen las fracciones específicas Y^{30} o Y^{31} tal como se definen en la presente reivindicación 1 Sin embargo, en D1, algunos compuestos se divulgan que si contienen una fracción que corresponde a Y^{30} o Y^{31}, pero en estos compuestos, la cadena C_2 entre el grupo que corresponde a G y el grupo que corresponde a Y^{30} o Y^{31} está ausente, ver, por ejemplo el segundo y tercer compuesto en D1, página 528
Los presentes compuestos difieren de los compuestos de D6 (ver por ejemplo la reivindicación 4 de D6) en que en los compuestos de D6 la fracción que corresponde a G es $C(R_1)$, y no NH u O, sin embargo, el grupo final T de D6 comprende definiciones que se acomodan a ciertas definiciones del grupo final correspondiente Y de la presente solicitud
Adicionalmente, D1 divulga que la fracción que corresponde a G puede ser de igual manera NH, O, o CR, ver por ejemplo el primer y segundo compuesto en D1, página 426, el primer y segundo compuesto, página 430, el primer y segundo compuesto, página 460, el primer y tercer compuesto y en la página 461, el segundo y tercer compuesto

V 3 4 Por lo tanto se observa que D1 divulga compuestos similares a los presentes, que tienen fracciones correspondientes a G que son NH u O D6 divulga compuestos similares a los presentes, que difieren de los presentes únicamente en que la fracción que corresponde a G es CR, y no NH u O, y que tienen como grupos finales, grupos que corresponden a Y^{30} o Y^{31} (en el caso en que los grupos Y^{30} o Y^{31} u sea cero, ver la reivindicación 6 de D6, V es $-CH(R_8)-$) La combinación de estas características técnicas de D1 y D6 conduciría directamente a los presentes compuestos Los compuestos reivindicados en la presente deben entonces ser considerados como estructuralmente obvios con respecto a D1 combinado con D6 Por consiguiente, la reivindicación 1 no puede considerarse inventiva.

V 3 5 Las reivindicaciones de compuesto 2-13, 24 y 36 y las reivindicaciones farmacéuticas 14-23 y 25-35 parecen no contribuir con ninguna característica técnica adicional que pueda considerarse como fundamento para el reconocimiento de nivel inventivo, al considerarse con respecto a los documentos citados del estado de la técnica anterior, particularmente D1 y D6 Entonces debe concluirse que estas reivindicaciones también carecen de nivel inventivo

V 4 Aplicación Industrial

V 4 1 La materia de la reivindicaciones 1-19, 23-28 y 36 se considera que es industrialmente aplicable

V 4 2 Para la evaluación de las reivindicaciones 20, 21, 29-35 sobre si son industrialmente aplicables, no existen criterios unificados entre los Estados pertenecientes al PCT La patentabilidad también puede depender de la formulación de las reivindicaciones La Oficina de Patentes Europea, EPO, por ejemplo, no reconoce como cumplimiento del requisito de la aplicación industrial, un contenido de reivindicaciones con respecto al uso de un compuesto en un tratamiento médico, pero si permite sin embrago, reivindicaciones con respecto a un compuesto para primer uso en un tratamiento médico y el uso de tal compuesto para la producción de un medicamento para un tratamiento médico nuevo

Ítem VIII
Ciertas observaciones sobre la solicitud internacional

Por razones de claridad, en las reivindicaciones, las expresiones "alquilo", "alquenilo", "alquinilo", "arilo", "heteroalquilo", "heteroarilo", "cicloalquilo", "heterociclilo" debieron haberse definido adecuadamente con respecto a su máximo número de átomos de carbono, su tamaño de anillo, y su posible número y tipo de heteroátomos, donde fuera aplicable Tales definiciones pueden encontrarse en las páginas 34 a la 39 de la descripción El término "éster farmacéuticamente aceptable" debió haberse definido según las páginas 43 y 44 de la descripción

PATENT COOPERATION TREATY

PATENT

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To

KALYANARAMAN, Palaiyur, S
Schering-Plough Corporation
Patent Department, K-6-1 1990
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530
ETATS-UNIS D'AMERIQUE

APR 17 2006

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	04.04.2006
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
IN06132	

International application No	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/005772	24 02 2005	27 02 2004

Applicant
SCHERING CORPORATION ET AL

1 The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application

2 A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices

3 Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices

4 **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301)

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)) Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims

Name and mailing address of the international preliminary examining authority	Authorized Officer
European Patent Office Gitschiner Str 103 D-10958 Berlin Tel +49 30 25901 0 Fax +49 30 25901 840	Geier, A Tel +49 30 25901 706

