06 29608

Libertad y Orden

REPUBLICA DE COLOMBIA

DIVISIÓN DE PROPIEDAD INDUSTRIAL

PCT

PATENTE DE INVENCIÓN

Industria y Comercio
SUPERINTENDENCIA

06 - 29608

TITULO INHIBIDORES MACROCICLICOS DE LA SERINA PROTESA NS3 DEL VIRUS DE LA HEPATITIS C

CIP C07K5/12, C07K5/00, A61K38/12 A61P31/12

SOLICITANTE SCHERING CORPORATION

DIRECCIÓN 2000 Galloping Hill Road, Kenilwort, NJ 07033-0530 E U A

APODERADO CARLOS R OLARTE

BOGOTA, Marzo 23 de 2006

P2006/000055

06155

OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 06029688 00000000 Folios: 721
Fecha (MM): 2006-03-24 17:24:25
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 0020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL : 26-04-2006

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, NJ 07033-0530 E.U.A.
Nacionalidad o Domicilio: ESTADOUNIDENSE
Lugar de Constitución: Kenilworth E.U.A.
Teléfono: _____ Fax: _____
E-mail: _____

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

(3) REPRESENTANTE APODERADO

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center Torre A, Calle 100 Nº. 8A-37 Piso 10
Teléfono: 601-7700 Fax: 601-7799
E-mail: office@olarteraisbeck.com

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

(4) INVENTOR (ES) (72)

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

(5) PCT (86)

Solicitud Internacional No. PCT/US2004/031136 Fecha Septiembre 23, 2004
Publicación Internacional No. WO 2005/030796 Fecha Abril 7, 2005

(6) Título (54) INHIBIDORES MACROCICLICOS DE LA SERINA PROTEASA NS3 DEL VIRUS DE LA HEPATITIS C

(7) Clasificación Internacional (51): C07K 5/12, C07D 245/00, A61K 38/12, A61P 31/12.

(8) Prioridad SI [X] N [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Septiembre 26, 2003	60/506.637

(9) Comprobante de pago No. 06 – 21.063 **Fecha:** Marzo 16, 2006

2 2

(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.
- [x] 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.
- [x] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA

C.C. 79.782.747 Btá T.P. 74.295

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

LISTA DE INVENTORES PCT/US2004/031136

SRIKANTH VENKATRAMAN
35 Roanoke Street, Woodbridge,
New Jersey 07095,
Estados Unidos de América
Nacionalidad: India

F. GEORGE NJOROGE
11 Softwood Way, Warren
New Jersey 07059,
Estados Unidos de América
Nacionalidad: Estadounidense

WANLI WU
41B Alva Court, Edison
New Jersey 08817,
Estados Unidos de América
Nacionalidad: Estadounidense

VIYYOOR M. GIRIJAVALLABHAN
10 Maplewood Drive, Parsippany
New Jersey 07054,
Estados Unidos de América
Nacionalidad: Estadounidense

BRIAN McKITTRICK
14 Millbrook Road, New Vernon
New Jersey, 07976,
Estados Unidos de América
Nacionalidad: Estadounidense

JING SU
1398 Graymill Drive, Scotch Plains,
New Jersey 07076,
Estados Unidos de América
Nacionalidad: Estadounidense

FRANCISCO VELÁSQUEZ
4 Alexandra Way, Clinton,
New Jersey 08809,
Estados Unidos de América
Nacionalidad: Mexicana

PATRICK A. PINTO
34 Battle Ridge Road,
Morris Plains, New Jersey 07950
Estados Unidos de América
Nacionalidad: Estadounidense

4 ✗

SUPERINDUSTRIA Y COMERCIO
Radicacion : 06029688 00000000 Folios: 721
Fecha (AAMM): 2006-03-24 17:24:35
Tramite : 811 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 21,063
FECHA : MARZO 16 DE 2006

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEGR	CONSIGNACION	BANCO POPULAR	050-00110-6	51156203	16/03/2006	3,933,000.00

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._____

5

5

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SCHERING CORPORATION

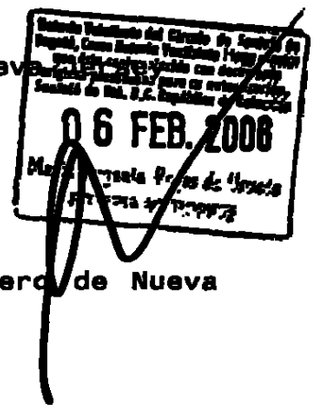
APOSTILLA

(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

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

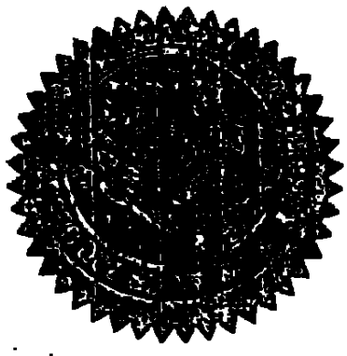
6. THE 29TH DAY OF AUGUST 2003

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

8. NO. A180345

9. SEAL/STAMP:

10. SIGNATURE



7 7

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

Notaría Veintinueve del Círculo de Santafé de Bogotá, Doctora Gloria Valderrama Hoyos certifica que dicha copia coincide con documento original presentado para su autenticación. Santafé de Bta. D.C. República de Colombia

06 FEB. 2004

María Eugenia Rojas de Urueta

Power of Attorney

The undersigned,
SCHERING CORPORATION

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

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

Poder

El suscrito,

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

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

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

Date/Fecha: August 7, 2003

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

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

Notarial Certification

On this date, August 7, 2003

The undersigned Notary Public certifies:

1. That Edward H. Mazer

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

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

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

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

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

Power of Attorney, dated November 4, 2002.

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad y domiciliado

suscribió el documento que antecede.

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

de

4. Que

con sede principal ubicada en

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

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

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

Notaría Veintiuno del Círculo de Santafé de Bogotá, Doctora Eugenia Rojas de Urrutia. Hago constar que dicha copia coincide con documento original presentado para su protocolización. Santafé de Bogotá, D.C. República de Colombia

06 FEB. 2006

Dra. Eugenia Rojas de Urrutia
NOTARIA VEINTIUNO

NOTARY PUBLIC (Signature):

Marguerite LaCorte

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

99

APOSTILLA

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

1. País: Estados Unidos de América
2. El presente documento público fue firmado por: Ashly M. Armstrong
3. Que actuó en su calidad de Notario Público de Nueva Jersey
4. Lleva el sello del mencionado Notario Público Ashly M. Armstrong

   Se certificó:
5. En Trenton, Nueva Jersey
6. El 7 de marzo de 2006
7. Por parte de Bradley I. Abelow, Tesorero New Jersey
8. Bajo el Número **A253361**
9. Aparece Sello del Estado de Nueva Jersey
10. Firmado por Bradley I. Abelow

Caso No. IN06005

RECONOCIMIENTO

Estado de Nueva Jersey

Condado de Unión

Por el presente certifico que anexa se encuentra una copia fiel de la cesión original a **SCHERING CORPORATION**, de una solicitud de patente titulada "**INHIBIDORES MACROCICLICOS DE LA SERINA PROTEASA NS3 DEL VIRUS DE LA HEPATITIS C**", ésta cesión que fue firmada por Srikanth Venkatraman, Jin Su, Francisco Velásquez, y Patrick A. Pinto el 20 de agosto de 2004, F. George Njoroge el 30 de Agosto de 2004, y Wanli Wu y Brian McKittrick el 28 de Septiembre de 2004.

Fecha: 27 de Febrero de 2006.

(Fdo.) Ashly M. Armstrong,
Notario Público de Nueva Jersey, cuyo cargo vence el 26 de Marzo de 2008 (Sello Oficial del Notario).

Caso de Patentes No.: IN06005US01

CESIÓN

Por buena y onerosa consideración pagada a favor nuestro,

(1) SRIKANTH VENKATRAMAN,
(2) F. GEORGE NJOROGE,
(3) WANLI WU,
(4) VIYYOOR M. GIRIJAVALLABHAN,
(5) BRIAN MCKITTRICK,
(6) JING SU,
(7) FRANCISCO VELÁSQUEZ,
(8) PATRICK A. PINTO,

cada uno domiciliado, de manera respectiva, en:

(1) Woodbridge, NJ,
(2) Warren, NJ,
(3) Edison, NJ,
(4) Parsippany, NJ,
(5) New Vernon, NJ,
(6) Scotch Plains, NJ,
(7) Clinton, NJ,
(8) Morris Plains, NJ.

por **SCHERING- CORPORATION**, una compañía constituida bajo las leyes del Estado de Nueva Jersey, Estados Unidos de América, con domicilio principal en 2000 Galloping Hill Road, Kenilworth, New Jersey 07033, Estados Unidos de América, (de aquí adelante conocido como "CESIONARIO", por la presente cada uno de nosotros vendemos, cedemos y transferimos a dicho CESIONARIO la totalidad de nuestro derecho, título e interés en todos los países del mundo y todos nuestros inventos y descubrimientos descritos en la solicitud de patente titulada **INHIBIDORES MACROCICLICOS DE LA SERINA PROTEASA NS3 DEL VIRUS DE LA HEPATITIS C** y oficialmente identificada por la Oficina de Marcas y Patentes de los Estados Unidos con el número de solicitud No. 10/948.367 presentada el 23 de septiembre de 2004, y/o por la Organización Mundial de la Propiedad Intelectual con el Número de Solicitud de Patente Internacional PCT/US2004/031136 presentada el 23 de septiembre de 2004, con derecho de presentar solicitudes de patente a nombre del CESIONARIO, su designado o cualquiera o todos nuestros nombres, a su elección, con respecto a las anteriores invenciones y descubrimientos en todos los países del mundo, junto con todos los derechos de prioridad en los anteriores países que deriven de la anterior solicitud de patente bajo la Convención Internacional para la Protección de la Propiedad Industrial, bajo la Convención Inter-americana con relación a Invenciones, Patentes, Diseños y Modelos Industriales y bajo cualquier otro convenio internacional bajo el cual los Estados Unidos ahora o en adelante se convierta en signatario, para cualquier o todas las Patentes que se otorgaran con respecto a cualquiera de las anteriores solicitudes de patente, para cualquier solicitud reivindicando beneficios de prioridad sobre una solicitud de patente provisional u otras solicitudes presentadas sobre dichos inventos, y para cualquier continuación, división, re-otorgamiento, renovación y extensión de la misma de cualesquiera de dichas Patentes, el mismo que debe ser poseído y usufructuado por dicho CESIONARIO, sus sucesores, cesionarios, u otros representantes legales, en todo su alcance por lo que implica el otorgamiento de una

patente, de manera tan entera como si hubiera sido poseída y usufructuada por nosotros si esta cesión y venta no se hubiera cristalizado.

Y por medio de la presente nosotros convenimos y acordamos que en cualquier momento, al requerirse y a expensas del CESIONARIO, ejecutaremos y entregaremos cualquier y todos los documentos necesarios o deseables para perfeccionar el título de los anteriores inventos o descubrimientos, solicitudes de patente, Patentes y continuaciones, divisiones, re-otorgamientos, renovaciones, y extensiones del mismo a nombre del CESIONARIO, sus cesionarios, sucesores, u otros representantes legales, incluyendo la ejecución y consecución de cualquier y todo documento adicional que evidencie esta cesión y venta según sea necesario o deseable para el registro del mismo ante la Oficina de Patentes de cualquier país en cuestión, y que nosotros, en cualquier momento, al requerirse y a expensas del CESIONARIO, ejecutaremos cualquier solicitud divisional o adicional para patentes de dichos inventos y descubrimientos, o cualquier parte o partes del mismo, y solicitudes de patentes de confirmación, registro e importación con base en dicha Patente y sobre Patentes que salgan otorgadas a partir de dichas solicitudes divisionales y adicionales y renovaciones y extensiones del mismo, y realizaremos las necesarias declaraciones juramentadas y realizaremos todos los actos jurídicos necesarios para ello, sin compensación adicional, pero a expensas del CESIONARIO, sus sucesores, cesionarios, u otros representantes legales.

Por medio de la presente autorizamos al CESIONARIO adicionar a este instrumento el número de solicitud y la fecha de presentación de dicha solicitud de patentes.

Ejecutado el 20 de agosto de 2004
SRIKANTH VENKATRAMAN, (firma ilegible) L.S.

RECONOCIMIENTO
Estado de Nueva Jersey)
Condado de Unión) s.s.:

Compareció ante mi el 20 de agosto de 2004 Srikanth Venkatraman, personaje conocido y el cual ejecutó el anterior instrumento, y el cual afirmó que ejecutó el mismo, por voluntad propia, por lo motivos expuestos en el mismo.
(sello)

(firmado: Ashly M. Armstrong)
Notario Público, Estado de New Jersey
Mi comisión vence el 26 de marzo de 2008

Ejecutado el 30 de agosto de 2004
F. GEORGE NJOROGE, (firma ilegible) L.S.

RECONOCIMIENTO
Estado de Nueva Jersey)
Condado de Unión) s.s.:

Compareció ante mi el 30 de agosto de 2004 F. George Njoroge, personaje conocido y el cual ejecutó el anterior instrumento, y el cual afirmó que ejecutó el mismo, por voluntad propia, por lo motivos expuestos en el mismo.
(sello)

(firmado: Ashly M. Armstrong)

Notario Público, Estado de New Jersey
Mi comisión vence el 26 de marzo de 2008

Ejecutado el 28 de septiembre de 2004
WANLI WU, (firma ilegible) L.S.

RECONOCIMIENTO
Estado de Nueva Jersey)
Condado de Unión) s.s.:

Compareció ante mi el 28 de septiembre de 2004 Wanli Wu, personaje conocido y el cual ejecutó el anterior instrumento, y el cual afirmó que ejecutó el mismo, por voluntad propia, por lo motivos expuestos en el mismo.
(sello)

(firmado: Ashly M. Armstrong)
Notario Público, Estado de New Jersey
Mi comisión vence el 26 de marzo de 2008

Ejecutado el 28 de septiembre de 2004
BRIAN McKITTRICK (firma ilegible) L.S.

RECONOCIMIENTO
Estado de Nueva Jersey)
Condado de Unión) s.s.:

Compareció ante mi el 28 de septiembre de 2004, Brian McKittrick, personaje conocido y el cual ejecutó el anterior instrumento, y el cual afirmó que ejecutó el mismo, por voluntad propia, por lo motivos expuestos en el mismo.
(sello)

(firmado: Ashly M. Armstrong)
Notario Público, Estado de New Jersey
Mi comisión vence el 26 de marzo de 2008

Ejecutado el 20 de agosto de 2004
JING SU, (firma ilegible) L.S.

RECONOCIMIENTO
Estado de Nueva Jersey)
Condado de Unión) s.s.:

Compareció ante mi el 20 de agosto de 2004, Jing Su personaje conocido y el cual ejecutó el anterior instrumento, y el cual afirmó que ejecutó el mismo, por voluntad propia, por lo motivos expuestos en el mismo.
(sello)

(firmado: Ashly M. Armstrong)
Notario Público, Estado de New Jersey
Mi comisión vence el 26 de marzo de 2008

Ejecutado el 20 de agosto de 2004
FRANCISCO VELÁSQUEZ, (firma ilegible) L.S.

RECONOCIMIENTO
Estado de Nueva Jersey)
Condado de Unión) s.s.:

Compareció ante mi el 20 de agosto de 2004, Francisco Velásquez personaje conocido y el cual ejecutó el anterior instrumento, y el cual afirmó que ejecutó el mismo, por voluntad propia, por lo motivos expuestos en el mismo.
(sello)

(firmado: Ashly M. Armstrong)
Notario Público, Estado de New Jersey
Mi comisión vence el 26 de marzo de 2008

Ejecutado el 20 de agosto de 2004
PATRICK A. PINTO, (firma ilegible) L.S.

RECONOCIMIENTO
Estado de Nueva Jersey)
Condado de Unión) s.s.:

Compareció ante mi el 20 de agosto de 2004, Patrick A. Pinto personaje conocido y el cual ejecutó el anterior instrumento, y el cual afirmó que ejecutó el mismo, por voluntad propia, por lo motivos expuestos en el mismo.
(sello)

(firmado: Ashly M. Armstrong)
Notario Público, Estado de New Jersey
Mi comisión vence el 26 de marzo de 2008

15 15

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
ASHLY M ARMSTRONG

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

4. BEARS THE SEAL/STAMP OF:
ASHLY M ARMSTRONG, NOTARY

CERTIFIED

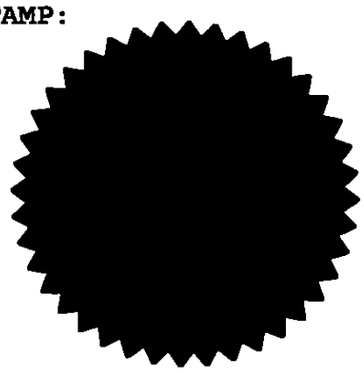
5. AT TRENTON, NEW JERSEY

6. THE 7TH DAY OF MARCH 2006

7. BY: Bradley I. Abelow, NEW JERSEY TREASURER

8. NO. A253361

9. SEAL/STAMP:



10. SIGNATURE

Bradley Abelow

Case IN06005

ACKNOWLEDGMENT

State of New Jersey }
}
County of Union }

I hereby certify that the attached is a true copy of the original Assignment from the inventors to **SCHERING CORPORATION**, of a patent application entitled, **"MACROCYCLIC INHIBITORS OF HCV NS3-SERINE PROTEASE"**, said Assignment having been executed by Srikanth Venkatraman, Jing Su, Francisco Velazquez, and Patrick A. Pinto on August 20, 2004, F. George Njoroge on August 30, 2004, and Wanli Wu and Brian McKittrick on September 28, 2004.

Date: February 27, 2006

Ashly M. Armstrong
Notary Public of New Jersey
My Commission Expires March 26, 2008

(Seal)

17 17

(Joint)

PATENT CASE: IN06005US01

ASSIGNMENT

For good and valuable consideration paid to us,

(1) *Srikanth Venkatraman*, (5) *Brian McKittrick*,
(2) *F. George Njoroge*, (6) *Jing Su*,
(3) *Wenli Wu*, (7) *Francisco Velazquez*,
(4) *Viyyoor M. Girijavallabhan*, (8) *Patrick A. Pinto*,

respectively residing at

(1) *Woodbridge, NJ*, (5) *New Vernon, NJ*,
(2) *Warren, NJ*, (6) *Scotch Plains, NJ*,
(3) *Edison, NJ*, (7) *Clinton, NJ*,
(4) *Parsippany, NJ*, (8) *Morris Plains, NJ*,

by **SCHERING CORPORATION**, a corporation organized under the laws of the State of New Jersey, United States of America, having its principal office at 2000 Galloping Hill Road, Kenilworth, New Jersey 07033 , United States of America, (hereinafter called "**ASSIGNEE**"), we each do hereby sell, assign and transfer to said **ASSIGNEE** our entire rights, title and interest in all countries of the world in and to any and all of our inventions and discoveries described in the patent application entitled

"Macrocyclic Inhibitors of Hepatitis C Virus NS3-Serine Protease"

and officially identified* by the United States Patent and Trademark Office as Application Number 10/948367 filed on September 23, 2004, and/or by the World Intellectual Property Organization as International Patent Application Number PCT/US2004/031136 filed on September 23, 2004, in and to the right to file patent applications in the name of **ASSIGNEE**, its designee, or in any or all of our names, at its election, on the aforesaid inventions and discoveries in all countries of the world, together with all rights of priority in the aforesaid countries deriving from the above-identified patent application under the International Convention for the Protection of Industrial Property, under the Inter-American Convention relating to Inventions, Patents, Designs and Industrial Models and under any other international arrangement to which the United States now is or hereafter becomes a signatory, in and to any and all Letters Patent that are granted from any of the aforesaid patent applications, in and to any applications claiming priority benefits to a provisional patent application or other applications filed on said inventions, and in and to any continuations, divisions, reissues, renewals and extensions thereof of any of said Letters Patent, the same to be held and enjoyed by said **ASSIGNEE**, its successors, assigns and other legal representatives, to the full ends of the terms for which all Letters Patent therefor may be granted, as fully and entirely as the same would have been held and enjoyed by us if this assignment and sale had not been made.

And we hereby covenant and agree that we will at any time, upon the request and at the expense of **ASSIGNEE**, execute and deliver any and all documents that may be necessary or desirable to perfect the title to the foregoing inventions and discoveries, patent applications, and Letters Patent and continuations, divisions, reissues, renewals and extensions thereof in **ASSIGNEE**, its successors, assigns or other legal

representatives, including the execution and procurement of any and all further documents evidencing this assignment and sale as may be necessary or desirable for recording the same in the Patent Office of any country concerned, and that we will, at any time, upon the request and at the expense of **ASSIGNEE**, execute any additional or divisional applications for patents for said inventions and discoveries, or any part or parts thereof, and applications for patents of confirmation, registration and importation based on said Letters Patent and on Letters Patent issuing from said additional or divisional applications and reissues, renewals and extensions therefor, and will make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein, without further compensation, but at the expense of **ASSIGNEE**, its successors, assigns or other legal representatives.

*We hereby authorize **ASSIGNEE** to insert in this instrument the Application Number and the filing date of said application for Letters Patent when officially notified thereof.

Executed this 20th day of Aug, 2004.

S. V. L.S.

SRIKANTH VENKATRAMAN

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this 20th day of August, 2004, personally appeared before me Srikanth Venkatraman to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

Ashley M. Armstrong
Notary Public

ASHLY M. ARMSTRONG
NOTARY PUBLIC OF NEW JERSEY
Commission Expires 3/26/2008

Executed this 30th day of Aug, 2004.

F. George Njoroge L.S.
F. GEORGE NJOROGE

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this 30th day of August, 2004, personally appeared before me F. George Njoroge to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

Ashly M. Armstrong
Notary Public
ASHLY M. ARMSTRONG
NOTARY PUBLIC OF NEW JERSEY
Commission Expires 3/26/2008

Executed this 28th day of September, 2004.

L.S.
WANLI WU

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this 28th day of September, 2004, personally appeared before me Wanli Wu to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

Ashly M. Armstrong
Notary Public
ASHLY M. ARMSTRONG
NOTARY PUBLIC OF NEW JERSEY
Commission Expires 3/26/2008

Executed this _____ day of _____, 20_____.

_____ L.S.

VIYYOOR M. GIRIJAVALLABHAN

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____, 20____, personally appeared before me Viyyoor M. Girijavallabhan to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this 28th day of September, 2004.

_____ L.S.

BRIAN McKITTRICK

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this 28th day of September, 2004, personally appeared before me Brian McKittrick to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

Ashly M. Armstrong
Notary Public
ASHLY M. ARMSTRONG
NOTARY PUBLIC OF NEW JERSEY
Commission Expires 3/26/2008

Executed this 20th day of August, 2004.

_____ L.S.
JING SU

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this 20th day of August, 2004, personally appeared before me Jing Su to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

Ashley M. Armstrong
Notary Public
ASHLEY M. ARMSTRONG
NOTARY PUBLIC OF NEW JERSEY
Commission Expires 3/26/2008

Executed this 20 day of August, 2004.

_____ L.S.
FRANCISCO VELAZQUEZ

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this 20th day of August, 2004, personally appeared before me Francisco Velazquez to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

Ashley M. Armstrong
Notary Public
ASHLEY M. ARMSTRONG
NOTARY PUBLIC OF NEW JERSEY
Commission Expires 3/26/2008

Executed this 20th day of August, 2004.

Patrick A. Pinto L.S.

PATRICK A. PINTO

ACKNOWLEDGEMENT

State of New Jersey)
) s.s.:
County of Union)

On this 20th day of August, 2004, personally appeared before me Patrick A. Pinto to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

Ashly M. Armstrong
Notary Public
ASHLY M. ARMSTRONG
NOTARY PUBLIC OF NEW JERSEY
Commission Expires 3/26/2008

23

23

APOSTILLA

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

1. País: Estados Unidos de América
2. El presente documento público fue firmado por: Ashly M. Armstrong
3. Que actuó en su calidad de Notario Público de Nueva Jersey
4. Lleva el sello del mencionado Notario Público Ashly M. Armstrong

   Se certificó:
5. En Trenton, Nueva Jersey
6. El 7 de marzo de 2006
7. Por parte de Bradley I. Abelow, Tesorero New Jersey
8. Bajo el Número **A253362**
9. Aparece Sello del Estado de Nueva Jersey
10. Firmado por Bradley I. Abelow

29

24

Caso No. IN06005

RECONOCIMIENTO

Estado de Nueva Jersey

Condado de Unión

Por el presente certifico que anexa se encuentra una copia fiel de la cesión original a **SCHERING CORPORATION**, de una solicitud de patente titulada **"INHIBIDORES MACROCICLICOS DE LA SERINA PROTEASA NS3 DEL VIRUS DE LA HEPATITIS C"**, ésta cesión que fue firmada por Viyyoor M. Girijavallabhan el 27 de Octubre de 2004.

Fecha: 27 de Febrero de 2006.

(Fdo.) Ashly M. Armstrong,
Notario Público de Nueva Jersey, cuyo cargo vence el 26 de Marzo de 2008 (Sello Oficial del Notario).

25

25

Caso de Patentes No.: IN06005US01

CESIÓN

Por buena y onerosa consideración pagada a favor nuestro,

(1)	SRIKANTH VENKATRAMAN,	(5)	BRIAN MCKITTRICK,
(2)	F. GEORGE NJOROGE,	(6)	JING SU,
(3)	WANLI WU,	(7)	FRANCISCO VELÁSQUEZ,
(4)	VIYYOOR M. GIRIJAVALLABHAN,	(8)	PATRICK A. PINTO,

cada uno domiciliado, de manera respectiva, en:

(1)	Woodbridge, NJ,	(5)	New Vernon, NJ,
(2)	Warren, NJ,	(6)	Scotch Plains, NJ,
(3)	Edison, NJ,	(7)	Clinton, NJ,
(4)	Parsippany, NJ,	(8)	Morris Plains, NJ.

por **SCHERING- CORPORATION**, una compañía constituida bajo las leyes del Estado de Nueva Jersey, Estados Unidos de América, con domicilio principal en 2000 Galloping Hill Road, Kenilworth, New Jersey 07033, Estados Unidos de América, (de aquí adelante conocido como "CESIONARIO", por la presente cada uno de nosotros vendemos, cedemos y transferimos a dicho CESIONARIO la totalidad de nuestro derecho, título e interés en todos los países del mundo y todos nuestros inventos y descubrimientos descritos en la solicitud de patente titulada **INHIBIDORES MACROCICLICOS DE LA SERINA PROTEASA NS3 DEL VIRUS DE LA HEPATITIS C** y oficialmente identificada por la Oficina de Marcas y Patentes de los Estados Unidos con el número de solicitud No. 10/948.367 presentada el 23 de septiembre de 2004, y/o por la Organización Mundial de la Propiedad Intelectual con el Número de Solicitud de Patente Internacional PCT/US2004/031136 presentada el 23 de septiembre de 2004, con derecho de presentar solicitudes de patente a nombre del CESIONARIO, su designado o cualquiera o todos nuestros nombres, a su elección, con respecto a las anteriores invenciones y descubrimientos en todos los países del mundo, junto con todos los derechos de prioridad en los anteriores países que deriven de la anterior solicitud de patente bajo la Convención Internacional para la Protección de la Propiedad Industrial, bajo la Convención Inter-americana con relación a Invenciones, Patentes, Diseños y Modelos Industriales y bajo cualquier otro convenio internacional bajo el cual los Estados Unidos ahora o en adelante se convierta en signatario, para cualquier o todas las Patentes que se otorgaran con respecto a cualquiera de las anteriores solicitudes de patente, para cualquier solicitud reivindicando beneficios de prioridad sobre una solicitud de patente provisional u otras solicitudes presentadas sobre dichos inventos, y para cualquier continuación, división, re-otorgamiento, renovación y extensión de la misma de cualesquiera de dichas Patentes, el mismo que debe ser poseído y usufructuado por dicho CESIONARIO, sus sucesores, cesionarios, u otros representantes legales, en todo su alcance por lo que implica el otorgamiento de una

patente, de manera tan entera como si hubiera sido poseída y usufructuada por nosotros si esta cesión y venta no se hubiera cristalizado.

Y por medio de la presente nosotros convenimos y acordamos que en cualquier momento, al requerirse y a expensas del CESIONARIO, ejecutaremos y entregaremos cualquier y todos los documentos necesarios o deseables para perfeccionar el título de los anteriores inventos o descubrimientos, solicitudes de patente, Patentes y continuaciones, divisiones, re-otorgamientos, renovaciones, y extensiones del mismo a nombre del CESIONARIO, sus cesionarios, sucesores, u otros representantes legales, incluyendo la ejecución y consecución de cualquier y todo documento adicional que evidencie esta cesión y venta según sea necesario o deseable para el registro del mismo ante la Oficina de Patentes de cualquier país en cuestión, y que nosotros, en cualquier momento, al requerirse y a expensas del CESIONARIO, ejecutaremos cualquier solicitud divisional o adicional para patentes de dichos inventos y descubrimientos, o cualquier parte o partes del mismo, y solicitudes de patentes de confirmación, registro e importación con base en dicha Patente y sobre Patentes que salgan otorgadas a partir de dichas solicitudes divisionales y adicionales y renovaciones y extensiones del mismo, y realizaremos las necesarias declaraciones juramentadas y realizaremos todos los actos jurídicos necesarios para ello, sin compensación adicional, pero a expensas del CESIONARIO, sus sucesores, cesionarios, u otros representantes legales.

Por medio de la presente autorizamos al CESIONARIO adicionar a este instrumento el número de solicitud y la fecha de presentación de dicha solicitud de patentes.

Ejecutado el 27 de octubre de 2004
VIYYOOR M. GIRIJAVALLABHAN, (firma ilegible) L.S.

RECONOCIMIENTO
Estado de Nueva Jersey)
Condado de Unión) s.s.:

Compareció ante mi el 27 de octubre de 2004, Viyyoor M. Girijavallabhan, personaje conocido y el cual ejecutó el anterior instrumento, y el cual afirmó que ejecutó el mismo, por voluntad propia, por lo motivos expuestos en el mismo.
(sello)

(firmado: Denise A. Buffardi)
Notario Público, Estado de New Jersey
Mi comisión vence el 17 de diciembre de 2006

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
ASHLY M ARMSTRONG

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

4. BEARS THE SEAL/STAMP OF:
ASHLY M ARMSTRONG, NOTARY

CERTIFIED

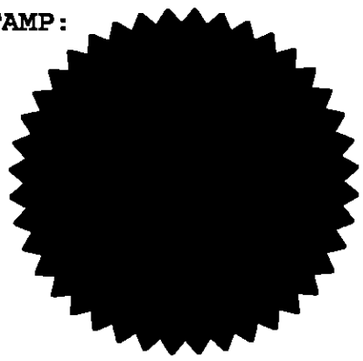
5. AT TRENTON, NEW JERSEY

6. THE 7TH DAY OF MARCH 2006

7. BY: Bradley I. Abelow, NEW JERSEY TREASURER

8. NO. A253362

9. SEAL/STAMP:



10. SIGNATURE

Bradley Abelow

Case IN06005

ACKNOWLEDGMENT

State of New Jersey }
}
County of Union }

I hereby certify that the attached is a true copy of the original Assignment from the inventors to **SCHERING CORPORATION**, of a patent application entitled, **"MACROCYCLIC INHIBITORS OF HCV NS3-SERINE PROTEASE"**, said Assignment having been executed by Viyyoor M. Girijavallabhan on October 27, 2004.

Date: February 27, 2006

Ashly M. Armstrong
Notary Public of New Jersey
My Commission Expires March 26, 2008

(Seal)

(Joint)

PATENT CASE: IN06005US01

ASSIGNMENT

For good and valuable consideration paid to us,

(1) *Srikanth Venkatraman*, (5) *Brian McKittrick*,
(2) *F. George Njoroge*, (6) *Jing Su*,
(3) *Wanli Wu*, (7) *Francisco Velazquez*,
(4) *Viyyoor M. Girijavallabhan*, (8) *Patrick A. Pinto*,

respectively residing at

(1) *Woodbridge, NJ*, (5) *New Vernon, NJ*,
(2) *Warren, NJ*, (6) *Scotch Plains, NJ*,
(3) *Edison, NJ*, (7) *Clinton, NJ*,
(4) *Parsippany, NJ*, (8) *Morris Plains, NJ*,

by **SCHERING CORPORATION**, a corporation organized under the laws of the State of New Jersey, United States of America, having its principal office at 2000 Galloping Hill Road, Kenilworth, New Jersey 07033 , United States of America, (hereinafter called "**ASSIGNEE**"), we each do hereby sell, assign and transfer to said **ASSIGNEE** our entire rights, title and interest in all countries of the world in and to any and all of our inventions and discoveries described in the patent application entitled

"Macrocyclic Inhibitors of Hepatitis C Virus NS3-Serine Protease"

and officially identified* by the United States Patent and Trademark Office as Application Number 10/948367 filed on September 23, 2004 , and/or by the World Intellectual Property Organization as International Patent Application Number PCT/US2004/031136 filed on September 23, 2004 , in and to the right to file patent applications in the name of **ASSIGNEE**, its designee, or in any or all of our names, at its election, on the aforesaid inventions and discoveries in all countries of the world, together with all rights of priority in the aforesaid countries deriving from the above-identified patent application under the International Convention for the Protection of Industrial Property, under the Inter-American Convention relating to Inventions, Patents, Designs and Industrial Models and under any other international arrangement to which the United States now is or hereafter becomes a signatory, in and to any and all Letters Patent that are granted from any of the aforesaid patent applications, in and to any applications claiming priority benefits to a provisional patent application or other applications filed on said inventions, and in and to any continuations, divisions, reissues, renewals and extensions thereof of any of said Letters Patent, the same to be held and enjoyed by said **ASSIGNEE**, its successors, assigns and other legal representatives, to the full ends of the terms for which all Letters Patent therefor may be granted, as fully and entirely as the same would have been held and enjoyed by us if this assignment and sale had not been made.

And we hereby covenant and agree that we will at any time, upon the request and at the expense of **ASSIGNEE**, execute and deliver any and all documents that may be necessary or desirable to perfect the title to the foregoing inventions and discoveries, patent applications, and Letters Patent and continuations, divisions, reissues, renewals and extensions thereof in **ASSIGNEE**, its successors, assigns or other legal

representatives, including the execution and procurement of any and all further documents evidencing this assignment and sale as may be necessary or desirable for recording the same in the Patent Office of any country concerned, and that we will, at any time, upon the request and at the expense of **ASSIGNEE**, execute any additional or divisional applications for patents for said inventions and discoveries, or any part or parts thereof, and applications for patents of confirmation, registration and importation based on said Letters Patent and on Letters Patent issuing from said additional or divisional applications and reissues, renewals and extensions therefor, and will make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein, without further compensation, but at the expense of **ASSIGNEE**, its successors, assigns or other legal representatives.

*We hereby authorize **ASSIGNEE** to insert in this instrument the Application Number and the filing date of said application for Letters Patent when officially notified thereof.

Executed this _____ day of _____ , 20_____.

_____ L.S.

SRIKANTH VENKATRAMAN

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____ , 20____, personally appeared before me Srikanth Venkatraman to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of _____, 20_____.

_____ L.S.

F. GEORGE NJOROGE

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____, 20____, personally appeared before me F. George Njoroge to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of _____, 20_____.

_____ L.S.

WANLI WU

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____, 20____, personally appeared before me Wanli Wu to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this 27 day of October, 2004.

_____ L.S.

VIYYOOR M. GIRIJAVALLABHAN

ACKNOWLEDGEMENT

State of NJ)
) s.s.:
County of Union)

On this 27th day of October, 2004, personally appeared before me Viyyoor M. Girijavallabhan to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public
DENISE A. BUFFARDI
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires Dec. 17, 2008

Executed this _____ day of _____, 20_____.

_____ L.S.

BRIAN McKITTRICK

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____, 20____, personally appeared before me Brian McKittrick to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

33 33

Executed this _____ day of _____ , 20_____.

_____ L.S.

JING SU

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____ , 20____, personally appeared before me Jing Su to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of _____ , 20_____.

_____ L.S.

FRANCISCO VELAZQUEZ

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____ , 20____, personally appeared before me Francisco Velazquez to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

34 37

Executed this _____ day of _____ , 20_____.

_____ L.S.

PATRICK A. PINTO

ACKNOWLEDGEMENT

State of _____)
) s.s.:
County of _____)

On this _____ day of _____ , 20____, personally appeared before me Patrick A. Pinto to me known, and known by me to be the same person described in and who executed the foregoing instrument, and acknowledged that he (she) executed the same, of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 April 2005 (07.04.2005)

PCT

(10) International Publication Number
WO 2005/030796 A1

(51) International Patent Classification[7]: C07K 5/12, C07D 245/00, A61K 38/12

(21) International Application Number: PCT/US2004/031136

(22) International Filing Date: 23 September 2004 (23.09.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 60/506,637 26 September 2003 (26.09.2003) US

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

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): VENKATRAMAN, Srikanth [IN/US]; 35 Roanoke Street, Woodbridge, NJ 07095 (US). NJOROGE, F., George [US/US]; 11 Softwood Way, Warren, NJ 07059 (US). WU, Wanli [CN/US]; 41B Alva Court, Edison, NJ 08817 (US). GIRIJAVALLABHAN, Viyyoor, M. [US/US]; 10 Maplewood Drive, Parsippany, NJ 07054 (US). MCKITTRICK, Brian [US/US]; 14 Millbrook Road, New Vernon, NJ 07976 (US). SU, Jing [US/US]; 1398 Graymill Drive, Scotch Plains, NJ 07076 (US). VELASQUEZ, Francisco [MX/US]; 4 Alexandra Way, Clinton, NJ 08809 (US). PINTO, Patrick, A. [US/US]; 34 Battle Ridge Road, Morris Plains, NJ 07950 (US).

(74) Agent: KALYANARAMAN, Palaiyur, S.; Schering-Plough Corporation, 2000 Galloping Hill Road, Mail Stop K-6-1 1990, 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, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

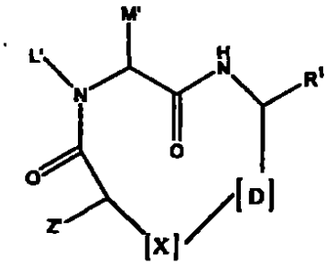
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(54) Title: MACROCYCLIC INHIBITORS OF HEPATITIS C VIRUS NS3 SERINE PROTEASE



(1)

(57) Abstract: The present invention discloses novel compounds which have HCV protease inhibitory activity as well as pharmaceutical compositions comprising such compounds and methods of using them to treat disorders associated with the HCV protease. The novel compounds typically include a 15-20 member macrocycle and have the general structure of structural Formula (1): wherein Z', L', M', R_1, X and D are defined herein.

WO 2005/030796 A1

MACROCYCLIC INHIBITORS OF HEPATITIS C VIRUS NS3 SERINE PROTEASE

Field of Invention

The present invention relates to novel hepatitis C virus ("HCV") protease inhibitors, pharmaceutical compositions containing one or more such inhibitors, methods of preparing such inhibitors and methods of using such inhibitors to treat hepatitis C and related disorders. This invention additionally discloses novel macrocyclic compounds as inhibitors of the HCV NS3/NS4a serine protease. This application claims priority from U.S. provisional patent application Serial Number 60/506,637 filed September 26, 2003.

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, equal to US 2003162167). NANBH is to be distinguished from other types of viral-induced liver disease, such as hepatitis A virus (HAV), hepatitis B virus (HBV), delta hepatitis virus (HDV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV), as well as from other forms of liver disease such as alcoholism and primary biliar cirrhosis.

Recently, an HCV protease necessary for polypeptide processing and viral replication has been identified, cloned and expressed; (*see*, e.g., U.S. Patent No. 5,712,145). This approximately 3000 amino acid polyprotein contains, from the amino terminus to the carboxy terminus, a nucleocapsid protein (C), envelope proteins (E1 and E2) and several non-structural proteins (NS1, 2, 3, 4a, 5a and 5b). NS3 is an approximately 68 kda protein, encoded by approximately 1893 nucleotides of the HCV genome, and has two distinct domains: (a) a serine protease domain consisting of approximately 200 of the N-terminal amino acids; and (b) an RNA-dependent ATPase domain at the C-terminus of the protein. The NS3 protease is considered a member of the

chymotrypsin family because of similarities in protein sequence, overall three-dimensional structure and mechanism of catalysis. Other chymotrypsin-like enzymes are elastase, factor Xa, thrombin, trypsin, plasmin, urokinase, tPA and PSA. The HCV NS3 serine protease is responsible for proteolysis of the polypeptide (polyprotein) at the NS3/NS4a, NS4a/NS4b, NS4b/NS5a and NS5a/NS5b junctions and is thus responsible for generating four viral proteins during viral replication. This has made the HCV NS3 serine protease an attractive target for antiviral chemotherapy. The inventive compounds can inhibit such protease. They also can modulate the processing of hepatitis C virus (HCV) polypeptide.

It has been determined that the NS4a protein, an approximately 6 kda polypeptide, is a co-factor for the serine protease activity of NS3. Autocleavage of the NS3/NS4a junction by the NS3/NS4a serine protease occurs intramolecularly (i.e., *cis*) while the other cleavage sites are processed intermolecularly (i.e., *trans*).

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

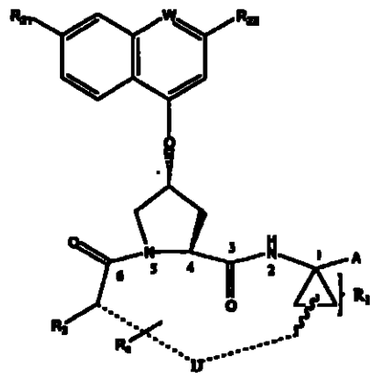
Inhibitors of HCV protease that have been reported include antioxidants (*see*, International Patent Application Publication No. WO 98/14181), certain peptides and peptide analogs (*see*, International Patent Application Publication No. WO 98/17679 (equal to US2002032175), Landro et al. (1997) Biochem. 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)).

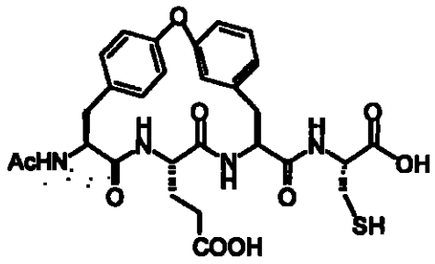
Reference is also made to the PCT Publications, No. WO 98/17679, published April 30, 1998 (Vertex Pharmaceuticals Incorporated); WO 98/22496, published May 28, 1998 (equal to U.S. 6,018,020 and U.S. 5,866,684; F. Hoffmann-La Roche AG); and WO 99/07734, published February 18, 1999 (equal to U.S. 6,143,715; 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 (equal to US2004002448 and U.S. 6,608,027; Assignee: Boehringer Ingelheim (Canada) Ltd.; Published October 12, 2000) which discloses peptide derivatives of the formula:

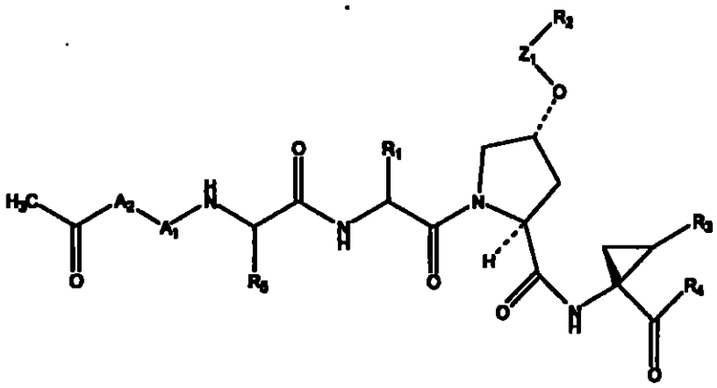


Reference is made to A. Marchetti *et al*, *Synlett*, S1, 1000-1002 (1999) describing the synthesis of bicylic analogs of an inhibitor of HCV NS3 protease. A compound disclosed therein has the formula:

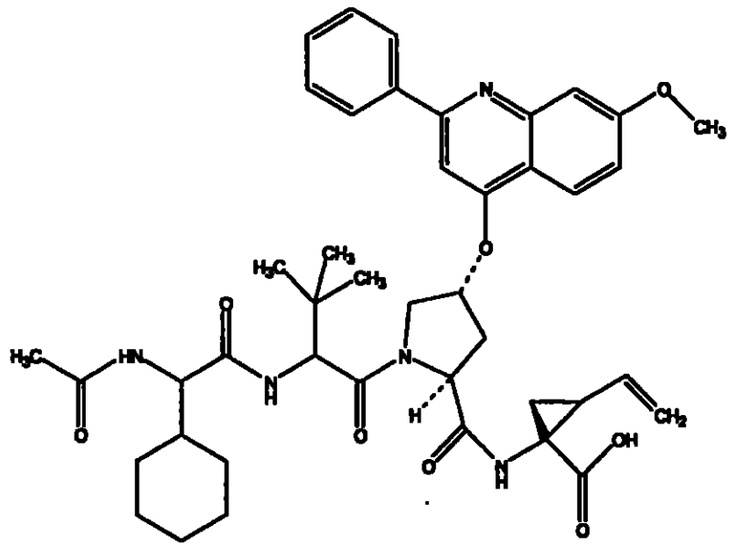


Reference is also made to W. Han *et al*, *Bioorganic & Medicinal Chem. Lett*, (2000) 10, 711-713, which describes the preparation of certain α-ketoamides, α-ketoesters and α-diketones containing allyl and ethyl functionalities.

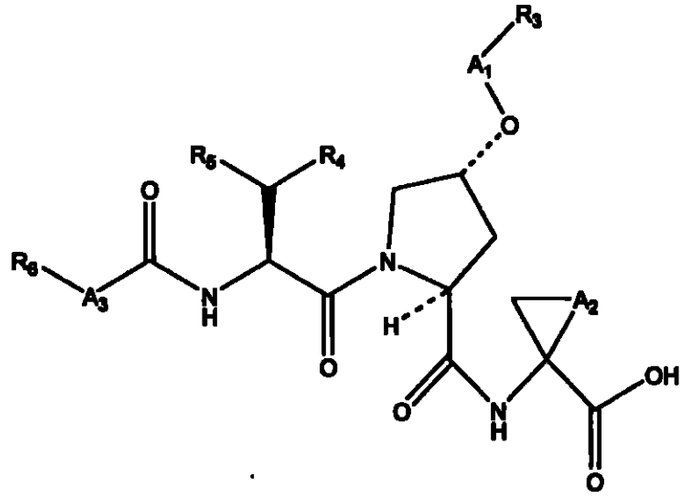
Reference is also made to WO 00/09558 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:



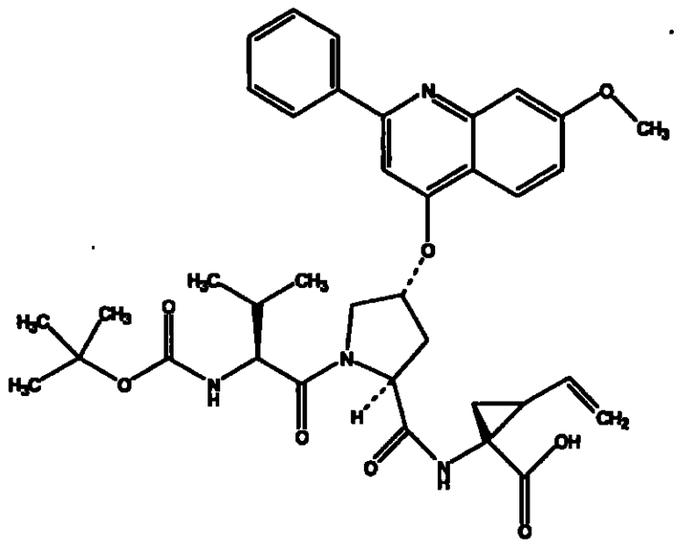
where the various elements are defined therein. An illustrative compound of that series is:



Reference is also made to WO 00/09543 (equal to US2002016442 and US 2002037998; Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:

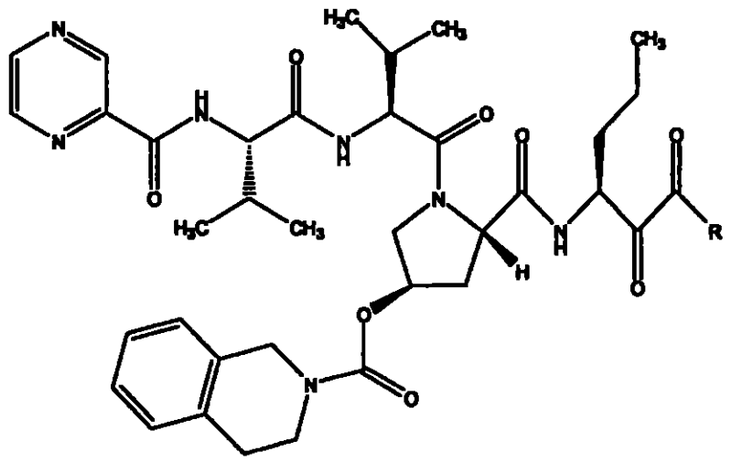


where the various elements are defined therein. An illustrative compound of that series is:



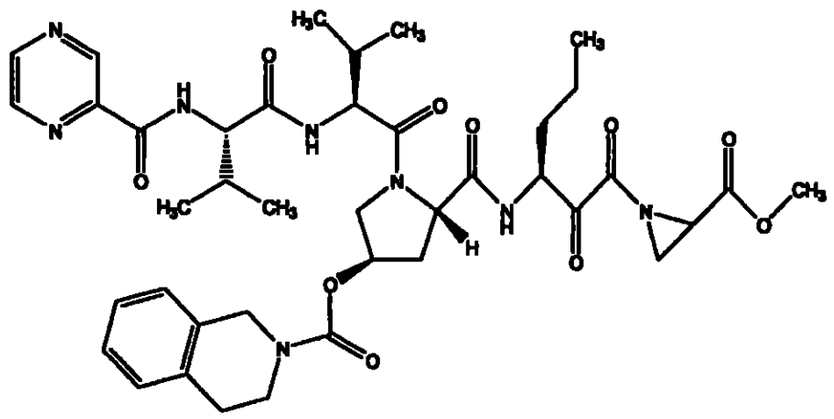
Current therapies for hepatitis C include interferon-α ($INF_α$) and combination therapy with ribavirin and interferon. *See*, e.g., Beremguer et al. (1998) Proc. Assoc. Am. Physicians 110(2):98-112. These therapies suffer from a low sustained response rate and frequent side effects. *See*, e.g., Hoofnagle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

Reference is further made to WO 01/74768 (equal to US 2003236242; 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:



42

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.

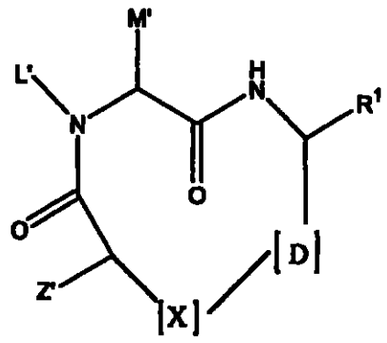
There is a need for methods for modulating the activity of serine proteases, particularly the HCV NS3/NS4a serine protease, using the compounds provided herein.