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference IN06132	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US2005/005772	International filing date *(day/month/year)* 24 02 2005	Priority date *(day/month/year)* 27 02 2004

International Patent Classification (IPC) or national classification and IPC
INV C07D209/52 C07D403/12 C07D401/12 C07D409/12 C07D417/12 C07K5/08 A61K31/40 A61K31/4025 A61K38/06 A61P31/12

Applicant
SCHERING CORPORATION ET AL

1 This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36

2 This REPORT consists of a total of 8 sheets including this cover sheet.

3. This report is also accompanied by ANNEXES comprising

a ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows

☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70 16 and Section 607 of the Administrative Instructions)

☐ sheets which supersede earlier sheets but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No I and the Supplemental Box

b ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions)

4 This report contains indications relating to the following items.

- ☒ Box No I Basis of the report
- ☐ Box No II Priority
- ☒ Box No III Non-establishment of opinion with regard to novelty Inventive step and industrial applicability
- ☐ Box No IV Lack of unity of invention
- ☒ Box No V Reasoned statement under Article 35(2) with regard to novelty Inventive step or industrial applicability, citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12 09 2005	04 04 2006

Name and mailing address of the International preliminary examining authority	Authorized officer
European Patent Office Gitschiner Str 103 D-10958 Berlin Tel +49 30 25901 0 Fax +49 30 25901 840	Hass, C Telephone No +49 30 25901

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No PCT/US2005/005772

Box No I Basis of the report

1 With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item

☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of

- ☐ international search (under Rules 12 3 and 23 1(b))
- ☐ publication of the international application (under Rule 12 4)
- ☐ international preliminary examination (under Rules 55 2 and/or 55 3)

2 With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*

Description, Pages

1 286 as originally filed

Claims, Numbers

1-36 as originally filed

☐ a sequence listing and/or any related table(s) see Supplemental Box Relating to Sequence Listing

3 ☐ The amendments have resulted in the cancellation of

- ☐ the description, pages
- ☐ the claims, Nos
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify)*:
- ☐ any table(s) related to sequence listing *(specify)*

4 ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70 2(c))

- ☐ the description, pages
- ☐ the claims, Nos
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify)*
- ☐ any table(s) related to sequence listing *(specify)*

* *If item 4 applies, some or all of these sheets may be marked "superseded "*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No PCT/US2005/005772

Box No III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1 The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application,

☒ claims Nos 20, 21, 29-35 (with regard to industrial applicability)

because

☐ the said international application, or the said claims Nos relate to the following subject matter which does not require an international preliminary examination (specify)

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos are so inadequately supported by the description that no meaningful opinion could be formed

☒ no international search report has been established for the said claims Nos 20, 21, 29-35 (with regard to industrial applicability)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions

☐ See separate sheet for further details

519 520

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No
PCT/US2005/005772

Box No V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement

1 Statement

Novelty (N)	Yes	Claims	1 36
	No	Claims	
Inventive step (IS)	Yes	Claims	
	No	Claims	1-36
Industrial applicability (IA)	Yes	Claims	1-19, 22-28, 36
	No	Claims	

2 Citations and explanations (Rule 70 7)

see separate sheet

Box No VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 20, 21, 29-35 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67 1(iv) PCT Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT)

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement

V 1 Cited documents

D1 US 2003/216325 A1 (SAKSENA ANIL K ET AL) 20 November 2003 (2003-11-20)

D2 WO 02/08244 A (SCHERING CORPORATION, CORVAS INTERNATIONAL, INC) 31 January 2002 (2002-01-31)

D3 WO 02/48172 A (SCHERING CORPORATION) 20 June 2002 (2002-06-20)

D4 WO 03/062228 A (SCHERING CORPORATION) 31 July 2003 (2003-07-31)

D5 J LAMAR ET AL "Novel P4 truncated tropeptidyl alpha-ketoamides as HCV protease inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol 14, no 1, 5 January 2004 (2004-01-05), pages 263-266, XP002343374

D6 WO 03/035060 A (VERTEX PHARMACEUTICALS INCORPORATED, PERNIE, ROBERT, B, PITLIK, JANOS,) 1 May 2003 (2003-05-01)

The indicated designations will be used throughout the examination procedure

V 2 Novelty

V 2 1 Documents D1 to D5 disclose compounds which differ from the compounds of present claim 1 in that their Y-corresponding moiety does not comprise the moieties Y^{30} or