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 having the general structure shown in structural Formula 1:



Formula 1

or pharmaceutically acceptable salts or solvates of said compound wherein:

(1) R^1 is $-C(O)R^5$ or $-B(OR)_2$;

(2) R^5 is H, -OH, $-OR^8$, $-NR^9R^{10}$, $-C(O)OR^8$, $-C(O)NR^9R^{10}$, $-CF_3$, $-C_2F_5$, $-C_3F_7$, $-CF_2R^6$, $-R^6$, $-C(O)R^7$ or $NR^7SO_2R^8$;

(3) R^7 is H, -OH, $-OR^8$,or $-CHR^9R^{10}$;

(4) R^6, 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, aryl, heteroalkyl, heteroaryl, cycloalkyl, arylalkyl, heteroarylalkyl, R^{14}, $-CH(R^{1'})CH(R^{1'})C(O)OR^{11}$, $-[CH(R^{1'})]_pC(O)OR^{11}$,

$-[CH(R^{1'})]_pC(O)NR^{12}R^{13}$,
$-[CH(R^{1'})]_pS(O_2)R^{11}$,
$-[CH(R^{1'})]_pC(O)R^{11}$,
$-[CH(R^{1'})]_pS(O_2)NR^{12}R^{13}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$,
$-CH(R^{1'})CH(R^{1'})C(O)NR^{12}R^{13}$,
$-CH(R^{1'})CH(R^{1'})S(O_2)R^{11}$,
$-CH(R^{1'})CH(R^{1'})S(O_2)NR^{12}R^{13}$,
$-CH(R^{1'})CH(R^{1'})C(O)R^{11}$,
$-[CH(R^{1'})]_pCH(OH)R^{11}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$,
$-C(O)N(H)CH(R^{2'})C(O)OR^{11}$,
$-C(O)N(H)CH(R^{2'})C(O)R^{11}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)NR^{12}R^{13}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})R'$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)OR^{11}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)CH(R^{3'})NR^{12}R^{13}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)NR^{12}R^{13}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)OR^{11}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)NR^{12}R^{13}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)N(H)CH(R^{5'})C(O)OR^{11}$, and
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)N(H)CH(R^{5'})C(O)NR^{12}R^{13}$;

wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, R^{12} and R^{13} can be the same or different, each being independently selected from the group consisting of: H, halogen, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkoxy, aryloxy, alkenyl, alkynyl, alkyl-aryl, alkyl-heteroaryl, heterocycloalkyl, aryl-alkyl and heteroaralkyl;

or R^{12} and R^{13} are linked together such that the combination is cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

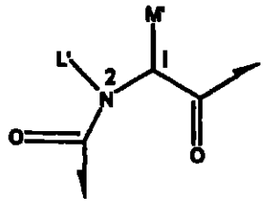
R^{14} is present or not and if present is selected from the group consisting of: H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, allyl, alkyl-heteroaryl, alkoxy, aryl-alkyl, alkenyl, alkynyl and heteroaralkyl;

(5) R and R' are present or not and if present can be the same or different, each being independently selected from the group consisting of: H, OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, alkylamino, arylamino, amino, amido, arylthioamino, arylcarbonylamino, arylaminocarboxy, alkylaminocarboxy, heteroalkyl, alkenyl, alkynyl, (aryl)alkyl, heteroarylalkyl, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen, (cycloalkyl)alkyl, aryl, heteroaryl, (alkyl)aryl, alkylheteroaryl, alkyl-heterocyclyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms;

(6) L' is H, OH, alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl;

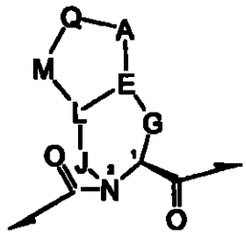
(7) M' is H, alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, arylalkyl, heterocyclyl or an amino acid side chain;

or L' and M' are linked together to form a ring structure such that the portion of structural Formula 1 represented by



(the numbers 1 and 2 having been added to show the location of a certain carbon atom and a certain nitrogen atom respectively)

is represented by structural Formula 2:



Formula 2

wherein in Formula 2:

E is present or absent and if present is C, CH, N or C(R);

J is present or absent, and when J is present, J is $(CH_2)_p$, (CHR-CHR')$_p$, $(CHR)_p$, $(CRR')_p$, $S(O_2)$, N(H), N(R) or O; when J is absent and G is present, L is directly linked to the nitrogen atom marked position 2;

p is a number from 0 to 6;

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

G is present or absent, and when G is present, G is $(CH_2)_p$, $(CHR)_p$, (CHR-CHR')$_p$ or $(CRR')_p$; when G is absent, J is present and E is directly connected to the carbon atom marked position 1;

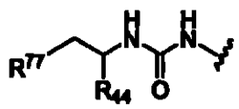
Q is present or absent, and when Q is present, Q is NR, PR, (CR=CR), $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, (CHR-CHR')$_p$, O, NR, S, SO, or SO_2; when Q is absent, M is (i) either directly linked to A or (ii) an independent substituent on L, said independent substituent being selected from -OR, -CH(R)(R'), $S(O)_{0-2}R$ or –NRR' or (iii) absent; when both Q and M are absent, A is either directly linked to L, or A is an independent substituent on E, said independent substituent being selected from -OR, -CH(R)(R'), $S(O)_{0-2}R$ or –NRR' or A is absent;

A is present or absent and if present A is O, O(R), $(CH_2)_p$, $(CHR)_p$, (CHR-CHR')$_p$, $(CRR')_p$, N(R), NRR', S, $S(O_2)$, -OR, CH(R)(R') or NRR'; or A is linked to M to form an cycloalkyl, aliphatic or heterocyclic bridge;

M is present or absent, and when M is present, M is halogen, O, OR, N(R), S, $S(O_2)$, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$, or $(CRR')_p$; or M is linked to A to form a cycloalkyl, aliphatic or heterocycloalkyl bridge;

(8) Z' is represented by either (i), (ii), (iii), (iv) or (v) shown below:

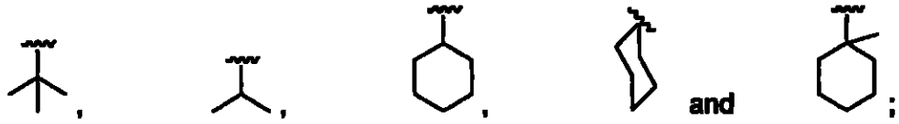
(i)



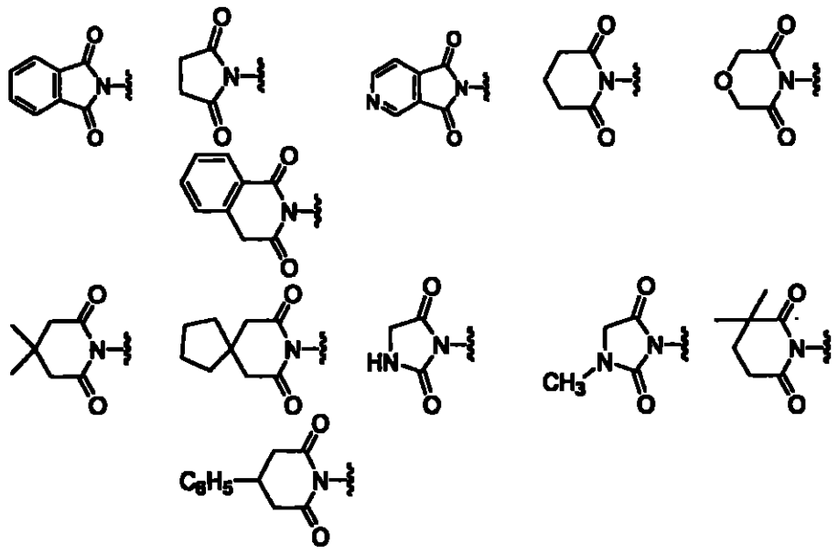
Formula A

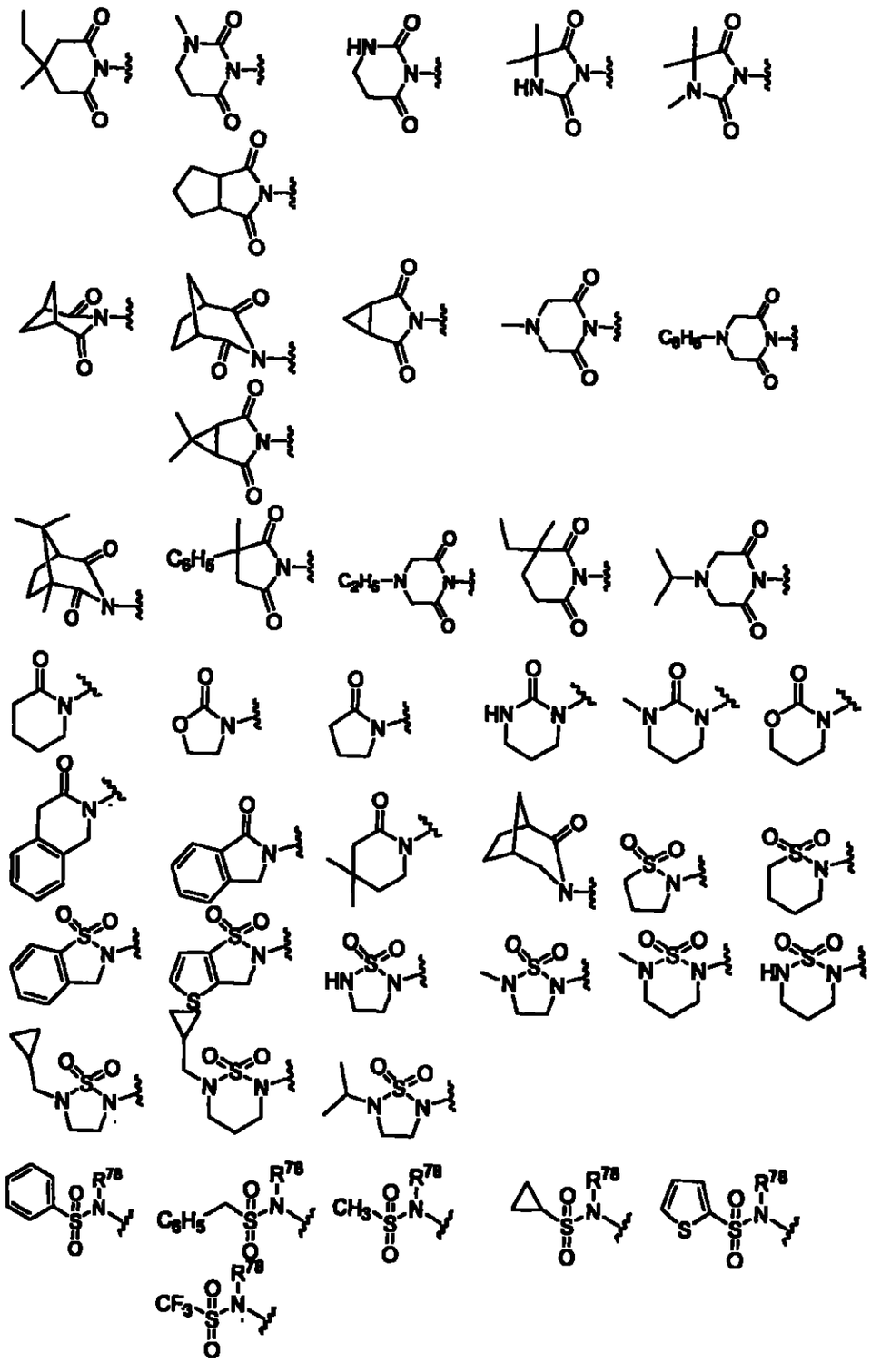
wherein:

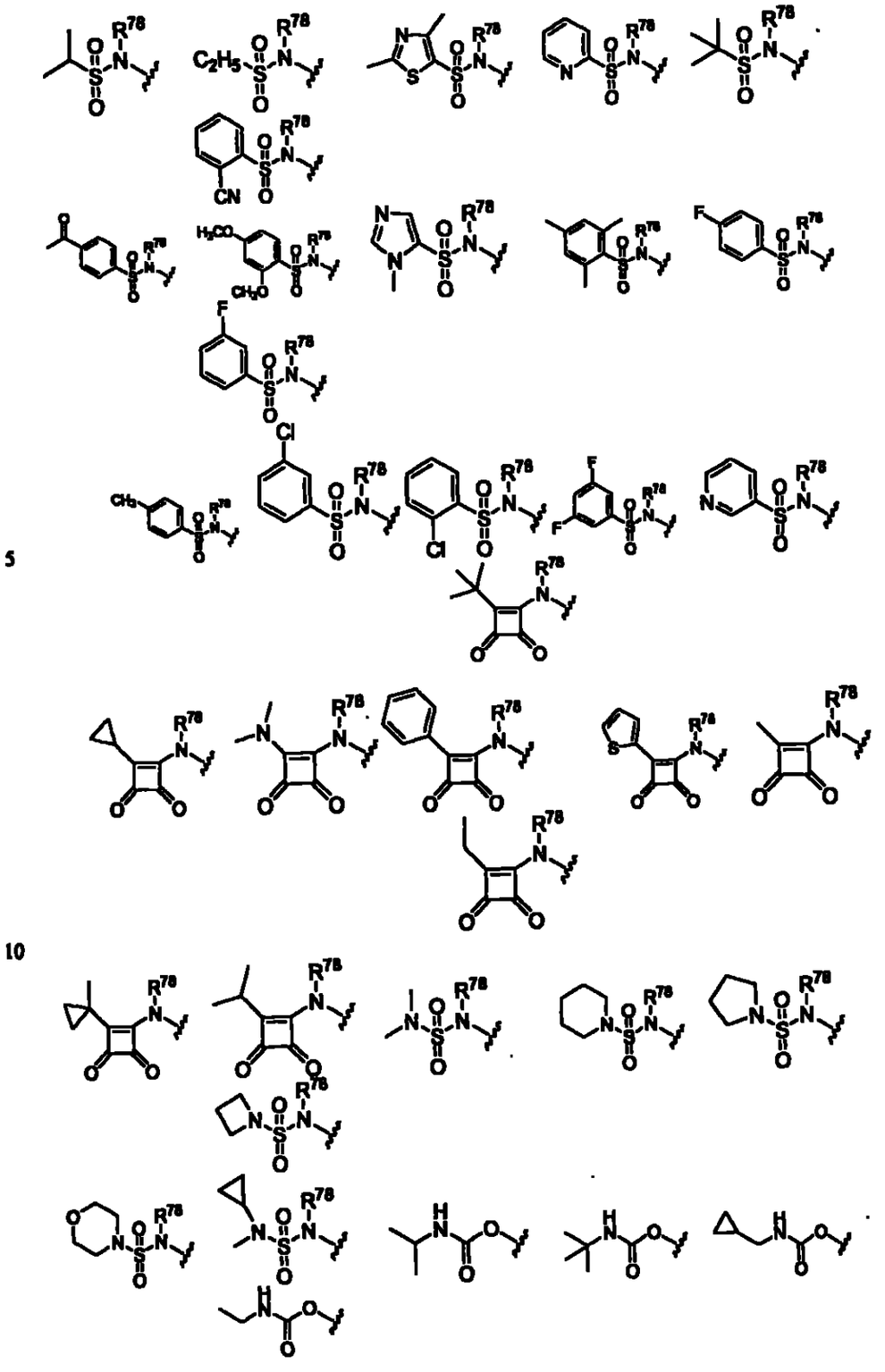
R^{44} is selected from the group consisting of:

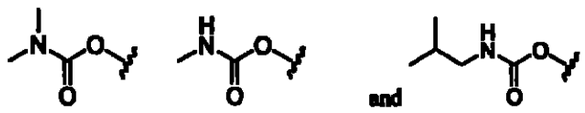


and R^{77} is selected from the group consisting of:



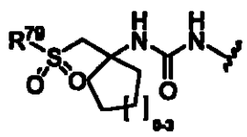






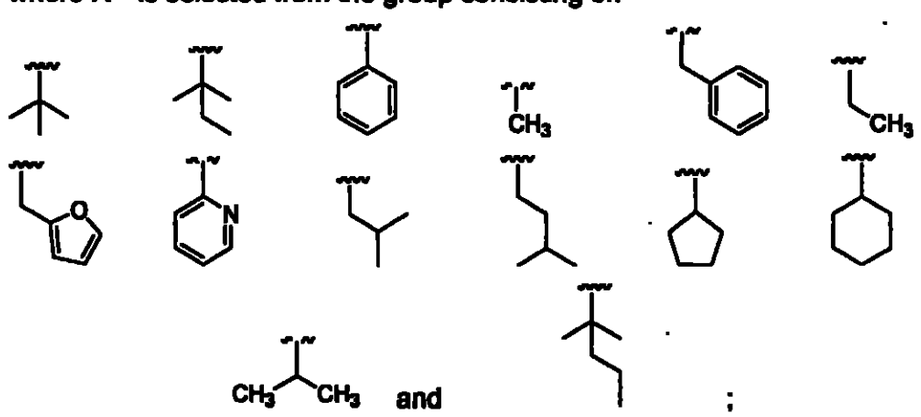
where R^{78} is selected from methyl, ethyl, isopropyl, tert-butyl and phenyl;

(ii)

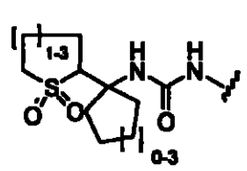


Formula B

where R^{78} is selected from the group consisting of:



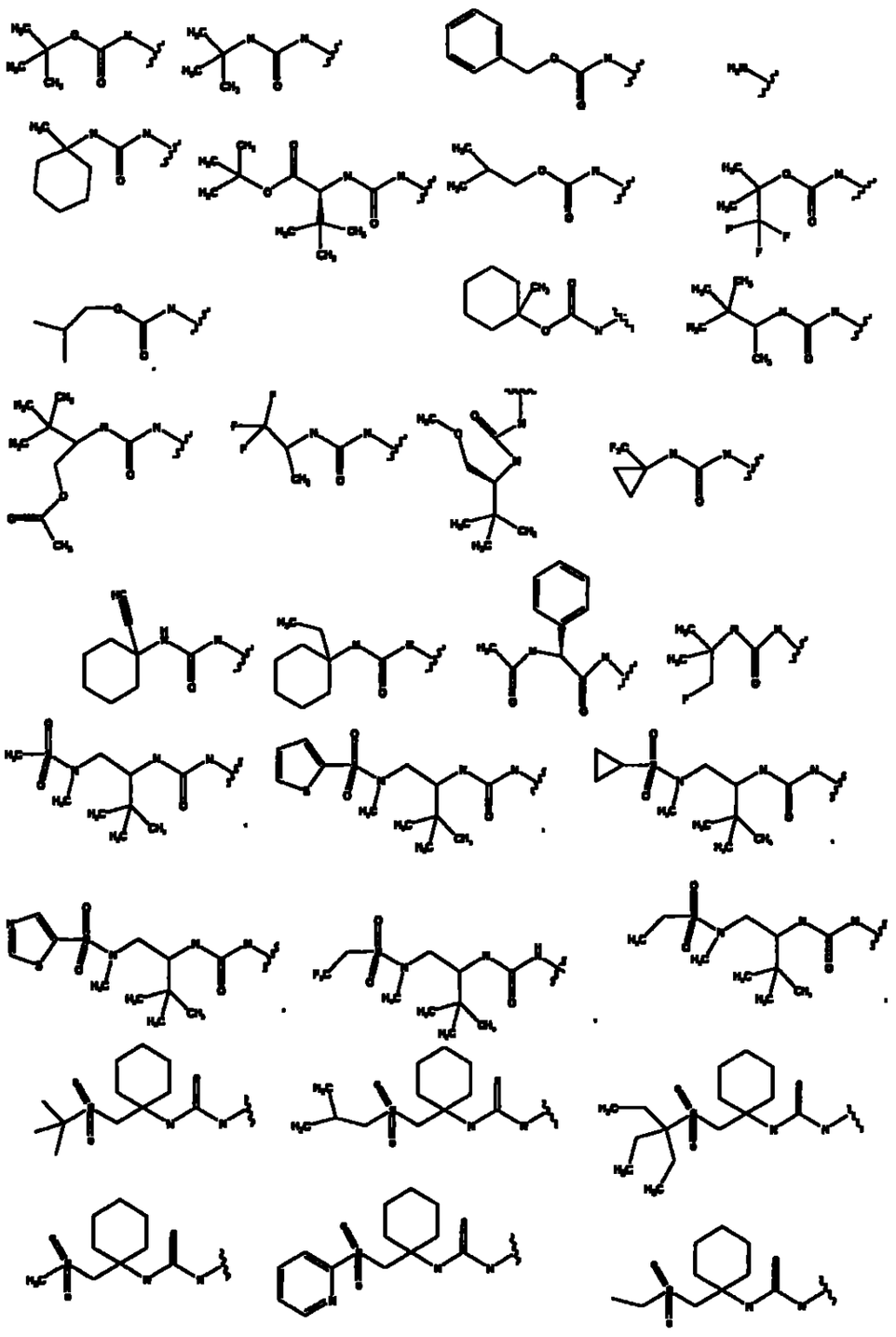
(iii)



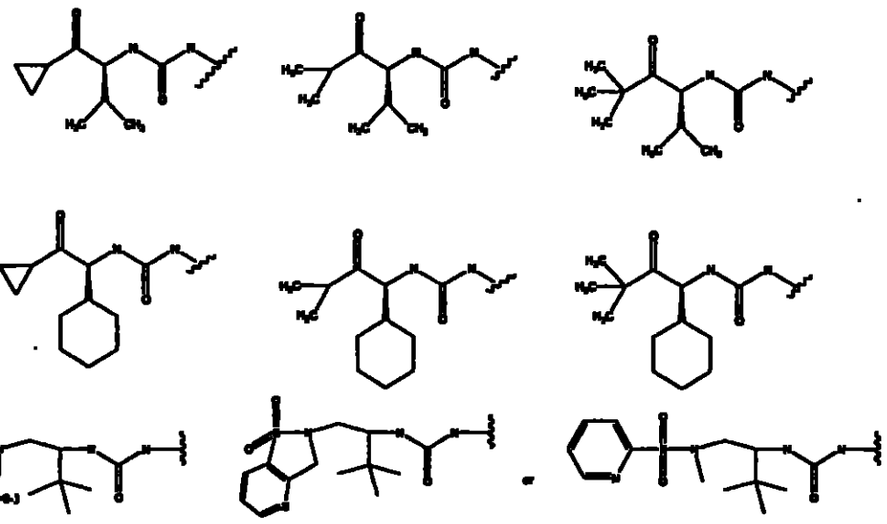
Formula C

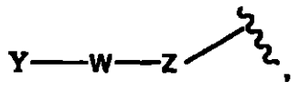
wherein the sulfone ring is optionally substituted with alkyl and cycloalkyl;

(iv) the moiety:



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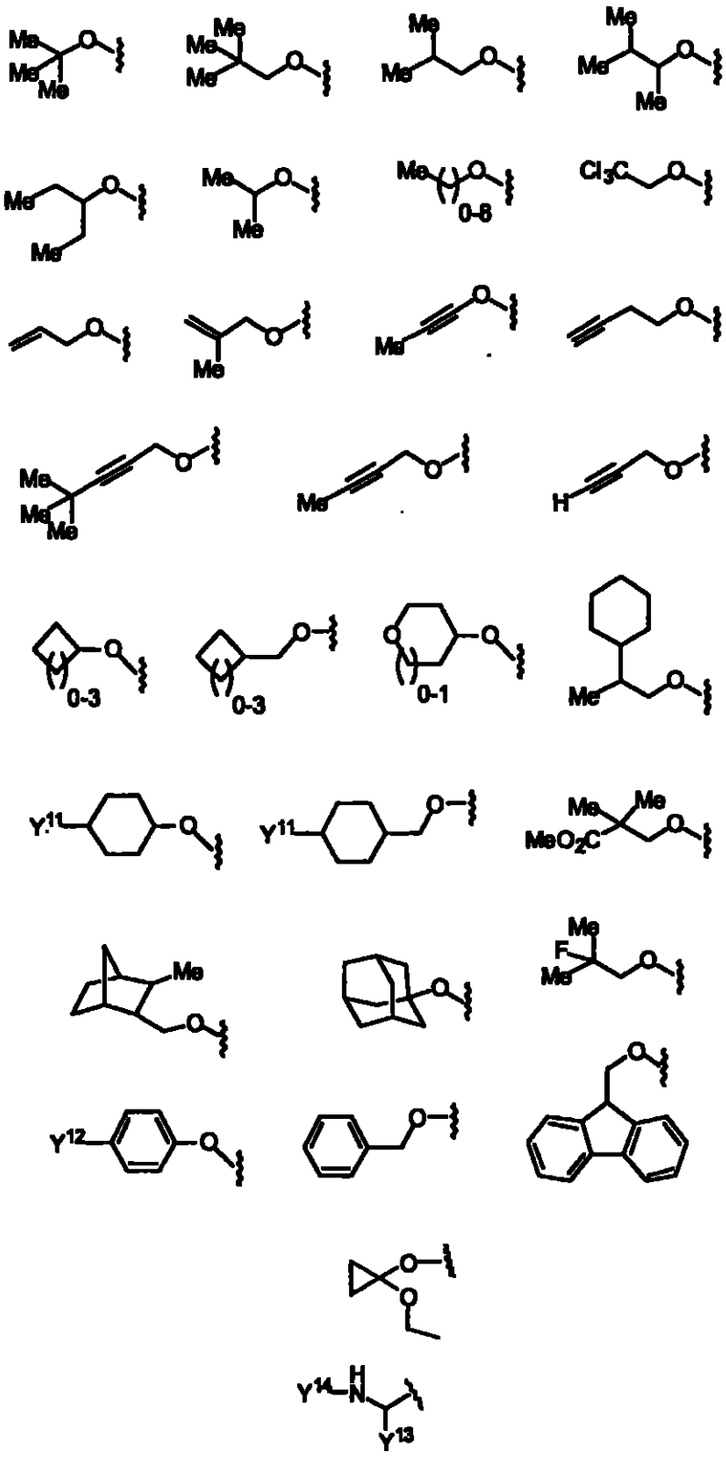


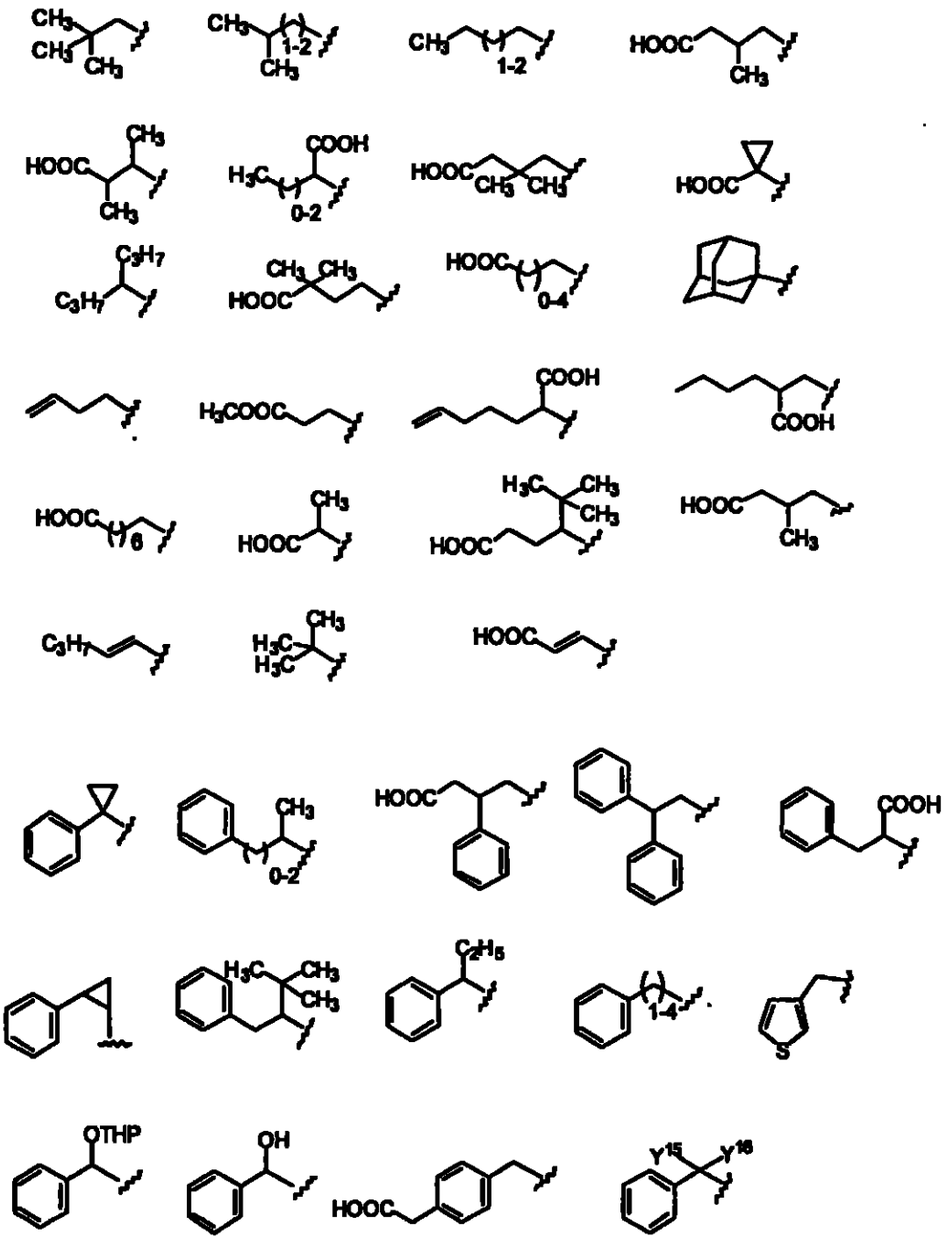
(v) the molety:  ,

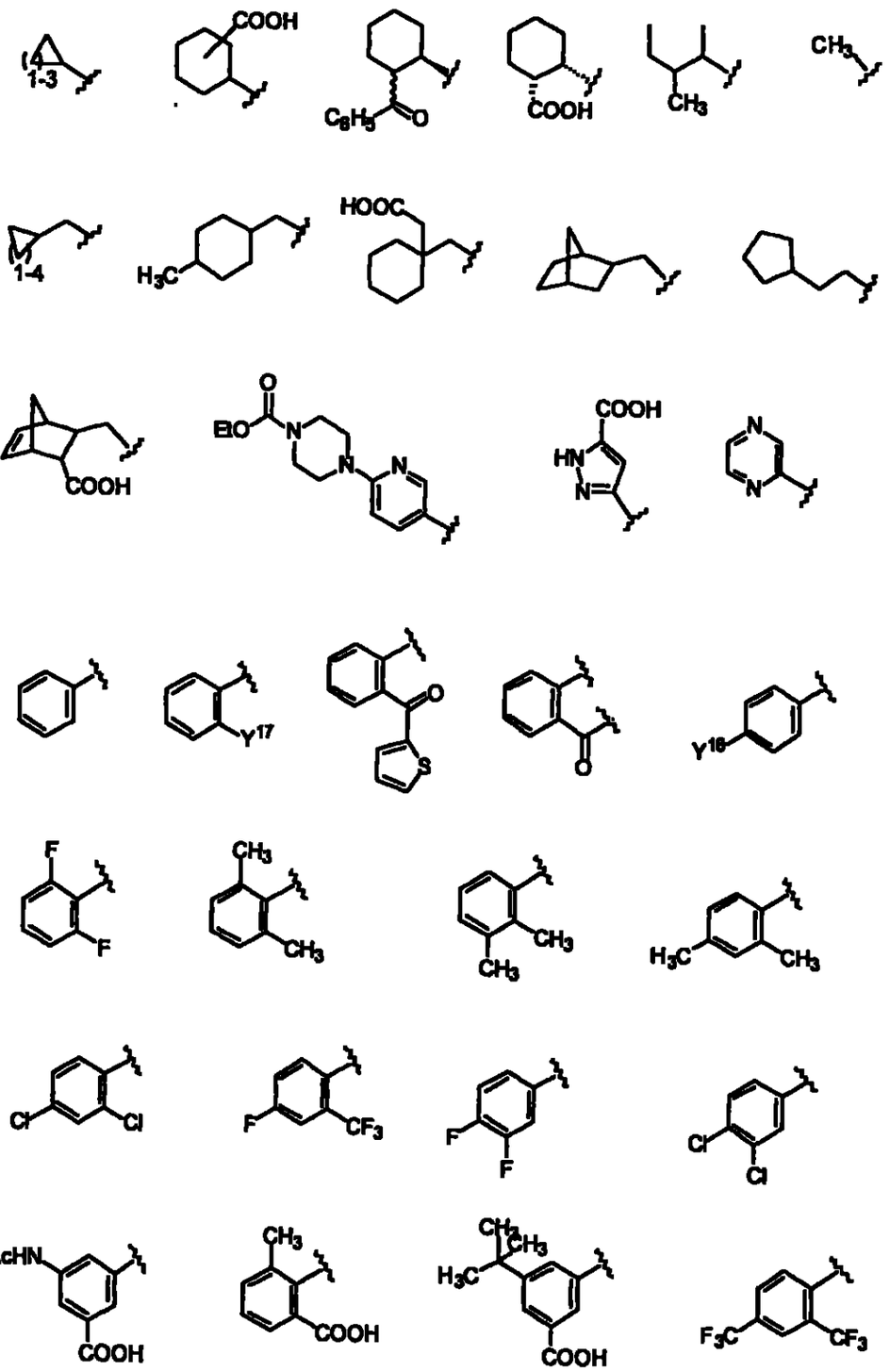
wherein W is –C(=O)- or -S(O_2)- ;

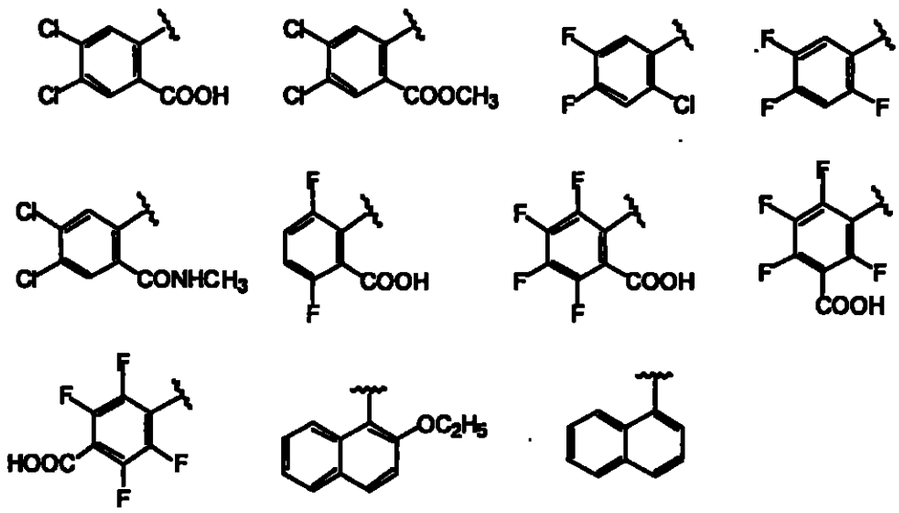
Z is O or N;

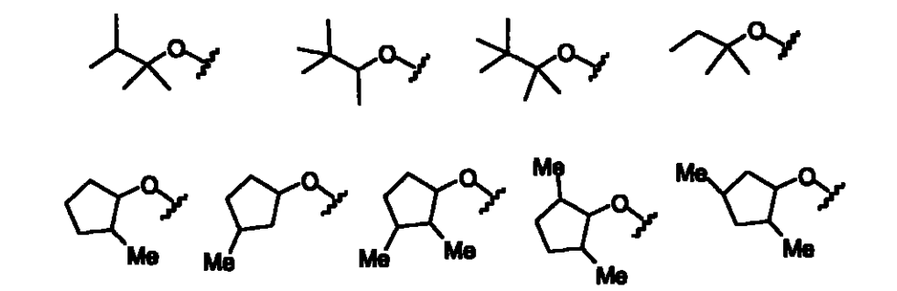
and Y is selected from the group consisting of:

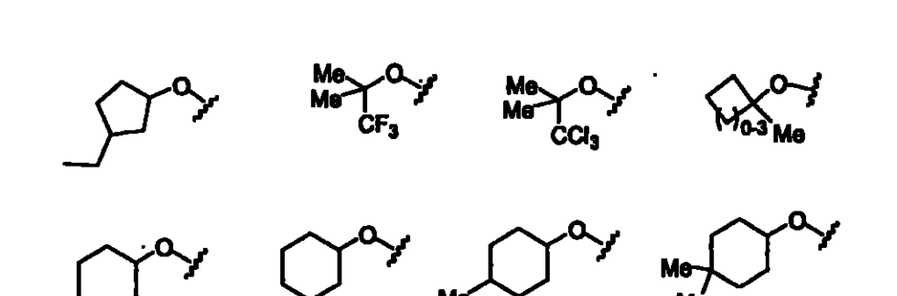

Me
Me
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Me
Me
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Me
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Me
Me
Me
Me
0-6
Cl3C
Me
Me
Me
Me
Me
Me
Me
H
0-3
0-3
0-1
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Y12
O
O
Y14
H
N
Y13

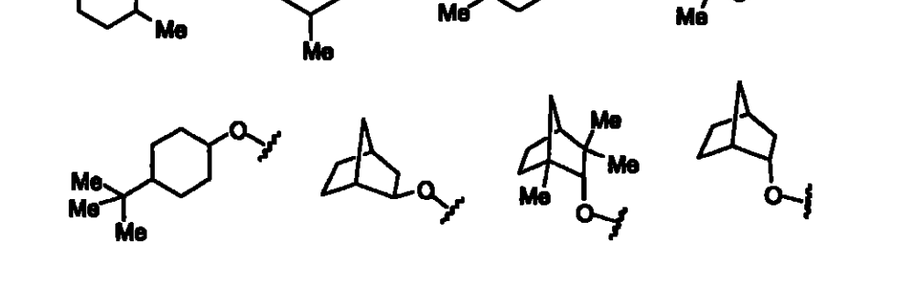


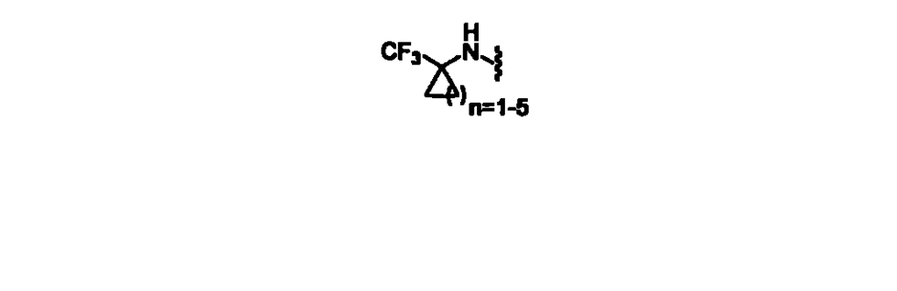

1-3
COOH
C_6H_5
O
COOH
CH_3
CH_3
1-4
H_3C
HOOC
COOH
EtO
N
N
N
COOH
HN
N
N
N
Y^{17}
O
S
O
Y^{16}
F
F
CH_3
CH_3
CH_3
CH_3
H_3C
CH_3
Cl
Cl
F
CF_3
F
F
Cl
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CH_3
CH_3
H_3C
COOH
F_3C
CF_3



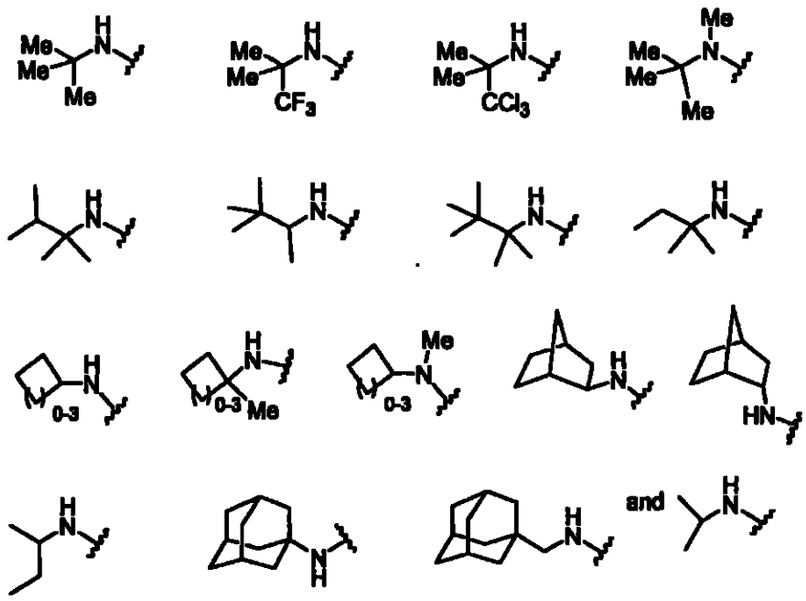








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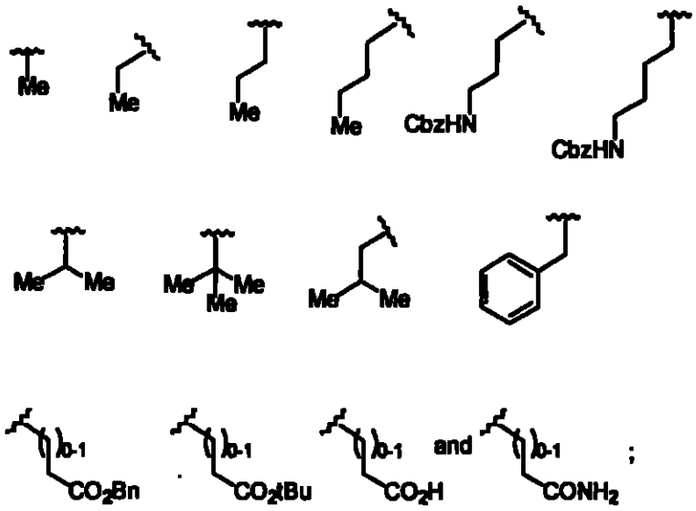


wherein:

Y^{11} is selected from the group consisting of: H, -C(O)OH, -C(O)OEt, -OMe, -Ph, -OPh, -NHMe, -NHAc, -NHPh, $-CH(Me)_2$, 1-triazolyl, 1-imidazolyl and $-NHCH_2COOH$;

Y^{12} is selected from the group consisting of: H, -C(O)OH, -C(O)OMe, -OMe, F, Cl and Br;

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



;

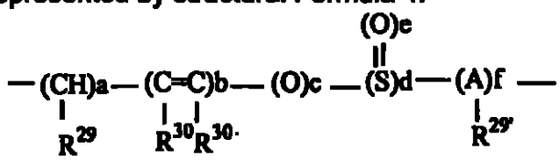
Y^{14} is $MeS(O_2)$-, -Ac, -Boc, -iBoc, -Cbz, or -Alloc;

Y^{15} and Y^{16} can be the same or different and are independently selected from the group consisting of: alkyl, aryl, heteroalkyl, and heteroaryl;

Y^{17} is $-CF_3$, $-NO_2$, $-C(O)NH_2$, -OH, $-C(O)OCH_3$, $-OCH_3$, $-OC_6H_5$, $-C_6H_5$, $-C(O)C_6H_5$, $-NH_2$, or –C(O)OH; and

Y^{18} is $-C(O)OCH_3$, $-NO_2$, $-N(CH_3)_2$, F, $-OCH_3$, $-C(H_2)C(O)OH$, -C(O)OH, $-S(O_2)NH_2$, or $-N(H)C(O)CH_3$;

(9) X is represented by structural Formula 4:



Formula 4

wherein in Formula 4, a is 2, 3, 4, 5, 6, 7, 8 or 9;

b, c, d, e and f can be the same or different, each being independently 0, 1, 2, 3, 4 or 5;

A is C, N, S or O;

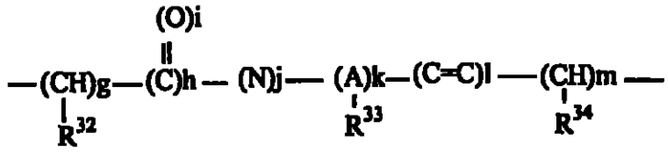
R^{29} and $R^{29'}$ are independently present or absent and if present can be the same or different, each being independently one or two substituents independently selected from the group consisting of: H, halo, alkyl, aryl, cycloalkyl, cycloalkylamino, cycloalkylaminocarbonyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), $-NH(cycloalkyl)$, $-N(alkyl)_2$, carboxyl, –C(O)O-alkyl, heteroaryl, aralkyl, alkylaryl, aralkenyl, heteroaralkyl, alkylheteroaryl, heteroaralkenyl, hydroxyalkyl, aryloxy, aralkoxy, acyl, aroyl, nitro, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkenyl, heterocyclyl, heterocyclenyl, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$- and $Y_1Y_2NSO_2$-, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl;

or

R^{29} and $R^{29'}$ are linked together such that the combination is an aliphatic or heteroaliphatic chain of 0 to 6 carbons;

R^{30} is present or absent and if present is one or two substituents independently selected from the group consisting of: H, alkyl, aryl, heteroaryl and cycloalkyl;

(10) D in Formula 1 is represented by structural Formula 5:



Formula 5

wherein in Formula 5, R^{32}, R^{33} and R^{34} are present or absent and if present are independently one or two substituents independently selected from the group consisting of: H, halo, alkyl, aryl, cycloalkyl, cycloalkylamino, spiroalkyl, cycloalkylaminocarbonyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -$N(alkyl)_2$, carboxyl, –C(O)O-alkyl, heteroaryl, aralkyl, alkylaryl, aralkenyl, heteroaralkyl, alkylheteroaryl, heteroaralkenyl, hydroxyalkyl, aryloxy, aralkoxy, acyl, aroyl, nitro, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkenyl, heterocyclyl, heterocyclenyl, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$- and $Y_1Y_2NSO_2$-, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl;

or

R^{32} and R^{34} are linked together such that the combination forms a portion of a cycloalkyl group;

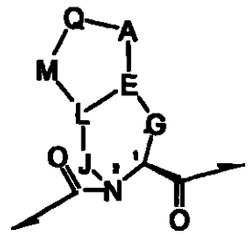
g is 1, 2, 3, 4, 5, 6, 7, 8 or 9;

h, i, j, k, l and m can be the same or different, each being independently 0, 1, 2, 3, 4 or 5; and

A is C, N, S or O,

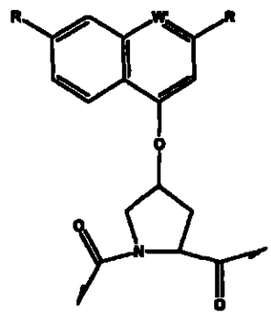
60 60

(11) provided that in Formula 1 when structural Formula 2:



Formula 2

is



and

W' is CH or N, both the following conditional exclusions (i) and (ii) apply:

conditional exclusion (i): Z' is not $-NH-R^{36}$, wherein R^{36} is H, C_6 aryl, C_{10} aryl, heteroaryl, $-C(O)-R^{37}$, $-C(O)-OR^{37}$ or $-C(O)-NHR^{37}$, wherein R^{37} is C_{1-6} alkyl or C_{3-6} cycloalkyl;

and

conditional exclusion (ii): R^1 is not –C(O)OH, a pharmaceutically acceptable salt of –C(O)OH, an ester of –C(O)OH or $-C(O)NHR^{38}$ wherein R^{38} is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, C_6 aryl, C_{10} aryl, or C_{7-16} aralkyl.

A further feature of the invention is pharmaceutical compositions containing as active ingredient at least one compound of Formula 1 (or its salts, esters, solvate or isomers) together with a pharmaceutically acceptable carrier or excipient.

The invention also provides methods for preparing compounds of Formula 1 as well as methods for treating diseases such as, for example, HCV, AIDS (Acquired Immune Deficiency Syndrome), and related disorders. The methods for such treatment comprise administering to a patient suffering from one or more of the above diseases or one or more related diseases a therapeutically effective amount of at least one compound of Formula 1 or a pharmaceutical composition comprising at least one compound of Formula 1.

Also disclosed is the use of at least one compound of Formula 1 for the manufacture of a medicament for treating HCV, AIDS, and related disorders.

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

In still yet further embodiments there is provided methods of modulating the activity of hepatitis C virus (HCV) protease, comprising contacting HCV protease with one or more inventive compounds as well as methods of treating or preventing HCV, or ameliorating one or more symptoms of hepatitis C, comprising administering an effective amount of one or more of the inventive compounds. Such modulation, treatment, prevention or amelioration can also be done with the inventive pharmaceutical compositions or formulations. 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.

Description of the Invention

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 alkyl group may be optionally 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)$_2$, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"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.

"Aliphatic" means and includes straight or branched chains of paraffinic, olefinic or acetylenic carbon atoms. The aliphatic group can be optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of H, halo, halogen, alkyl, aryl, cycloalkyl, cycloalkylamino, alkenyl, heterocyclic, alkynyl, cycloalkylaminocarbonyl, hydroxyl, thio, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, carboxyl, –C(O)O-alkyl, heteroaryl, aralkyl, alkylaryl, aralkenyl, heteroaralkyl,

alkylheteroaryl, heteroaralkenyl, heteroalkyl, carbonyl, hydroxyalkyl, aryloxy, aralkoxy, acyl, aroyl, nitro, amino, amido, ester, carboxylic acid aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkenyl, heterocyclyl, heterocyclenyl, carbamate, urea, ketone, aldehyde, cyano, sulfonamide, sulfoxide, sulfone, sulfonyl urea, sulfonyl, hydrazide, hydroxamate, S(alkyl)Y_1Y_2N-alkyl-, Y_1Y_2N-alkyl-, Y_1Y_2NC(O)- and $Y_1Y_2NSO_2$-, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl.

"Heteroaliphatic" means an otherwise aliphatic group that contains at least one heteroatom (such as oxygen, nitrogen or sulfur). The term heteroaliphatic includes substituted heteroaliphatic.

"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.

"Heteroalkyl" means an alkyl as defined above, wherein one or more hydrogen atoms are substituted by a heteroatom selected from N, S, or O.

"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,

64 64

thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

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

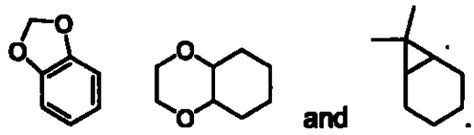
"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

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

"Halogen" 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:

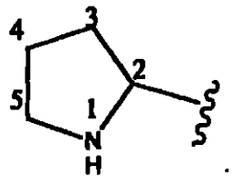


and

"Heterocyclyl" or "heterocycloalkyl" or "heterocyclic" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are

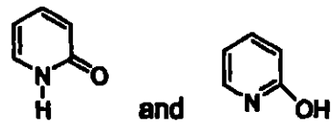
as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



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

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



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 "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 carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

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

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

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

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

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

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

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

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

71 74

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 webaite). 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.

One or more compounds of the invention may also exist as, or optionally converted to, a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*,

AAPS PharmSciTech., 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

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

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates 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.

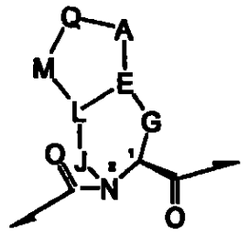
Polymorphic forms of the compounds of Formula I and of the salts, solvates and prodrugs of the compounds of Formula I, are intended to be included in the present invention.

In general, the arrows ⟶ and ⟵ on structural Formulas in this application refer to the respective points of connection of the concerned Formula to the points shown in the structure of its parent Formula.

In one embodiment, the present invention discloses compounds of Formula 1 as inhibitors of HCV protease, especially the HCV NS3/NS4a serine protease, or a pharmaceutically acceptable derivative thereof, where the various definitions are given above.

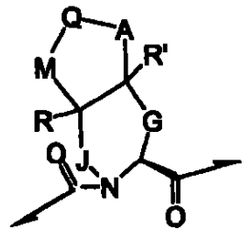
In another embodiment, R^1 is ketoamide, acid, ketoacid, ketoester, ketoaldehyde, diketone, boronic acid or trifluoroketone.