Y^{31} as defined in present claim 1 (see the relevant passages cited in the international search report), or if the Y-corresponding moiety does actually comprise a moiety Y^{30} or Y^{31}, there is no group present which corresponds to G (in Y), see e g D1, pages 408 and 528)

V.2 2 Document D6 discloses compounds wherein the G-corresponding moiety is not NH or O, but $C(R_1)$

V 2 3 Therefore the subject-matter of claim 1 and also of claims 2 to 36 is considered novel

V 3 ***Inventive step***

V 3 1 According to the description, the problem underlying the present application is to provide further compounds which are active as HCV protease inhibitors

V 3 2 All of the documents D1 to D6 disclose compounds having HCV protease inhibitory activity

V 3 3 The present compounds differ from the compounds of D1 to D5 in that most of these the prior art compounds do not have the specific moieties Y^{30} and Y^{31} as defined in present claim 1 However, in D1, some compounds are disclosed which do have a moiety corresponding to Y^{30} or Y^{31}, but in these compounds, the C_2 chain between the G-corresponding and the Y^{30}- or Y^{31}-corresponding group is absent, see e g D1, page 528, second and third compound
The present compounds differ from the D6 compounds (see e g claim 4 of D6) in that in the D6 compounds the G-corresponding moiety is $C(R_1)$, not NH or O, however, the end group T of D6 comprises definitions which fit to some of the definitions of the corresponding end group Y of the present application
Moreover, D1 discloses that the G-corresponding moiety can be equally NH, O or CR, see e g D1, page 426, first and second compound, page 430, first and second compound, page 460, first and third compound and page 461, second and third compound

V 3 4 It is thus noted that D1 discloses compounds similar to the present ones, having G-corresponding moieties which are NH or O D6 discloses compounds similar to the

present ones, which are different from the present ones only in that the G-corresponding moiety is CR, not NH or O, and which have, as terminating groups, Y^{30}- and Y^{31}-corresponding groups (in case that in present groups Y^{30} and Y^{31} u is zero and, see claim 4 of D6, V is -CH(R_8)-) The combination of these technical features of D1 and D6 would lead directly to the present compounds The presently claimed compounds must thus be considered as structurally obvious with regard to D1 combined with D6 Therefore claim 1 cannot be considered to involve an inventive step

V 3 5 Compound claims 2-13, 24 and 36 and pharmaceutical claims 14-23 and 25-35 do not appear to bring any additional technical feature which could be considered as basis for the acknowledgement of an inventive step, when considered with regard to the cited prior art documents, especially D1 and D6 So it must be concluded that these claims are also lacking inventive step

V 4 Industrial applicability

V 4 1 The subject-matter of claims 1-19, 23-28 and 36 is considered to be industrially applicable

V 4 2 For the assessment of the present claims 20, 21, 29-35 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States The patentability can also be dependent upon the formulation of the claims The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment

Re Item VIII
Certain observations on the international application

For reasons of clarity, in the claims, the expressions "alkyl", "alkenyl", "alkynyl", "aryl", "heteroalkyl", "heteroaryl", "cycloalkyl", "heterocyclyl" should have been properly defined

as to their maximum number of C atoms, their ring size and their possible number and kind of heteroatoms, where applicable Such definitions can be found on pages 34 to 39 of the description The term "pharmaceutically acceptable ester" should have been defined according to pages 43 and 44 of the description

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

(19) World Intellectual Property Organization
International Bureau

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22 September 2005 (22 09.2005)

PCT

(10) International Publication Number
WO 2005/087721 A3

(51) International Patent Classification[7] C07D 209/52, 403/12, 401/12 409/12 417/12 C07K 5/08, A61K 31/40, 31/4025, 38/06 A61P 31/12

(21) International Application Number
PCT/US2005/005772

(22) International Filing Date 24 February 2005 (24.02 2005)

(25) Filing Language. English

(26) Publication Language: English

(30) Priority Data
60/548,507 27 February 2004 (27.02.2004) US

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

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(74) Agent KALYANARAMAN, Palaiyur, S, Schering Plough Corporation Patent Department, K-6 1 1990, 2000 Galloping Hill Road, Kenilworth NJ 07033-0530 (US)

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

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

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

Published
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report
10 November 2005

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

WO 2005/087721 A3

(54) Title: 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.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/005772

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/52 C07D403/12 C07D401/12 C07D409/12 C07D417/12
C07K5/08 A61K31/40 A61K31/4025 A61K38/06 A61P31/12

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.
Y	US 2003/216325 A1 (SAKSENA ANIL K ET AL) 20 November 2003 (2003-11-20) claims, tables 1-5	1-36
A	WO 02/08244 A (SCHERING CORPORATION, CORVAS INTERNATIONAL, INC) 31 January 2002 (2002-01-31) cited in the application page 50 - page 86 page 142 - page 180 examples XXII,XXV,XXXIX page 289 - page 467 claims	1-36

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[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
5 September 2005	15/09/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040 Tx. 31 651 epo nl Fax: (+31-70) 340-3016	Hass, C

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

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/005772

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 02/48172 A (SCHERING CORPORATION) 20 June 2002 (2002-06-20) cited in the application page 33 - page 39, claims 28,29,49-60,93,94, table A	1,7, 14-23,36
A	WO 03/062228 A (SCHERING CORPORATION) 31 July 2003 (2003-07-31) claims, example 1, table 1	1,10-12, 14-23,36
A	J LAMAR ET AL "Novel P4 truncated tropeptidyl alpha-ketoamides as HCV protease inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol 14, no 1, 5 January 2004 (2004-01-05), pages 263-266, XP002343374 page 264, compound 5a	1,22
Y	WO 03/035060 A (VERTEX PHARMACEUTICALS INCORPORATED, PERNIE, ROBERT, B, PITLIK, JANOS,) 1 May 2003 (2003-05-01) claims 4,5,13,14,29-39	1-36

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/005772

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 20, 21, 29-35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition

2. [ ] Claims Nos
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out specifically

3. [ ] Claims Nos
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1 [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee this Authority did not invite payment of any additional fee

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid specifically claims Nos.

4. [ ] No required additional search fees were timely paid by the applicant. Consequently this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos..

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/005772

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OLARTERAISBECK 06/173

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad 06-082842- -00000-0000
Fec 2006-08-22 17:24:04 Dep 2020 NUEVAS CREACIONES
Tra 11 PATENTES Y
Cla 379 FABENACIONALII
Act 411 PRESENTACION Folios 527

527

Industria y Comercio
SUPERINTENDENCIA

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

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REPRESENTANTE APODERADO	**Nombre** J IAN RAISBECK **Dirección:** World Trade Center, Torre A, Calle 100 No 8ª-37 Piso 10 **Teléfono.** 601-7700 **Fax** 601-7799 **E-mail** office@olarteraisbeck com	**IDENTIFICACIÓN** C C. [x] NIT [ ] C.E. [ ] Otro [ ] **Cual** _____ **Número** 79 376 996 **TP** 135.799
INVENTOR (ES) (72)	**Nombre** VER PAGINA ADJUNTA **Dirección:** VER PAGINA ADJUNTA **Nacionalidad o Domicilio** VER PAGINA ADJUNTA	

(3) **PCT (86)**

Solicitud Internacional No PCT/US2005/005772 Fecha Febrero 24, 2005

Publicación Internacional No WO 2005/087721 Fecha Septiembre 22, 2005

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

Clasificación Internacional (51) C07D 207/00

Prioridad SI [X] NO [ ]	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	Febrero 27, 2004	60/548,507

(5) **Comprobante de pago No** 06-63 709 **Fecha** Agosto 22, 2006

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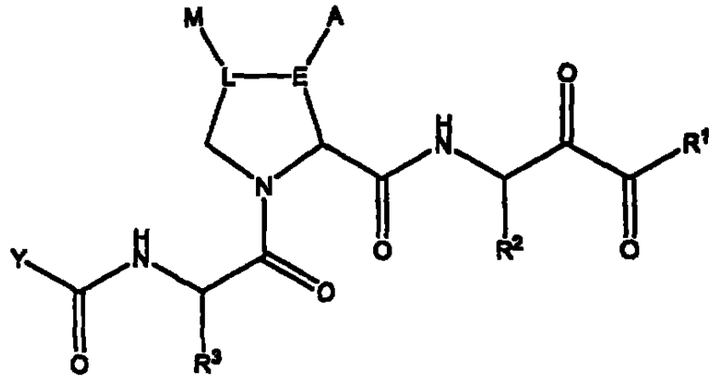
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Nacionalidad Estadounidense

REIVINDICACIONES

Habiendo así especialmente descrito y determinado la naturaleza de la presente invención y la forma cómo la misma ha de ser llevada a la práctica se declara reivindicar como de propiedad y derecho exclusivo

1 Un compuesto o enantiómeros, estereoisómeros, rotámeros, tautómeros, diastereómeros y racematos de dicho compuesto, o una sal, solvato o éster de dicho compuesto farmacéuticamente aceptable, teniendo dicho compuesto la estructura general mostrada en la Fórmula I