In another embodiment, the present invention discloses compounds of Formula 1 wherein the portion of structural Formula 1 represented by structural Formula 2:



is

Formula 2



;

where the arrows ⟶ and ⟵ refer to points of connection of Formula 2 to the points shown in Formula 1, and

G and J immediately may or may not be present and if present can be the same or different and are independently selected from the group consisting of $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$;

A and M immediately may or may not be present and if present can be the same or different and are independently selected from the group

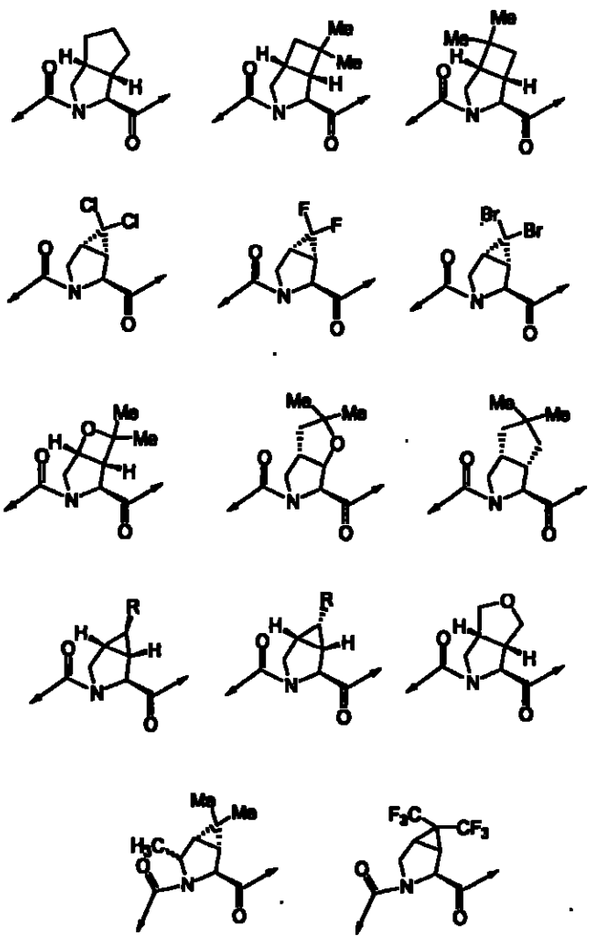
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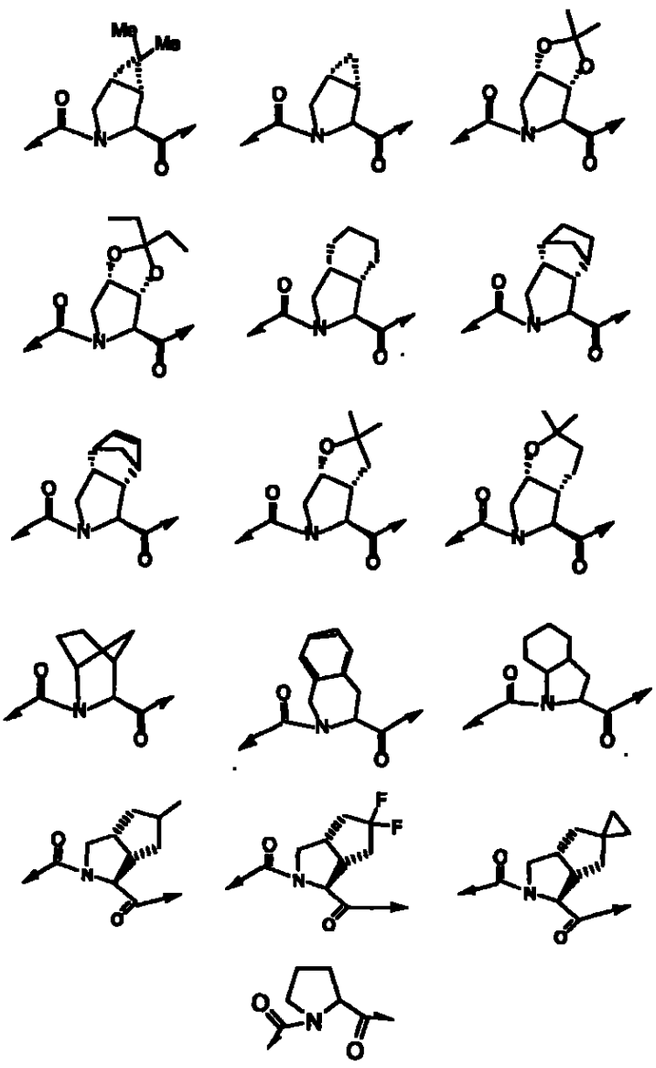
consisting of O, S, $S(O_2)$, N(R), $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$; or A and M are linked together to form an cycloalkyl or heterocyclic bridge; and

Q may or may not be present and if present is $(CH_2)_p$, N(R), O, S, $S(O_2)$, $(CHR)_p$, or $(CRR')_p$.

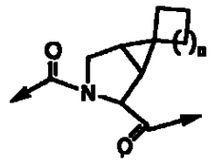
When Q is absent, and either M or A is absent, the remaining (present) A or M can optionally form a cycloalkyl or heterocyclyl structure with the carbon C(R) or C(R') in Formula I. Some representative examples are shown in some of the structures that follow below.

In an embodiment of the present invention, the portion represented by structural Formula 2 is selected from the following structures:



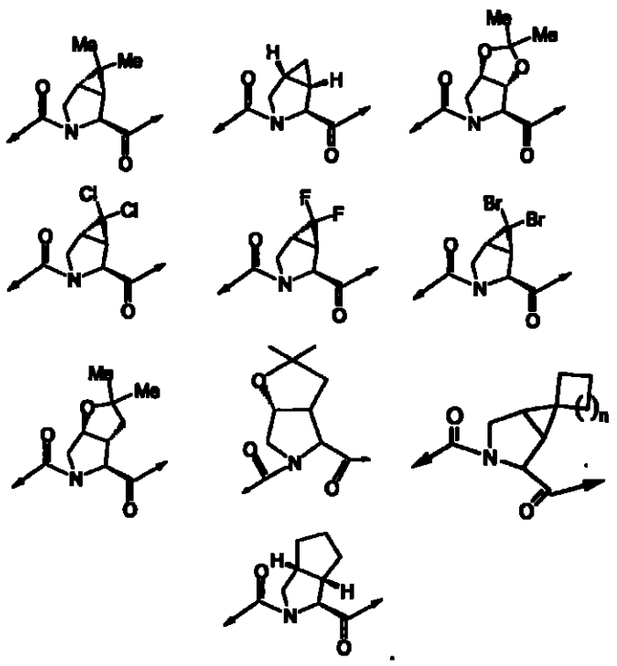


and

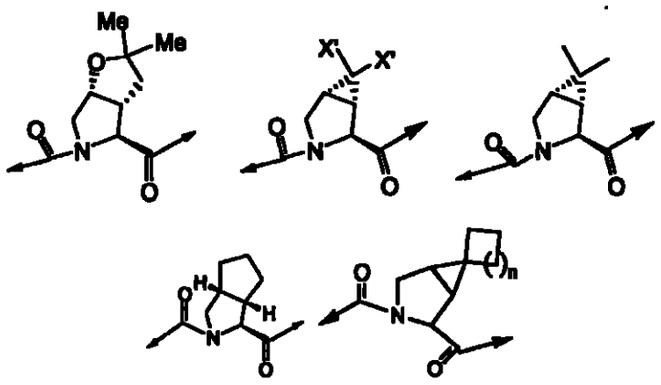


wherein n= 0-4.

In another embodiment of the present invention, the portion of structural Formula 1 represented by structural Formula 2 is selected from the following structures:

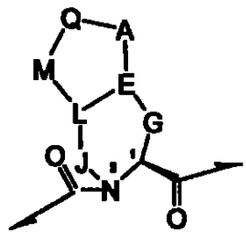


In another embodiment of the present invention, the portion of structural Formula 1 represented by structural Formula 2 is selected from the following structures:



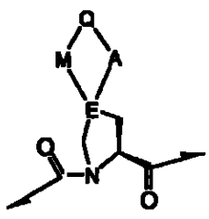
wherein X' is H, F, Cl or Br.

In still another embodiment of the present invention, the portion of structural Formula 1 represented by structural Formula 2:



is

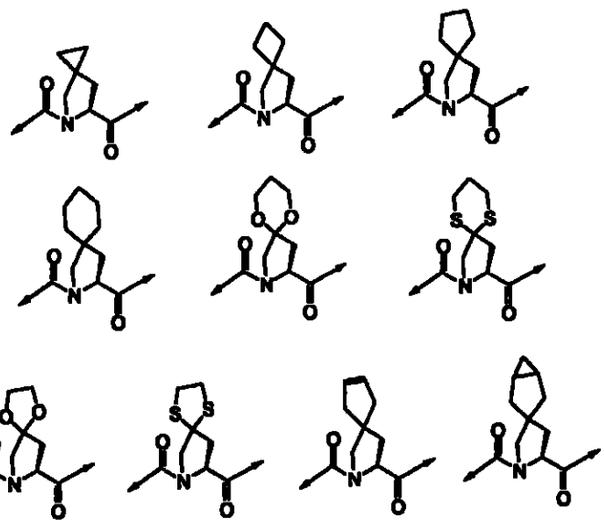
Formula 2



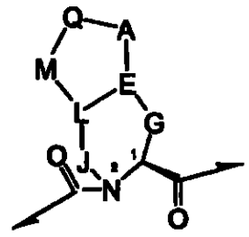
; and

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

In still yet another embodiment of the present invention, the portion of structural Formula 1 represented by structural Formula 2 is selected from the following structures:

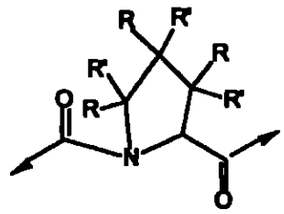


In another aspect of the present invention, the portion of structural Formula 1 represented by structural Formula 2:

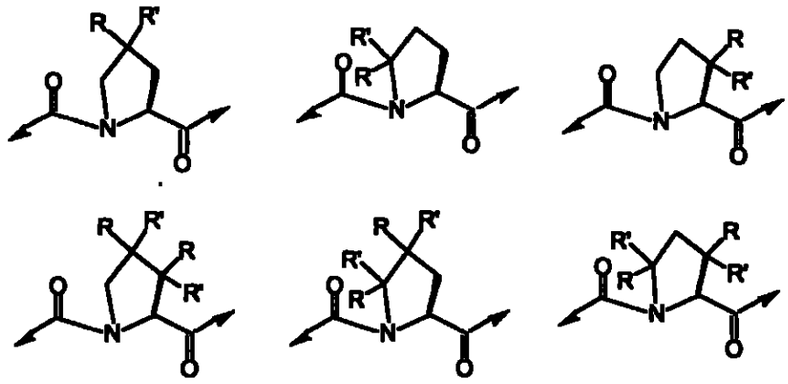


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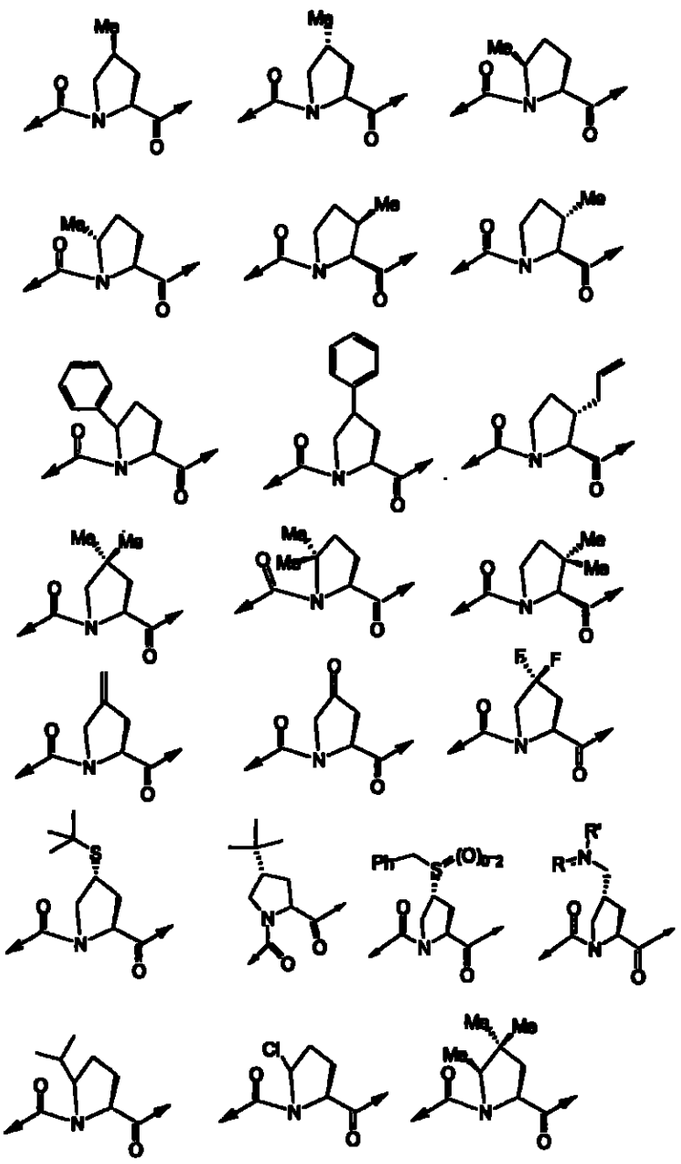
Formula 2



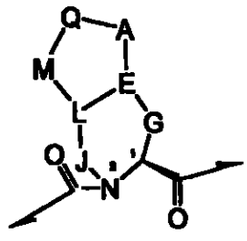
In still another aspect of the present invention, the portion of structural Formula 1 represented by structural Formula 2 is selected from the following structures:



In yet another aspect of the present invention, the portion of structural Formula 1 represented by structural Formula 2 is selected from the following structures:

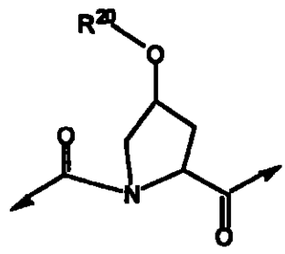


In still yet another aspect of the present invention, the portion of structural Formula 1 represented by structural Formula 2:



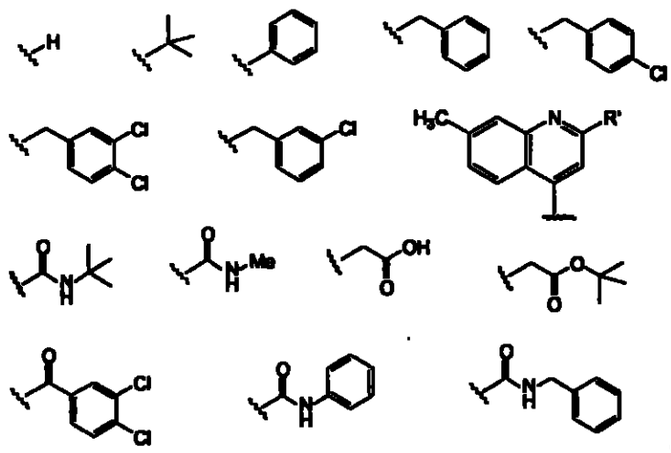
Formula 2

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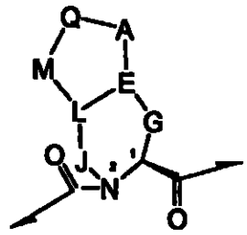


; and

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



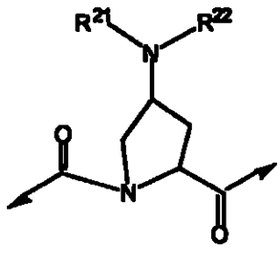
In another aspect of the present invention, the portion of structural Formula 1 represented by structural Formula 2:



Formula 2

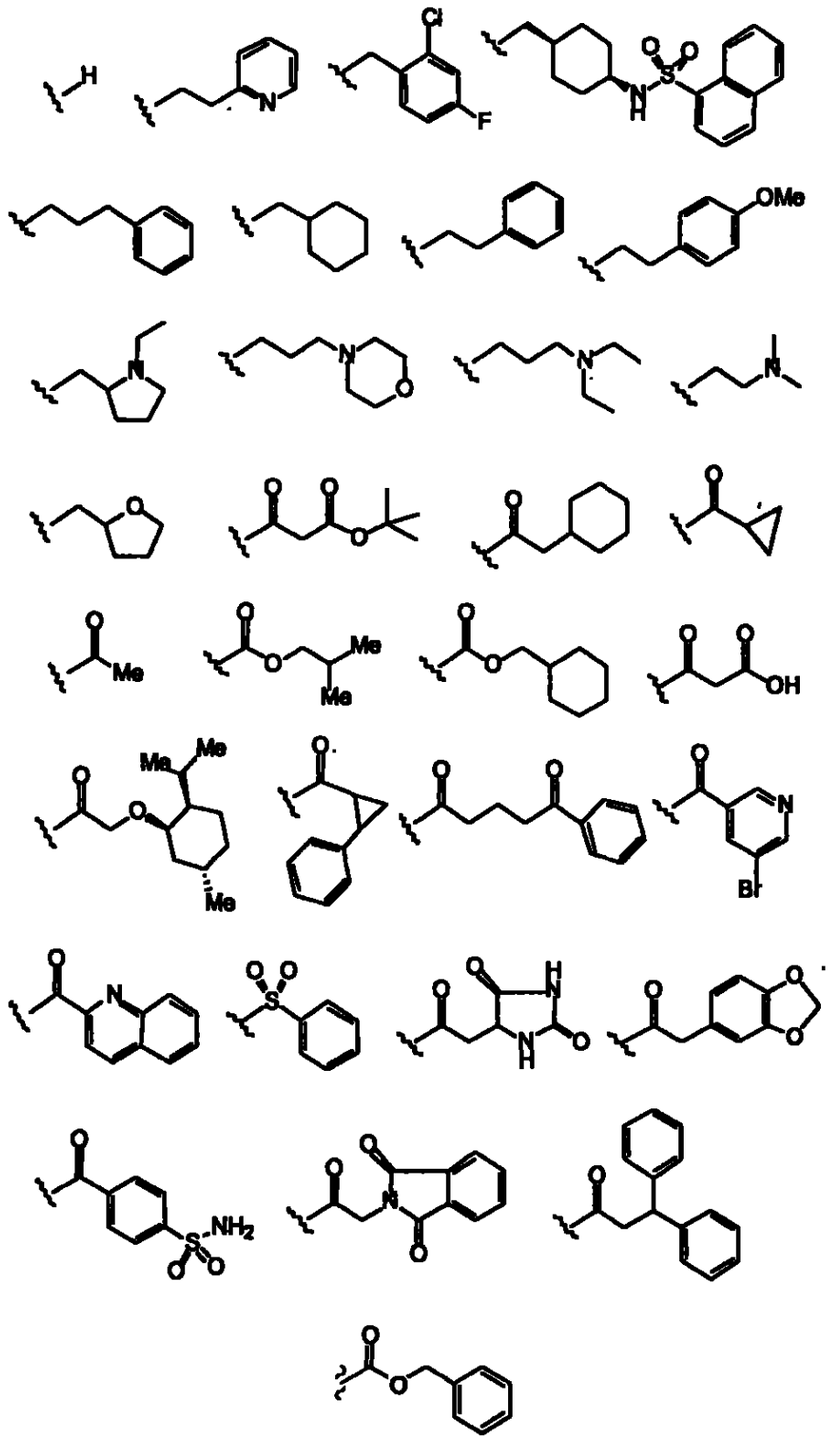
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; and

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



In another aspect of the present invention, L and M are absent, and J is directly linked to E.

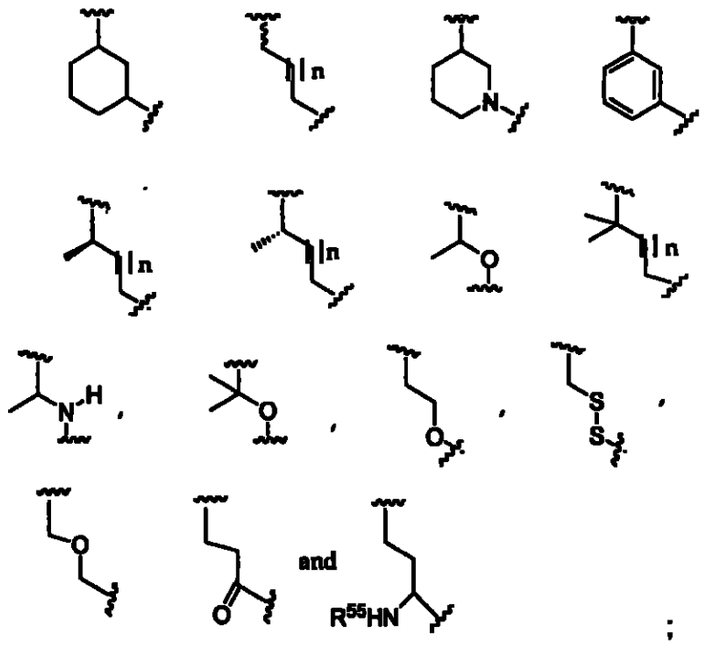
In another aspect of the present invention, L, J and M are absent and E is directly linked to N.

In another aspect of the present invention, G and M are absent.

In still another aspect of the present invention, M' is

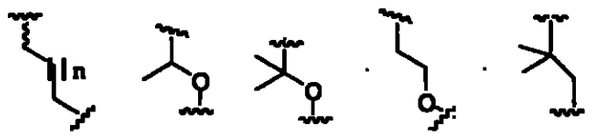


In yet another aspect of the present invention, X is selected from the group consisting of the following structures:



and R^{55} is alkyl, cycloalkyl, carbamate or urea; and n= 0-5.

In still yet another aspect of the present invention, X is selected from the group consisting of the following structures:



In still yet another aspect of the present invention, R^1 is a ketoamide, ketoaldehyde, diketone, ketoacid or ketoester.

In another embodiment of the present invention, R^1 is -$C(O)C(O)NR^9R^{10}$;

R^9 is H; and

R^{10} is H, -R^{14},

-$[CH(R^{1'})]_pC(O)OR^{11}$,

-$[CH(R^{1'})]_pC(O)NR^{12}R^{13}$,

-$[CH(R^{1'})]_pS(O_2)R^{11}$,

-$[CH(R^{1'})]_pS(O_2)NR^{12}R^{13}$,

-$[CH(R^{1'})]_pC(O)R^{11}$,

-$CH(R^{1'})C(O)N(H)C(H)(R^{2'})C(O)OR^{11}$,

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

-$CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$.

In another embodiment of the present invention, R^{10} is H, -R^{14},

-$CH(R^{1'})C(O)OR^{11}$,

-$CH(R^{1'})CH(R^{1'})C(O)OR^{11}$,

-$CH(R^{1'})C(O)NR^{12}R^{13}$,

-$CH(R^{1'})CH(R^{1'})C(O)NR^{12}R^{13}$,

-$CH(R^{1'})CH(R^{1'})S(O_2)R^{11}$,

-$CH(R^{1'})CH(R^{1'})S(O_2)NR^{12}R^{13}$,

-$CH(R^{1'})CH(R^{1'})C(O)R^{11}$,

-$CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$,

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

-$CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$;

$R^{1'}$ is H or alkyl; and

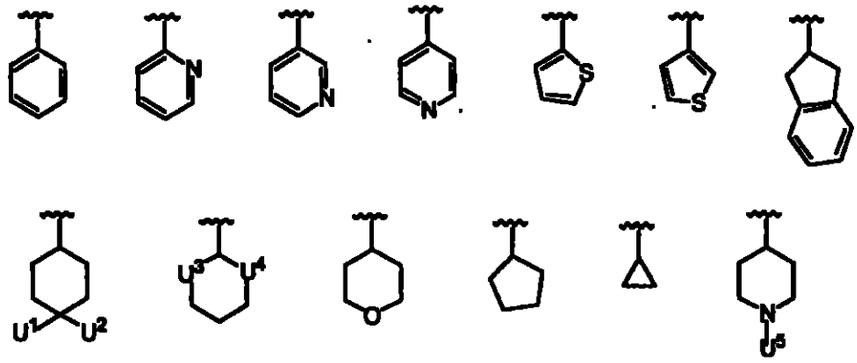
$R^{2'}$ is phenyl, substituted phenyl, hetero atom-substituted phenyl, cycloalkyl, heterocycloalkyl, piperidyl or pyridyl.

In another embodiment of the present invention, $R^{1'}$ is H.

In still another embodiment of the present invention, R^{11} is H, methyl, ethyl, allyl, *tert*-butyl, benzyl, α-methylbenzyl, α,α-dimethylbenzyl, 1-methylcyclopropyl or 1-methylcyclopentyl;

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

R^Z is independently selected from the group consisting of the following structures:

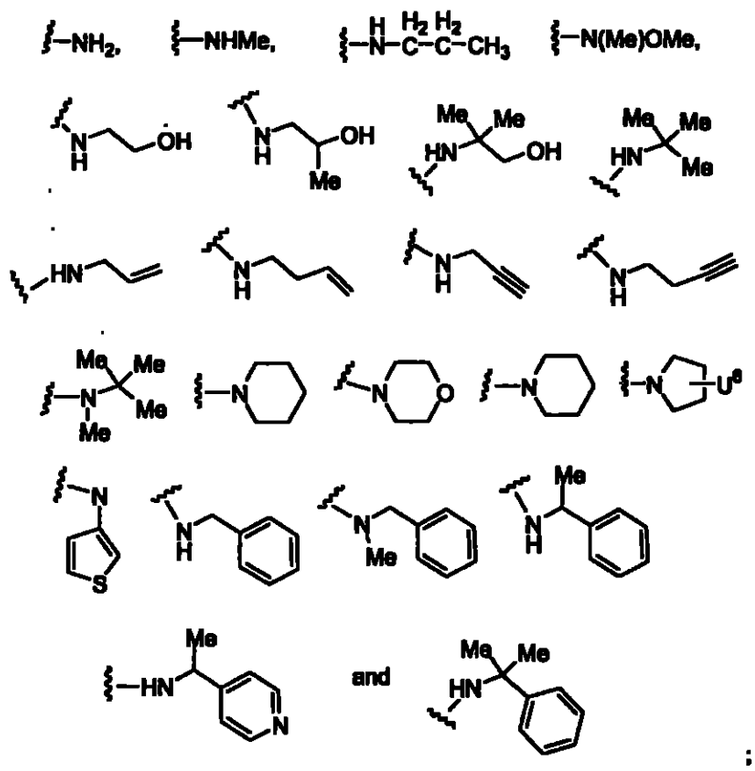


wherein U^1 and U^2 may be same or different and are independently selected from the group consisting of: H, F, $-CH_2C(O)OH$, $-CH_2C(O)OMe$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, $-CH_2C(O)NMe_2$, azido, amino, hydroxyl, substituted amino and substituted hydroxyl ;

U^3 and U^4 are the same or different and are independently O or S;

U^5 is alkyl sulfonyl, aryl sulfonyl, heteroalkyl sulfonyl, heteroaryl sulfonyl, alkyl carbonyl, aryl carbonyl, heteroalkyl carbonyl, heteroaryl carbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl or a combination thereof;

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

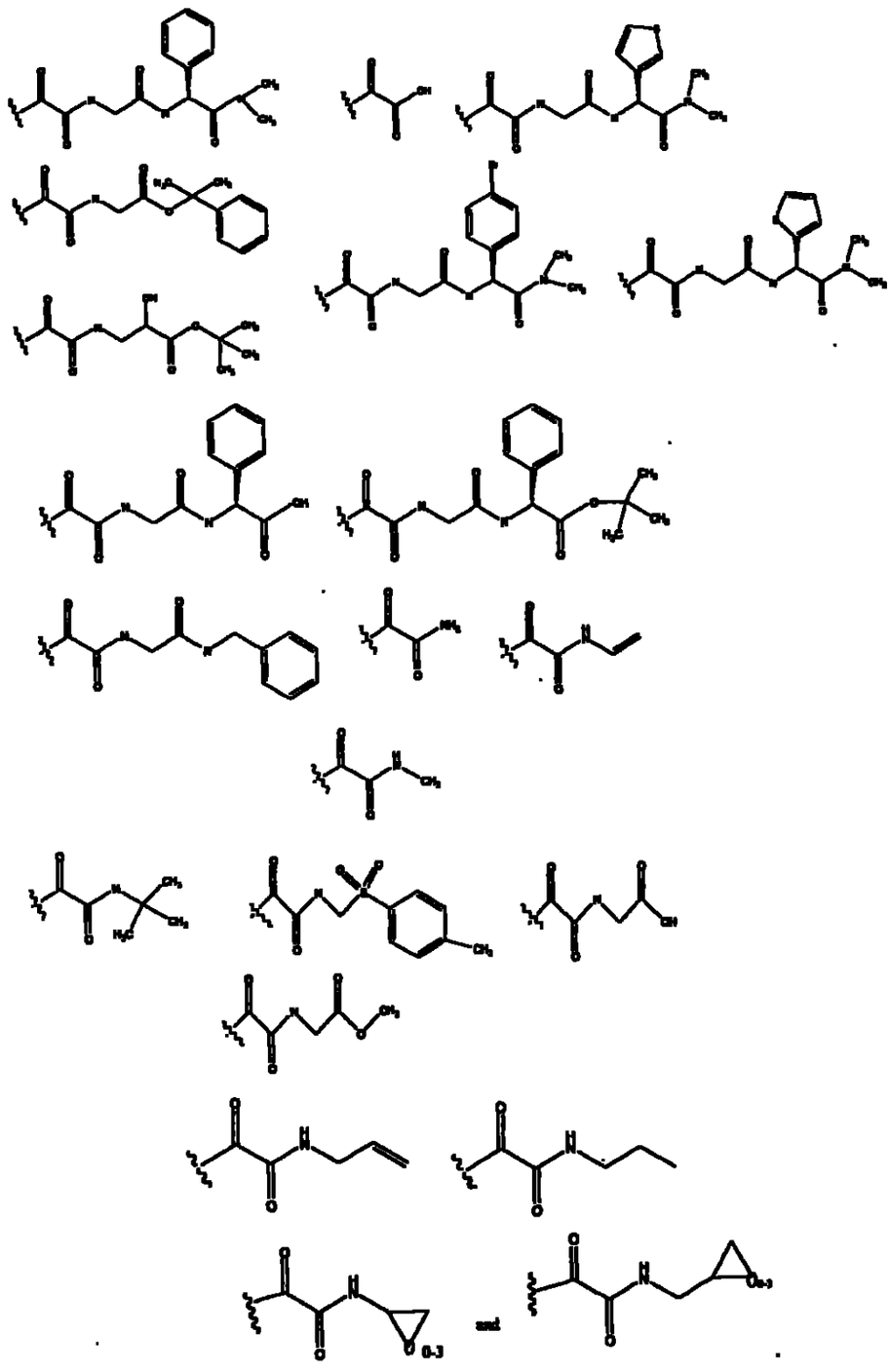


U^6 is H, OH, or CH_2OH, and

R^{14} is selected from the group consisting of: H, $-CH_3$, Et, *n*-propyl, methoxy, cyclopropyl, *n*-butyl, 1-but-3-ynyl, benzyl, α-methylbenzyl, phenethyl, allyl, 1-but-3-enyl, $-OCH_3$ and cyclopropylmethyl.

In still another embodiment of the present invention, R^1 is selected from the following structures:

87 87



In another aspect of the present invention, D and X taken together form a divalent C7-C12 unbranched paraffinic linking chain forming a portion of a 14-19 member macrocycle.

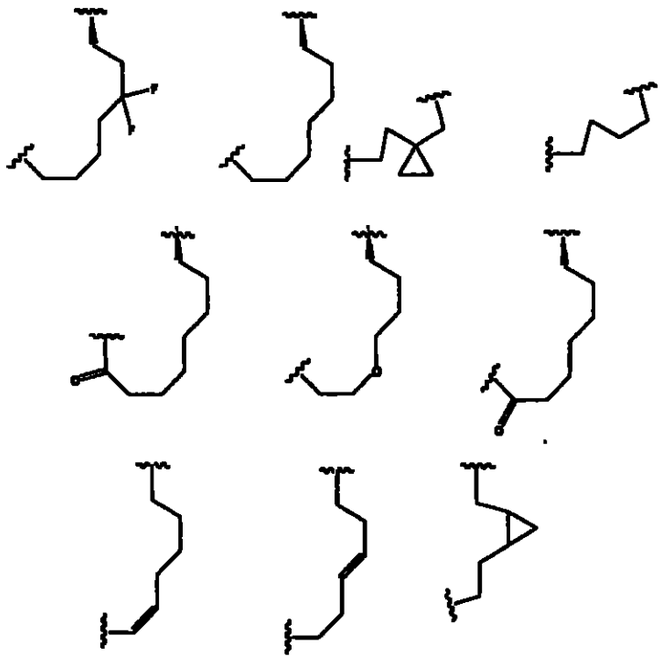
In another aspect of the present invention, D and X taken together form a C8 or C9 unbranched paraffinic linking chain forming a portion of a 15 or 16 membered heterocycle.

In another aspect of the present invention, D and X taken together form a divalent C7-C12 unbranched olefinic linking chain forming a portion of a 14-19 member macrocycle having a single degree of unsaturation.

In another aspect of the present invention, D and X taken together form a C8 or C9 unbranched olefinic linking claim forming a portion of a 15 or 16 member heterocycle having a single degree of unsaturation.

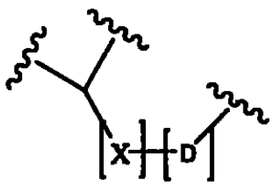
In another aspect of the present invention, D and X taken together form a divalent C2 – C12 unbranched aliphatic chain forming a portion of a 9-19 membered heterocycle.

In another aspect of the present invention, D is selected from the following structures:

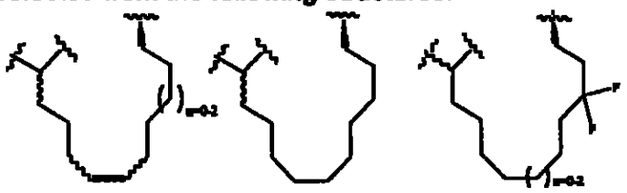


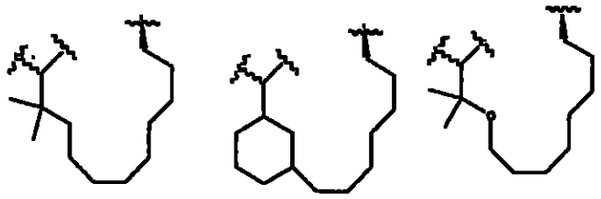
Q 89

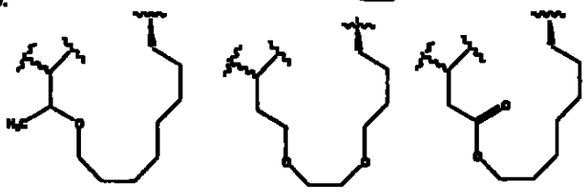
In still yet another aspect of the present invention, the portion of Formula 1 represented by

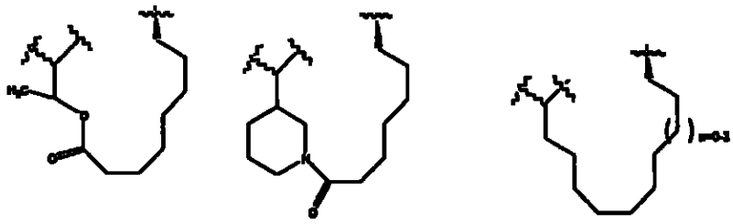


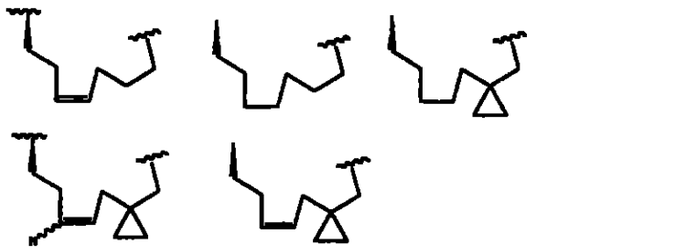
is selected from the following structures:



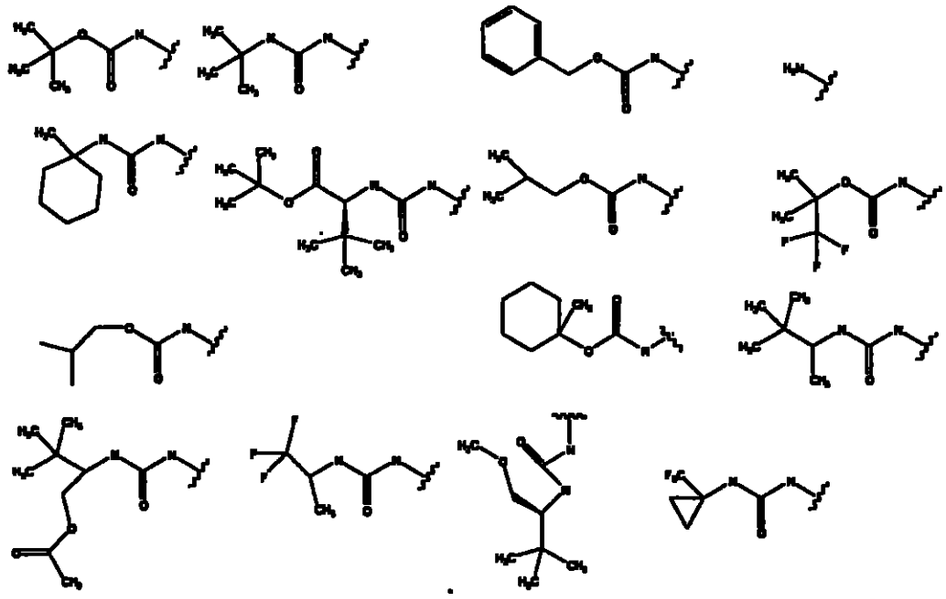


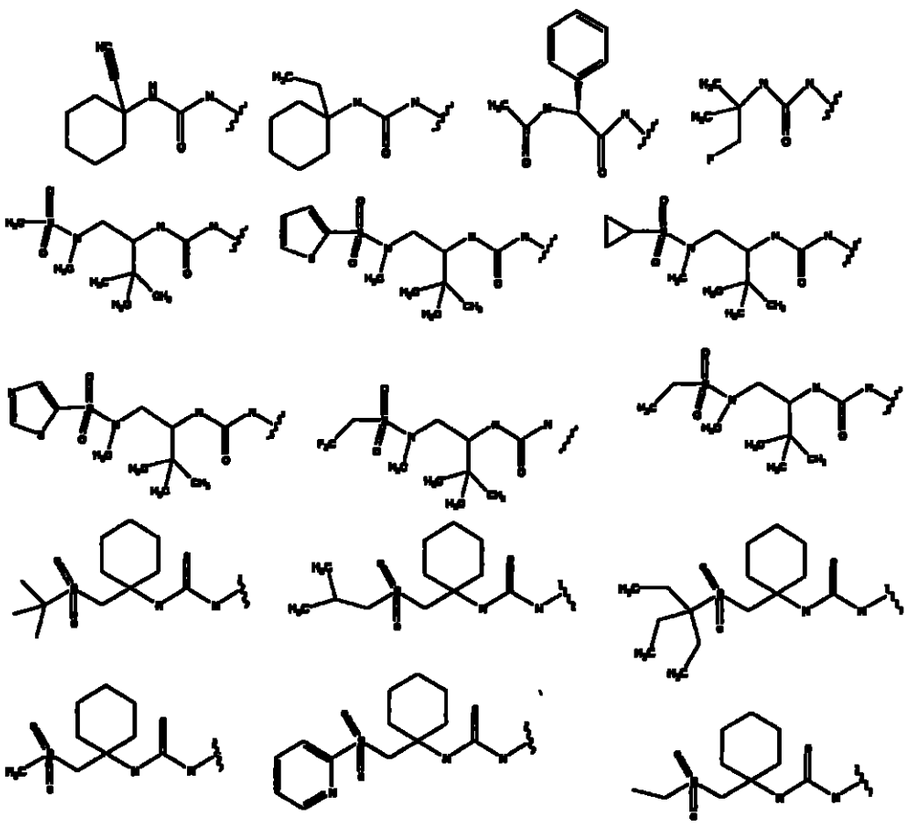


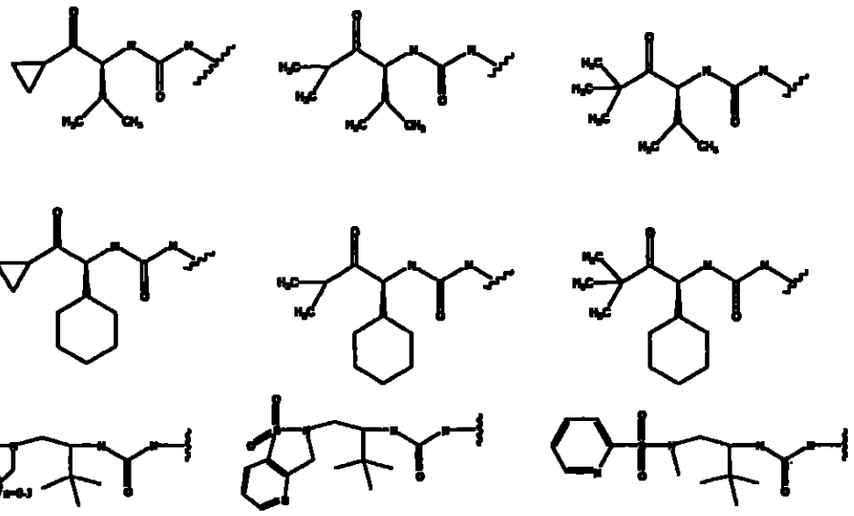




In another embodiment of the present invention, Z' is selected from the group consisting of:



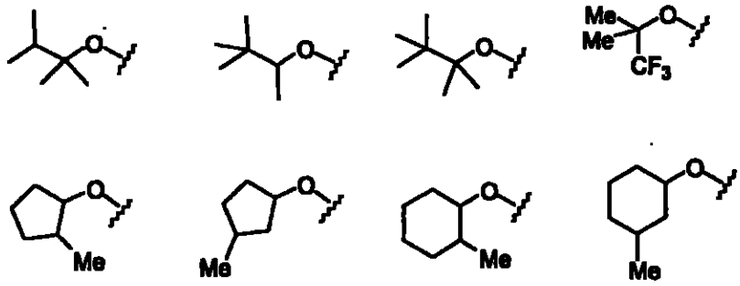


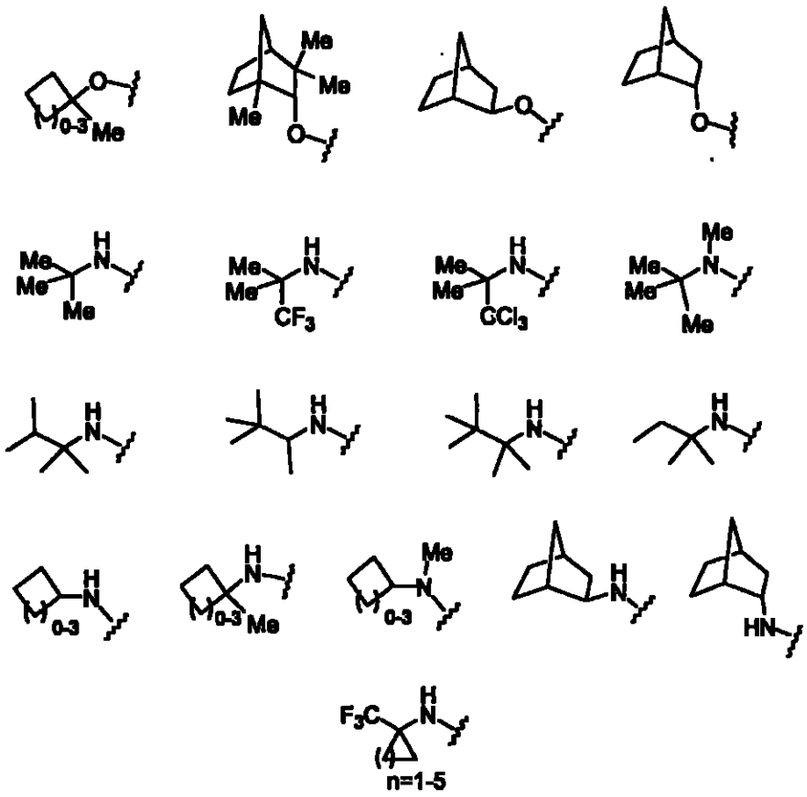


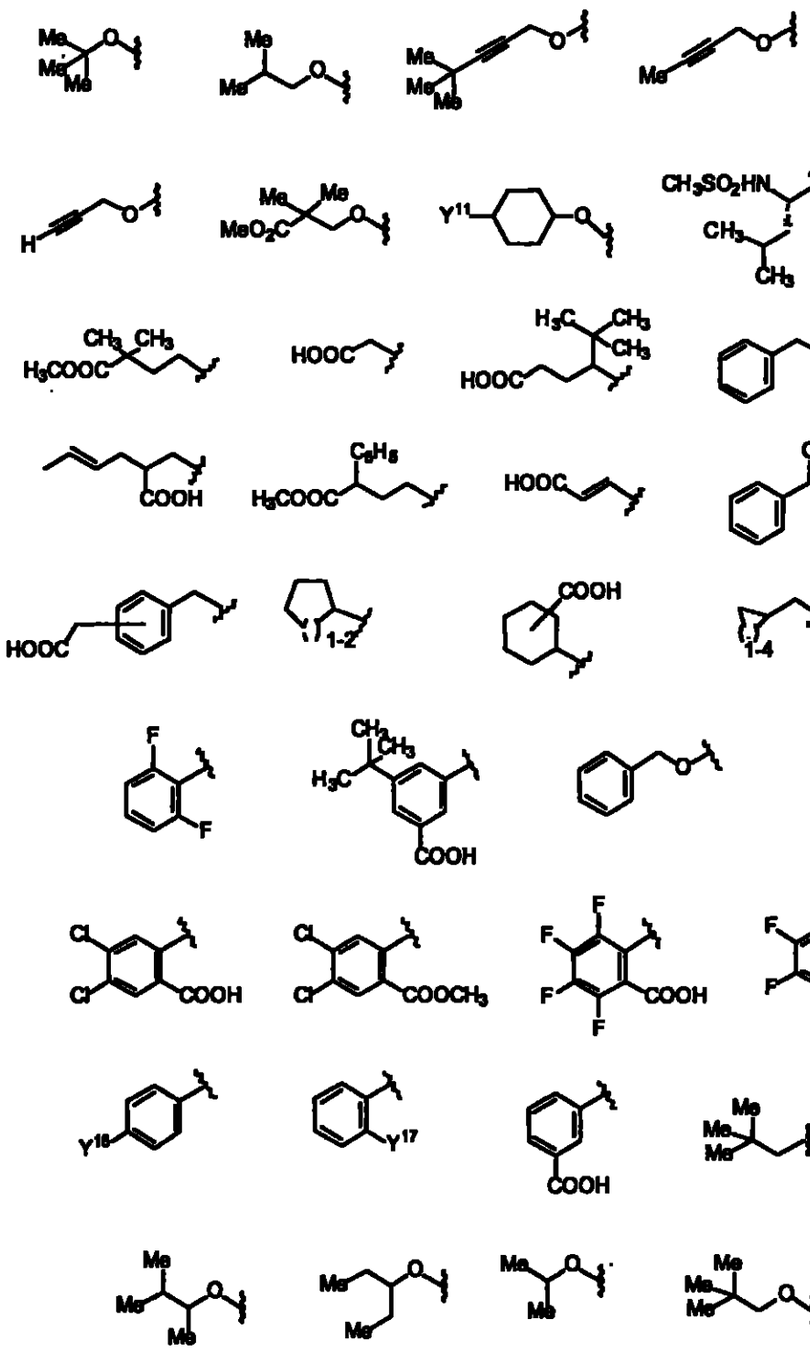
In another embodiment of the present invention, W is C=O.

In another embodiment of the present invention, Z is N.