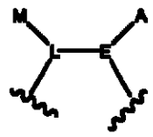


Fórmula I

en la cual

R^1 es H, OR^8, NR^9R^{10}, o CHR^9R^{10}, en la cual R^8, R^9 y R^{10} pueden ser iguales o diferentes, siendo cada uno seleccionado independientemente del grupo formado por H, alquil-, alquenil-, alquinil-, aril-, heteroalquil-, heteroaril-, cicloalquil-, heterocicil-, arilalquil-, y heteroarilalquilo,

A y M pueden ser iguales o diferentes, siendo cada uno seleccionado independientemente entre R, NR^9R^{10}, SR, SO_2R, y halo, o A y M están conectados entre sí (en otras palabras, A-E-L-M tomados en forma conjunta) de modo que la porción



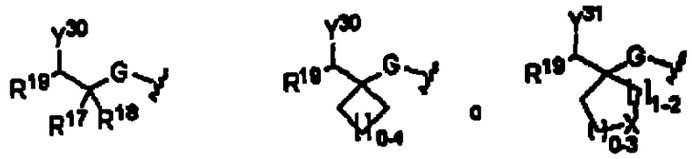
que se muestra más arriba en la Fórmula I forma ya sea un cicloalquilo de tres, cuatro, seis, siete u ocho miembros, un heterocicilo de cuatro a ocho miembros, un arilo de seis a diez miembros o un heteroarilo de cinco a diez miembros,

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

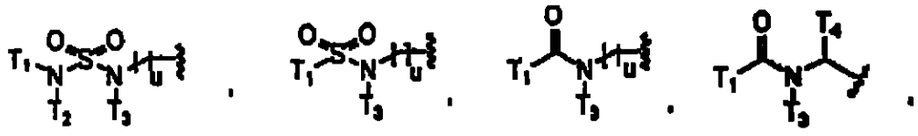
L es C(H), C(R), $CH_2C(R)$, o $C(R)CH_2$,

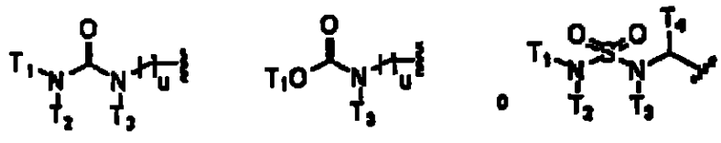
R, R', R^2, y R^3 pueden ser iguales o diferentes, siendo cada uno seleccionado independientemente del grupo formado por H, alquil-, alquenil-, alquinil-, cicloalquil-, heteroalquil-, heterocicil-, aril-, heteroaril-, (cicloalquil)alquil-, (heterocicil)alquil-, aril-alquil-, y heteroaril-alquil-, o alternativamente R y R' en NRR' están conectados entre si de modo que NR^9R^{10} forma un heterocicilo de cuatro a ocho miembros,

Y se selecciona de las siguientes porciones



donde Y^{30} e Y^{31} se seleccionan entre





donde u es un N° 0-6

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad 06-082842- -00000-0000
Fec 2006-08-22 17:24:04 Dep 2020 NUECREACIONES
Tra 11 PATENTEIYII
Eve 379 FASENACIONALII
Act 411 PRESENTACION Folios 527

532

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- ◇ Indicación de que se solicita la concesión de una patente [ ]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ◇ Descripción de la invención [ ]
- ◇ Dibujos de ser estos pertinentes [ ]
- ◇ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- ◇ Indicación de que se solicita el registro de Diseño Industrial [ ]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ◇ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- ◇ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- ◇ Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ◇ Representación gráfica del esquema trazado [ ]
- ◇ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Fernanda B
Firma Responsable

Fecha 21-AG 6

Carrera 13 No 27-00 Piso 5, 7 y 10
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REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCI

Bogotá,
2020

Doctor(a)
RAISBECK J IAN
Apoderado(a) y/o Representante de
SCHERING CORPORATION

REFERENCIA	Radicación No	6 82842
	Solicitud internacional	US2005/005772
	Fecha inicio fase nacional	27/09/2006
	Trámite	11
	Evento	379
	Actuación	420
	Oficio No	11915

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que

1 La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante (Art 26-k) Decisión 486

2 Debe aclarar el número de reivindicaciones, por cuanto la publicación internacional difiere del petitorio presentado en fase nacional

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5 2, literal e), del capítulo quinto del título primero de la Circular Unica No 10 de 2001

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha
aalvarado 20 OCT 2006