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



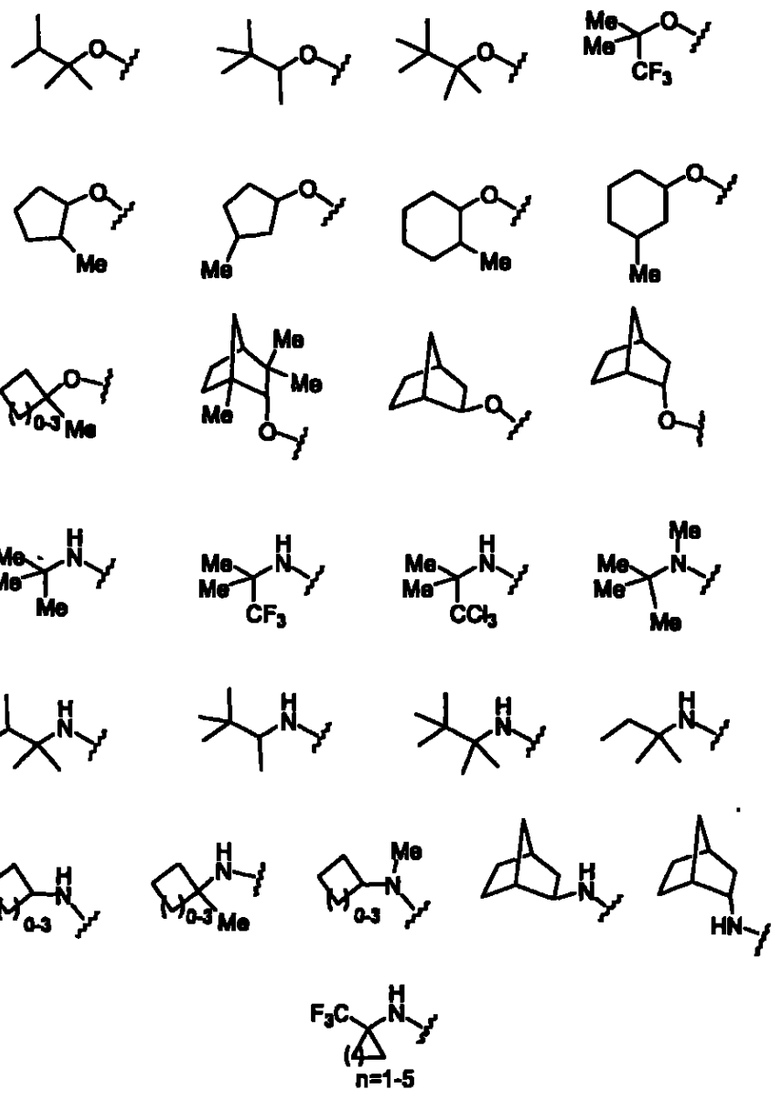

Me
Me
Me
O
0-3
Me
O
O
H
N
Me
Me
Me
H
N
Me
Me
CF3
H
N
Me
Me
CCl3
Me
N
Me
Me
Me
H
N
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N
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N
H
N
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0-3
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H
N
(4
n=1-5

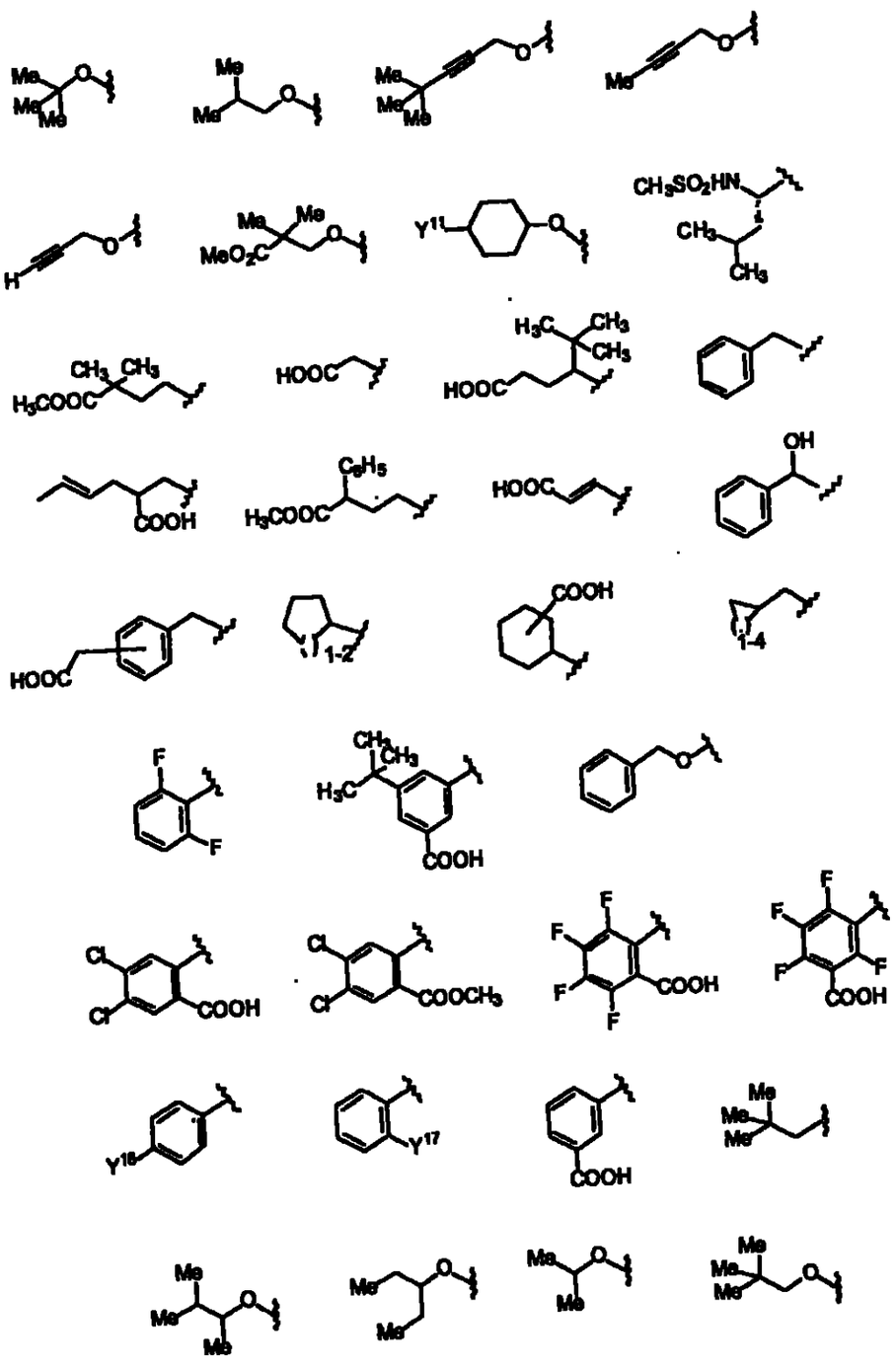

Me
Me
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O
Me
Me
Me
O
Me
Me
Me
O
Me
O
H
O
Me
Me
MeO2C
O
Y11
O
CH3SO2HN
CH3
CH3
CH3
CH3
H3COOC
HOOC
H3C
CH3
CH3
HOOC
COOH
C2H5
H3COOC
HOOC
OH
HOOC
1-2
COOH
1-4
F
F
CH2
CH3
H3C
COOH
O
Cl
Cl
COOH
Cl
Cl
COOCH3
F
F
F
COOH
F
F
F
F
COOH
Y16
Y17
COOH
Me
Me
Me
Me
Me
Me
Me
O
Me
Me
Me
O
Me
Me
Me
O

wherein Y^{17} is CF_3, NO_2, $C(O)NH_2$, OH, NH_2 or C(O)OH; and

Y^{18} is F or C(O)OH.

In still another embodiment of the present invention, Y is selected from the group consisting of the following structures:

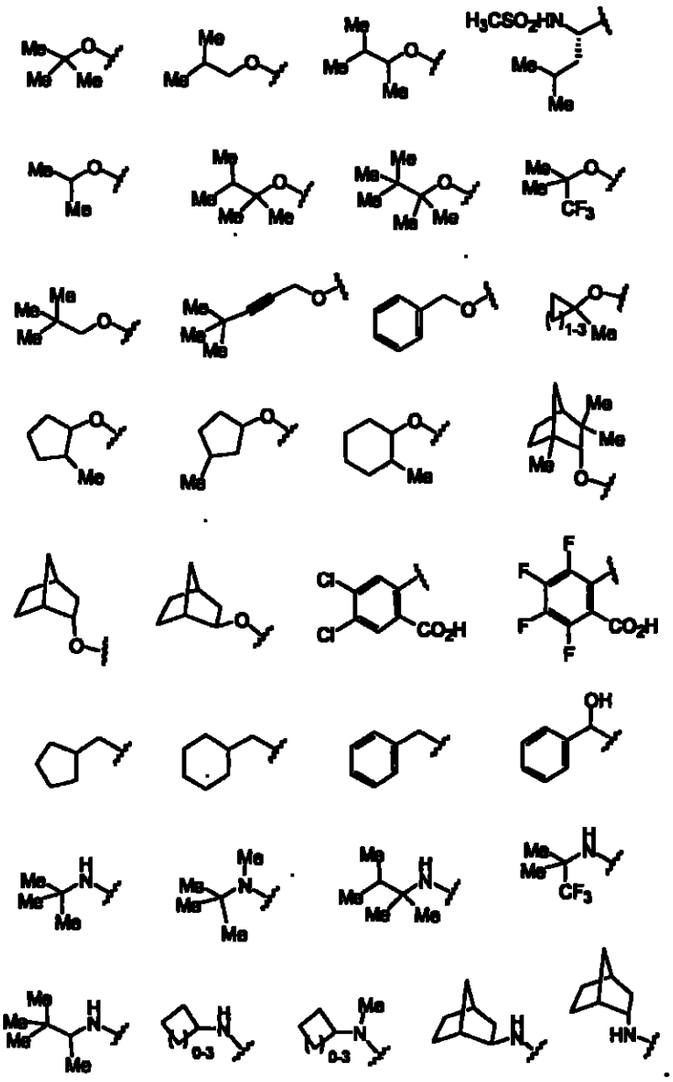



Me
Me
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O
Me
Me
Me
Me
Me
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O
Me
H
O
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Me
MeO2C
O
Y11
O
CH3SO2HN
CH3
CH3
CH3
CH3
H3COOC
HOOC
H3C
CH3
CH3
HOOC
COOH
C6H5
H3COOC
HOOC
OH
HOOC
1-2
COOH
1-4
F
F
CH3
CH3
H3C
COOH
O
Cl
Cl
COOH
Cl
Cl
COOCH3
F
F
F
COOH
F
F
F
F
COOH
Y16
Y17
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Me
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Me
O

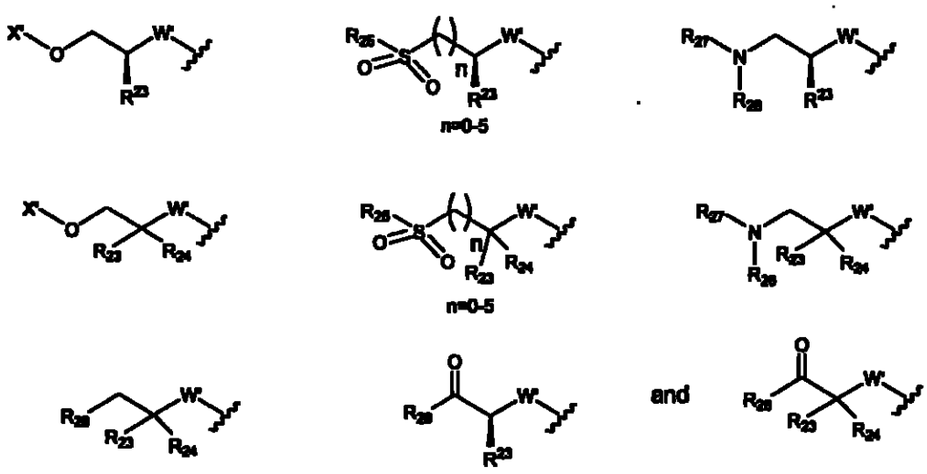
wherein Y^{17} is CF_3, NO_2, $C(O)NH_2$, OH, NH_2 or C(O)OH; and

Y^{18} is F or C(O)OH.

In still another embodiment of the present invention, Y is selected from the group consisting of the following structures:



In still yet another embodiment of the present invention, Y is selected from the group consisting of the following structures:



W' is N or O;

R^{23} is H, alkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl wherein each of said aryl, heteroaryl, cycloalkyl, heterocycloalkyl may be substituted with an alkyl moiety;

R^{24} is H, alkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl wherein each of said aryl, heteroaryl, cycloalkyl, heterocycloalkyl may be substituted with an alkyl moiety;

or R^{23} and R^{24} taken together form a cyclic ring containing a carbocycle or heterocycle;

R^{25} is H, alkyl, heteroalkyl, aryl, heteroaryl, alkylamino, arylamino, heteroalkylamino or cycloalkyl,

R^{26} is selected from the group consisting of: H, carbamate, sulfonamides, alkylcarbonyl, alkylsulfonyl, arylsulfonyl, heteroaryl, sulfonyl, heteroalkylsulfonyl, aryloxycarbonyl, heteroalkoxycarbonyl, heteroaryloxycarbonyl, alkylaminoarbonyl, arylaminocarbonyl and urea;

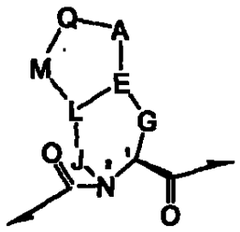
R^{27} is H, alkyl, cycloalkyl, aryl or heteroaryl;

R^{28} is H, alkyl, heteroalkyl, aryl or heteroaryl; and

X'-O- is an ether, ester or carbamate.

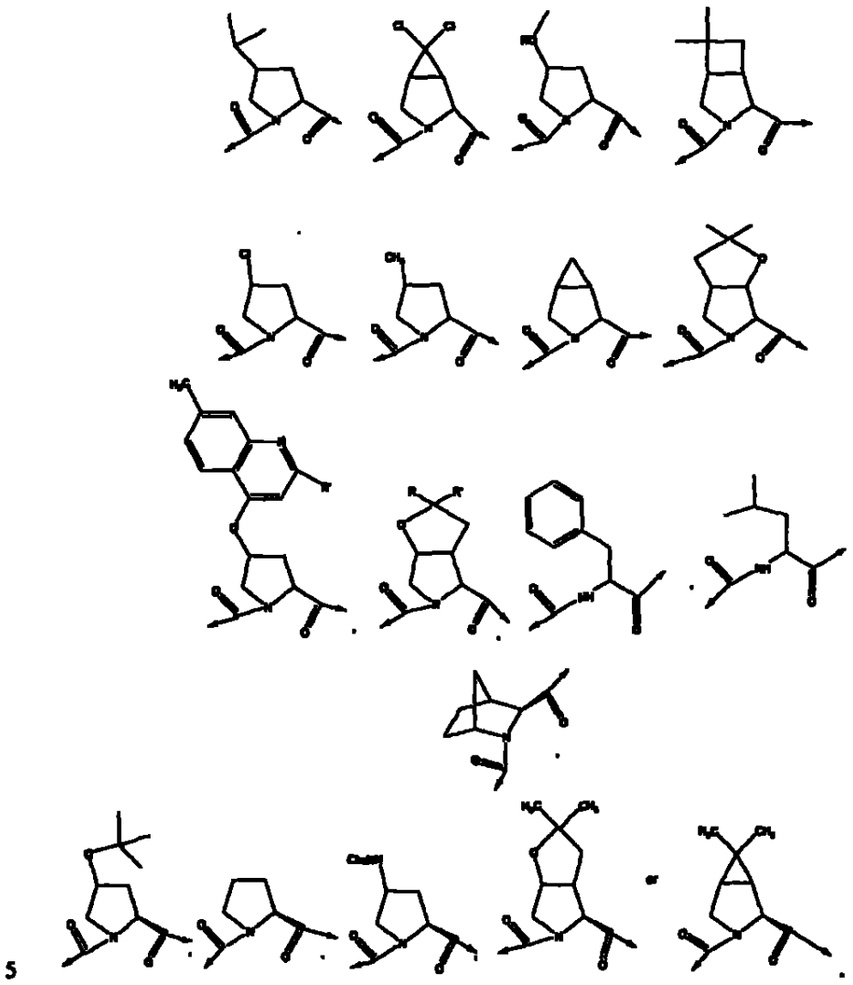
In still yet another embodiment of the present invention:

(a) the portion of Formula 1 represented by structural Formula 2:

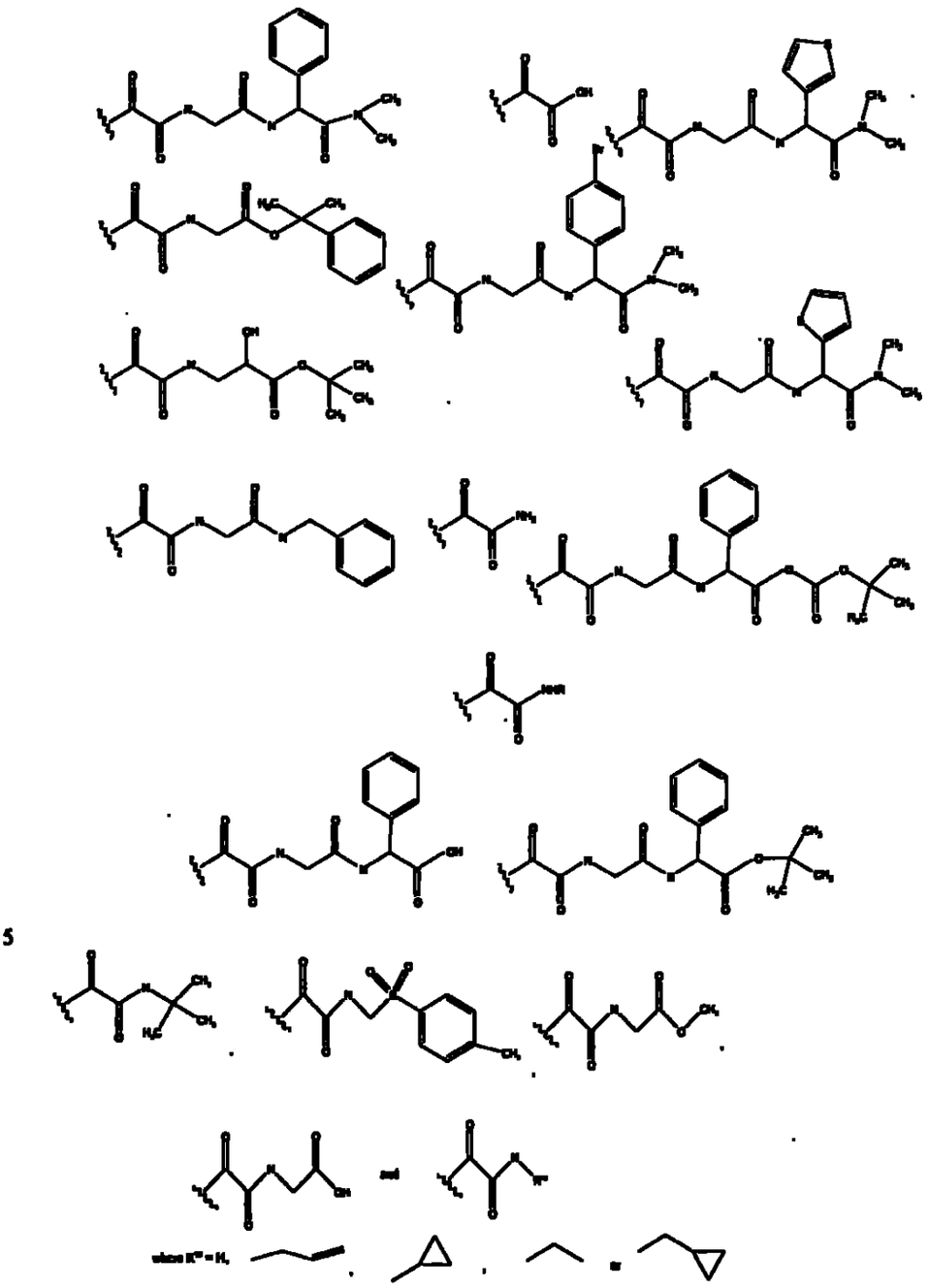


is

Formula 2

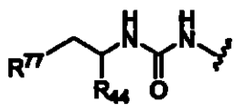


(b) R^1 is selected from the following structures:



(c) Z' is represented by either (i), (ii), or (iii) shown below:

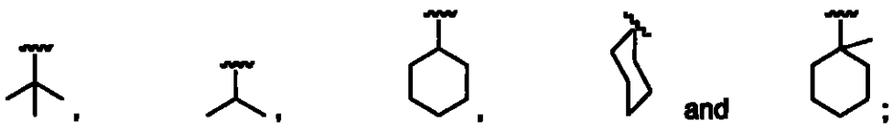
(i)



Formula A

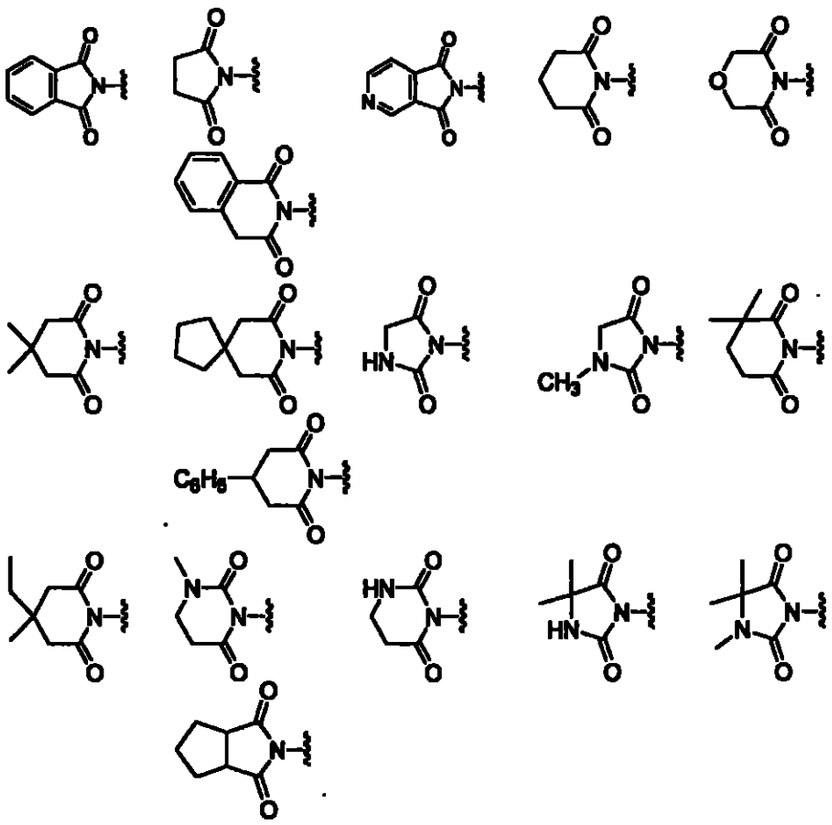
wherein:

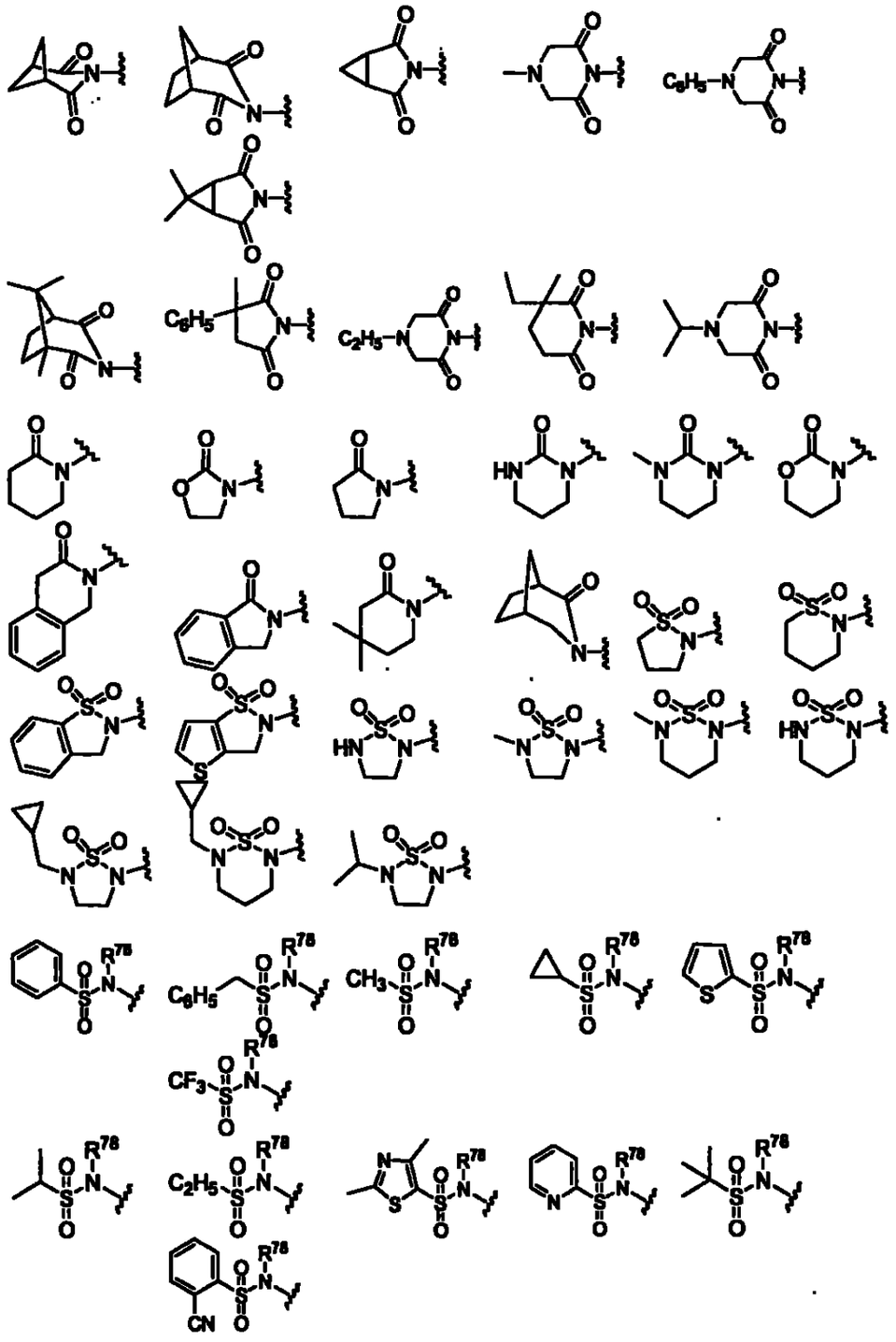
R^{44} is selected from the group consisting of:

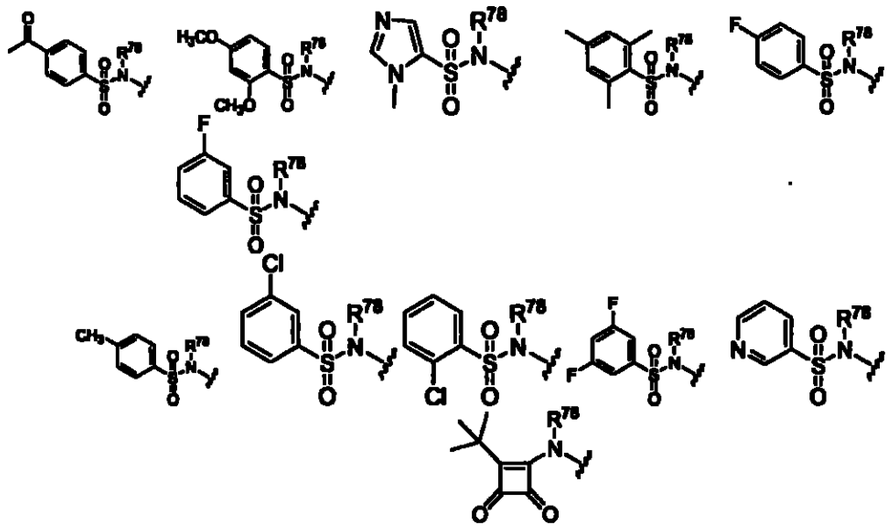


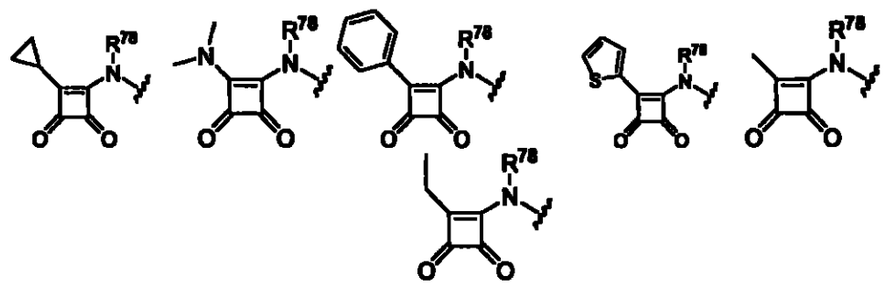
and ;

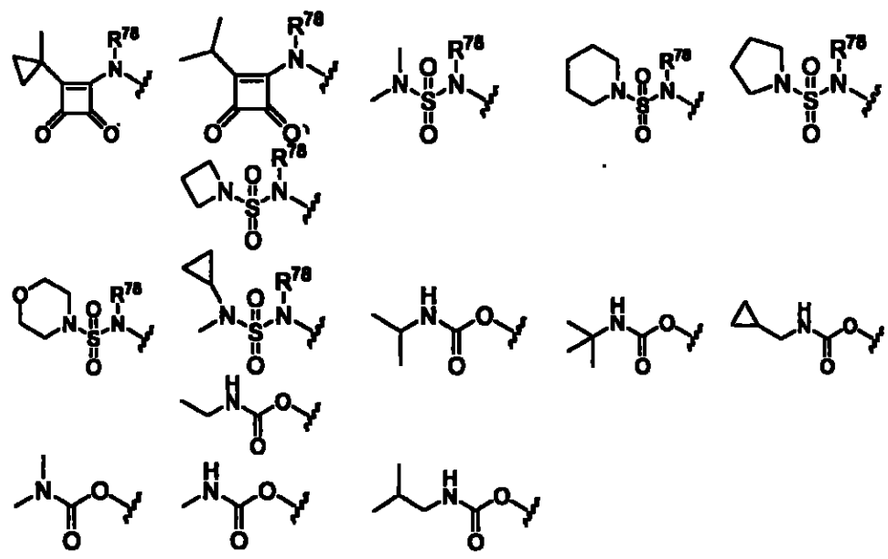
and R^{77} is selected from the group consisting of:





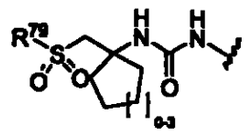






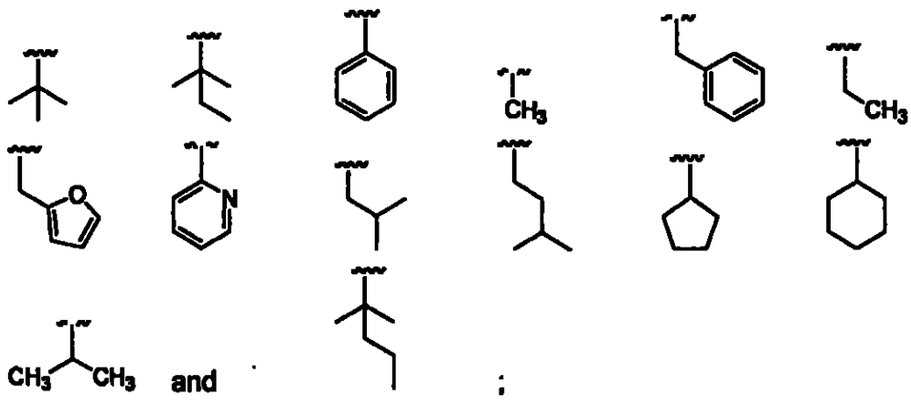
where R^{78} is selected from methyl, ethyl, isopropyl, tert-butyl and phenyl;

(ii)



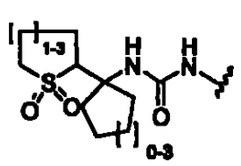
Formula B

where R^{79} is selected from the group consisting of:



and ;

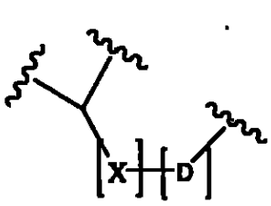
(III)



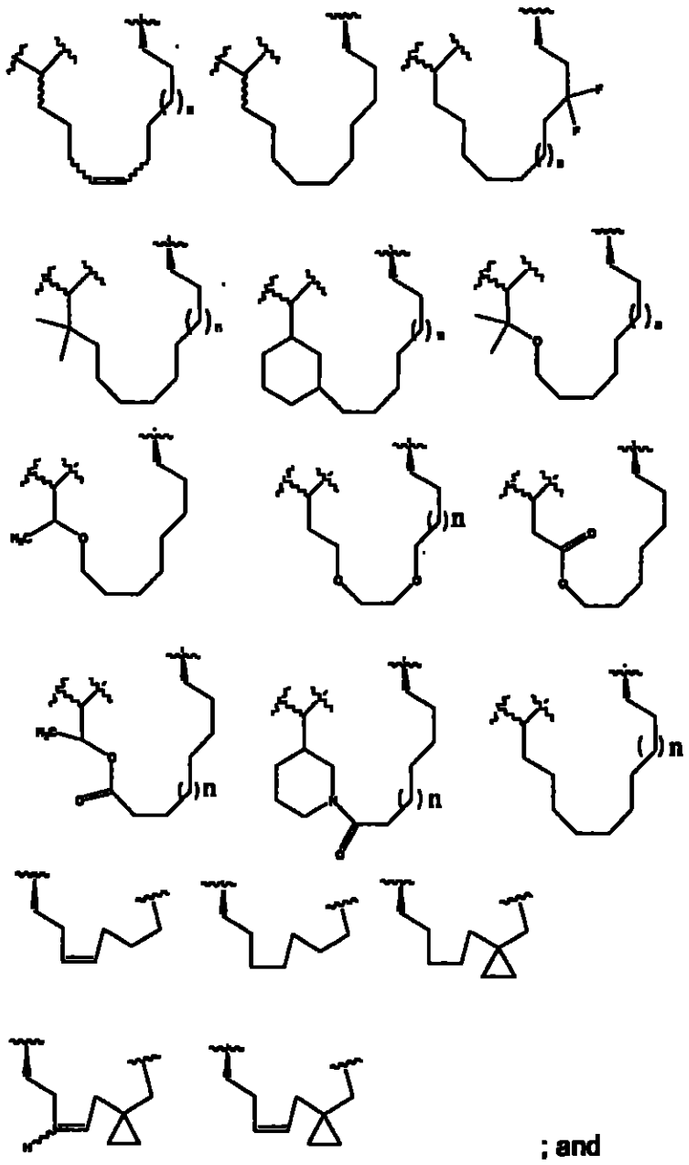
Formula C

wherein the sulfone ring is optionally substituted with alkyl and cycloalkyl; and

(d) the portion of Formula 1 represented by



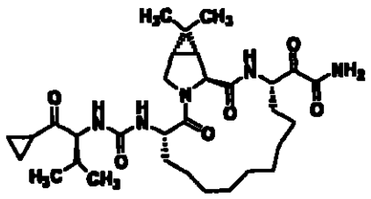
is selected from the following structures:

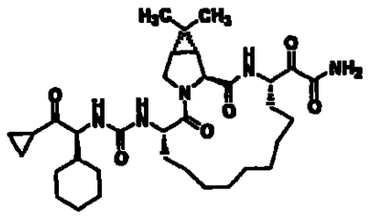


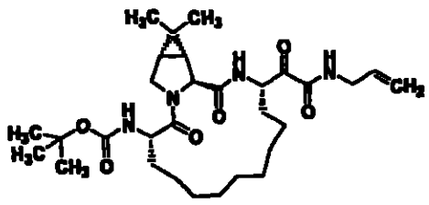
; and

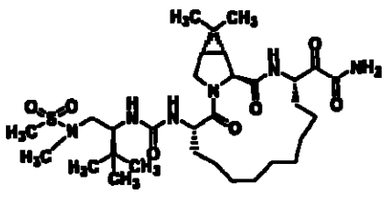
n= 0 to 3.

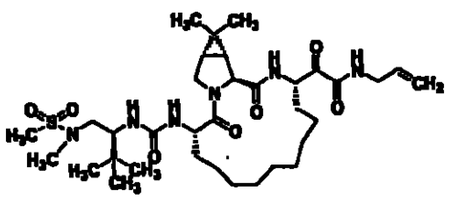
Further the following compounds are non-limiting representatives of embodiments of the present invention:

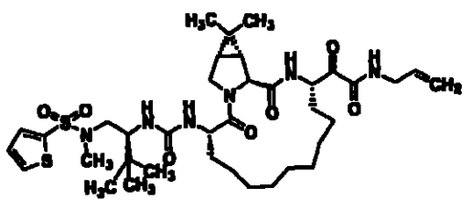


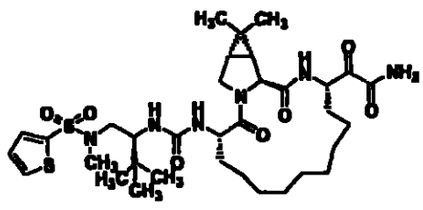


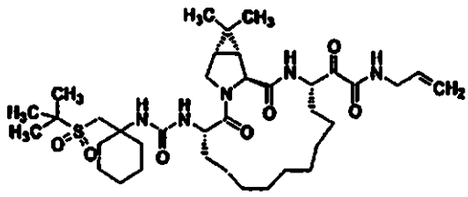


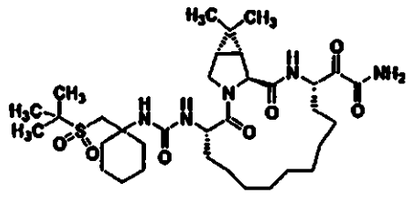


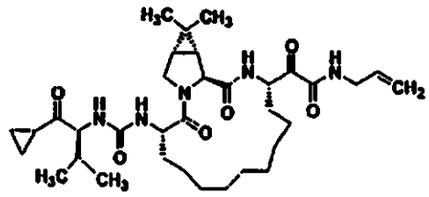


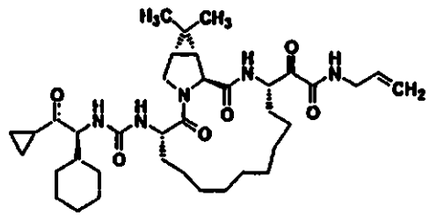


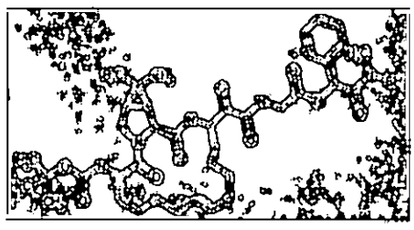


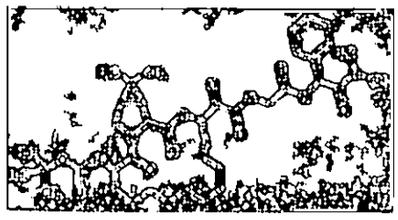


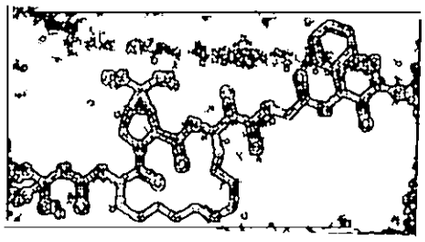


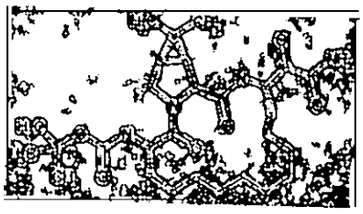






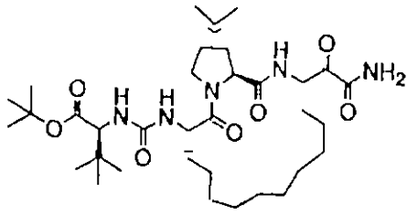


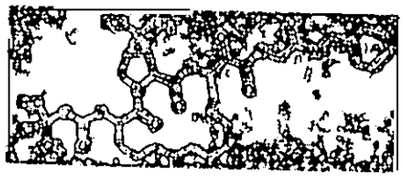


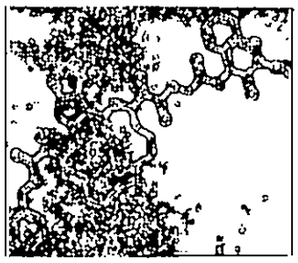


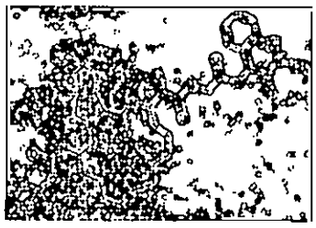





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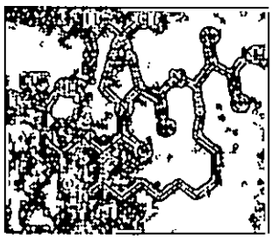


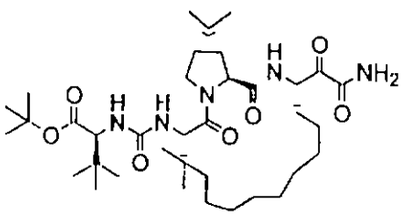


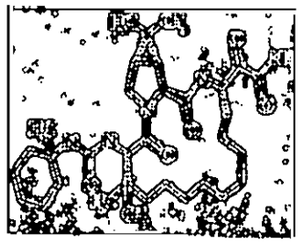


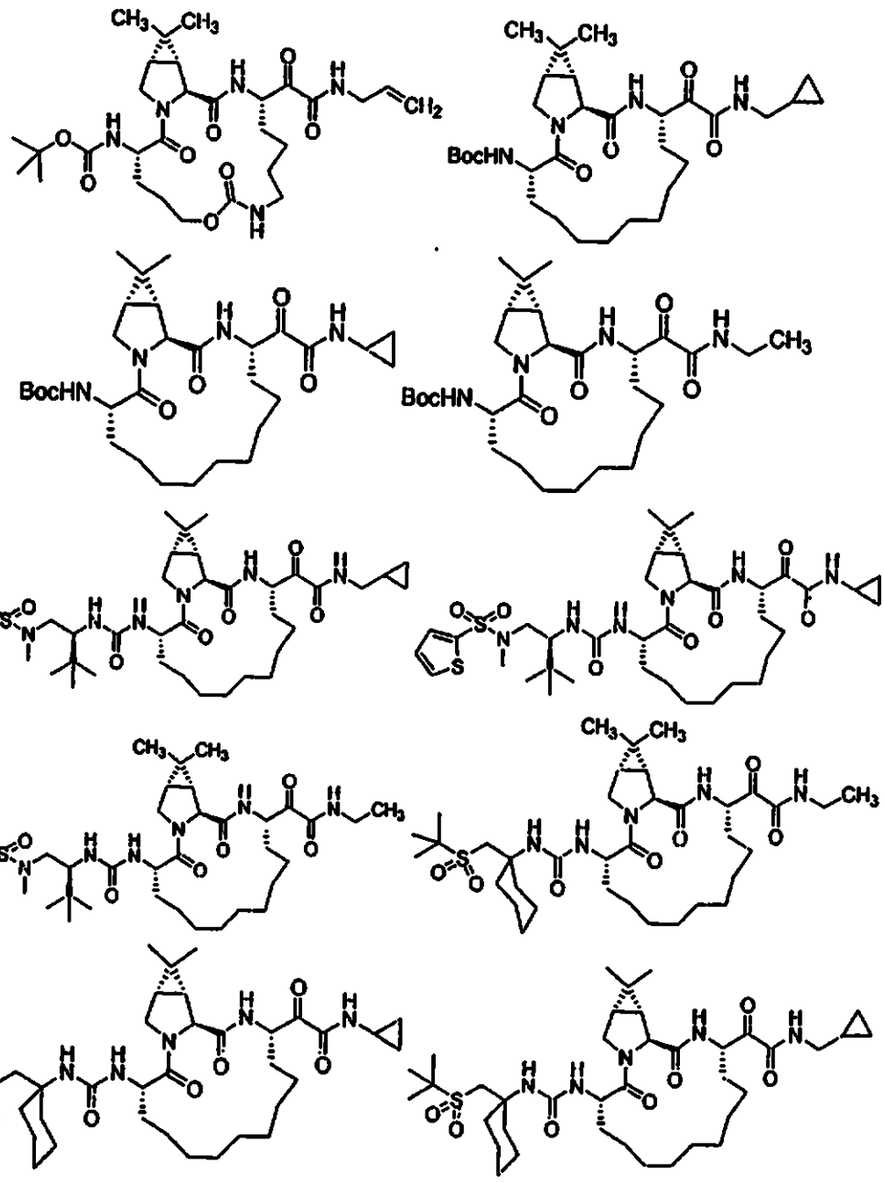


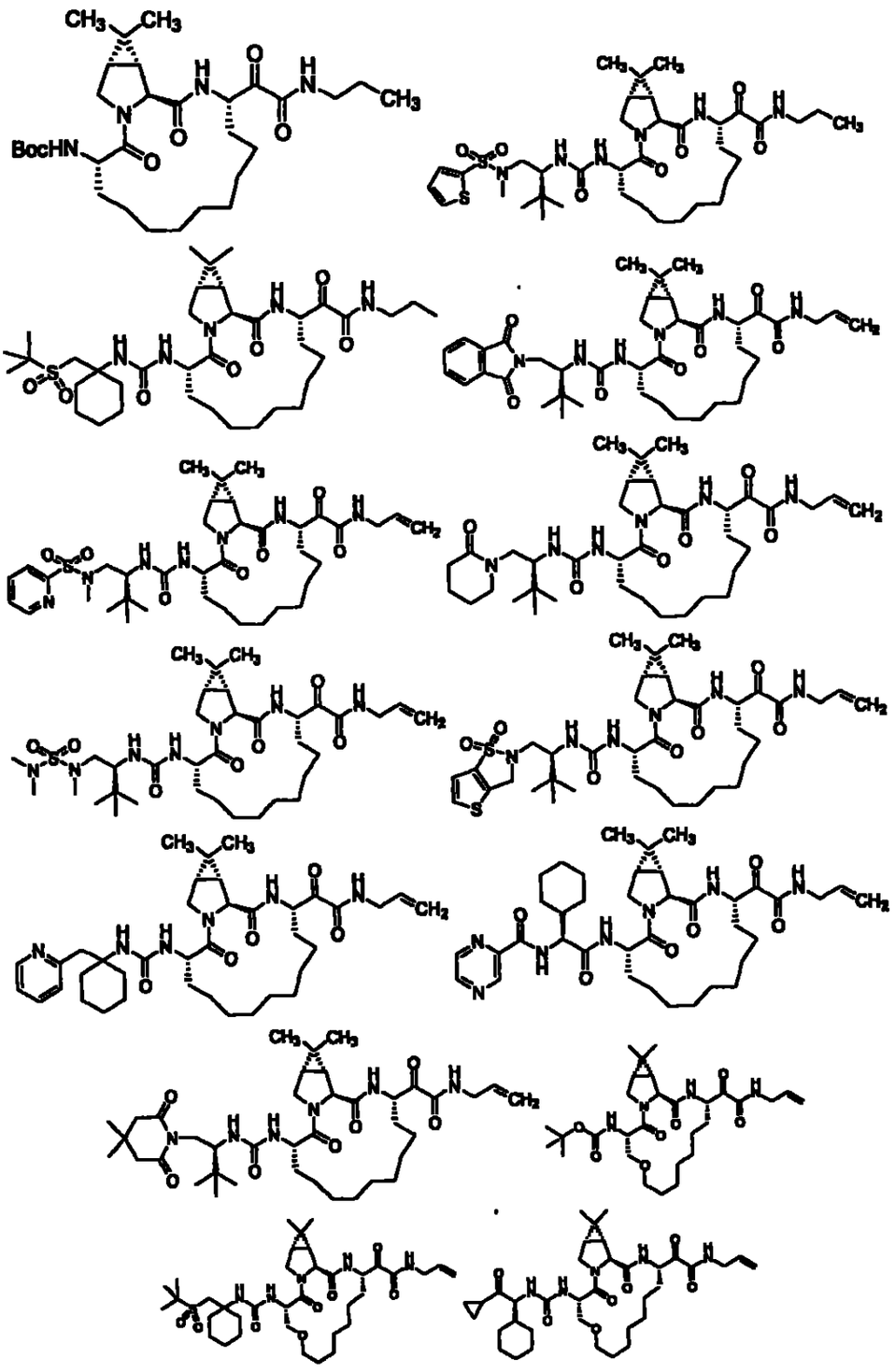


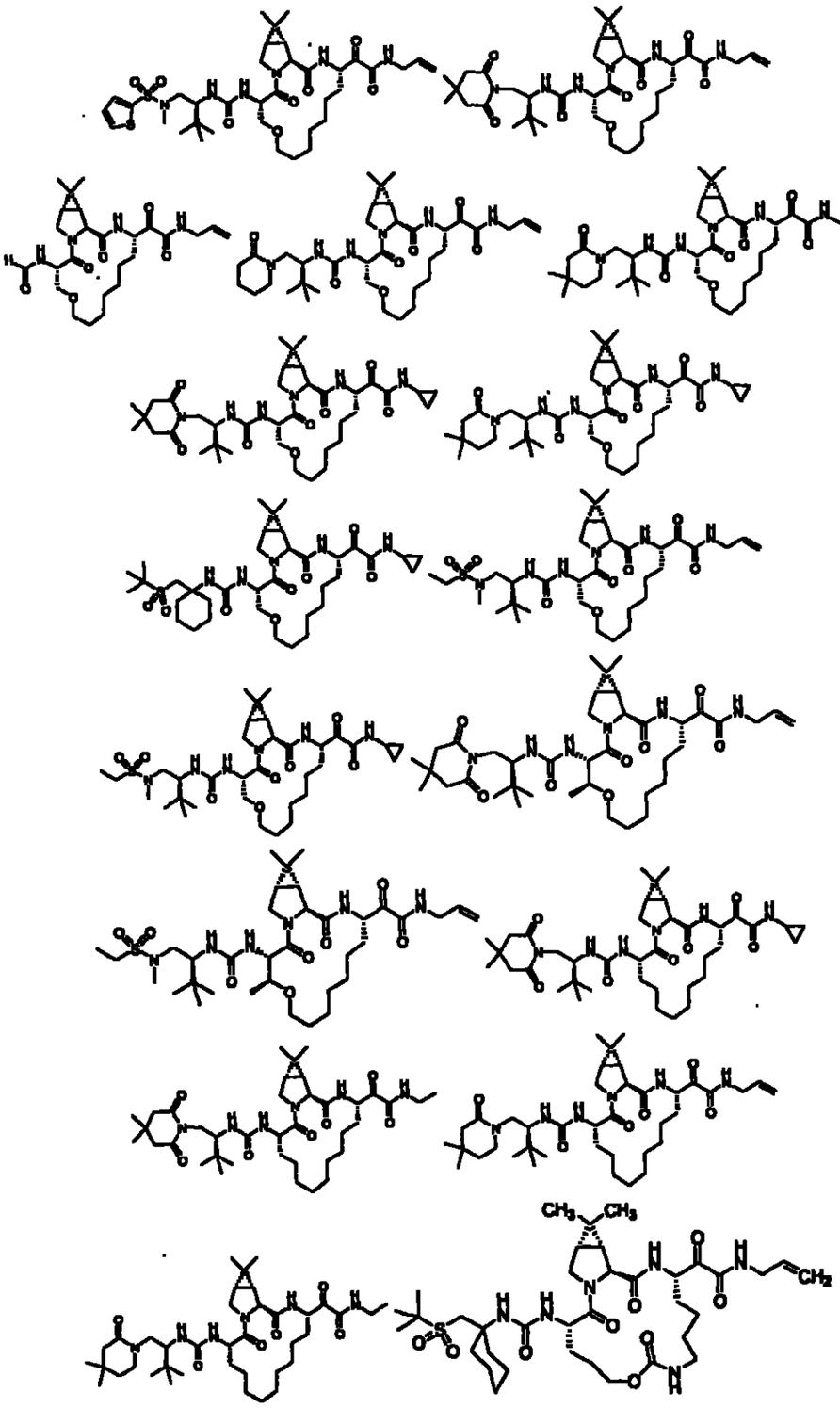


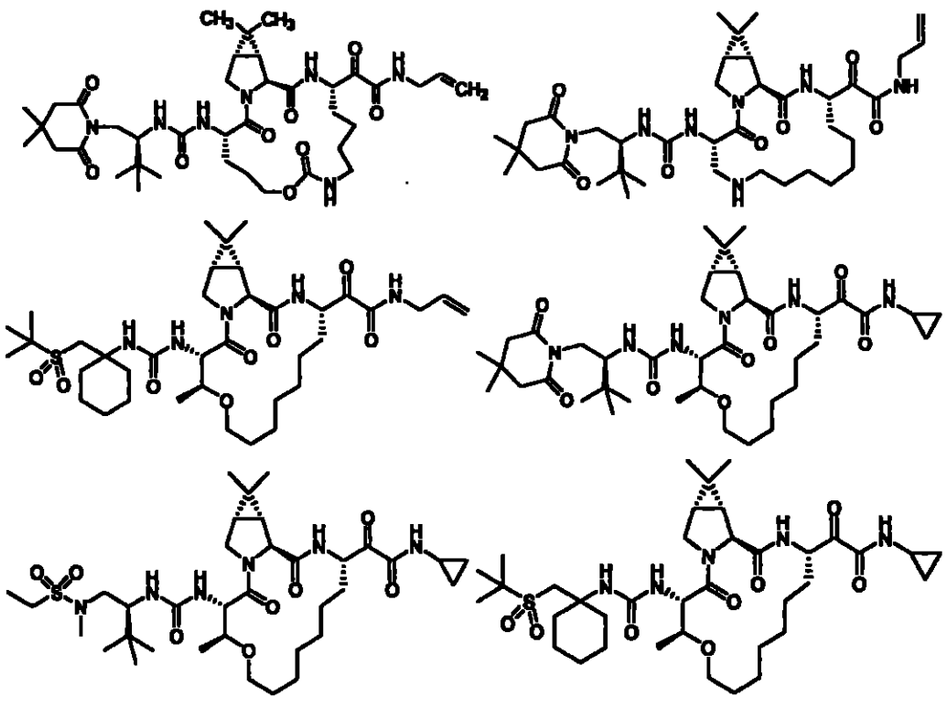












In still yet another aspect of the invention there is provided a pharmaceutical composition comprising as an active ingredient a compound of Formula 1 which is for use in treating disorders associated with HCV. The composition would generally include a pharmaceutically acceptable carrier. The composition may contain one or more additional agents such as, for example, an antiviral agent, an interferon or pegylated interferon and the like. A preferred antiviral agent is ribavirin and a preferred interferon is α-interferon.

A method of treating disorders associated with the HCV protease comprises administering to a patient in need of such treatment therapeutically effective amounts of a compound of Formula 1, or a pharmaceutical composition which comprises therapeutically effective amounts of a compound of Formula 1. The administration may be oral or subcutaneous.

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 a pharmaceutically acceptable carrier. These and other aspects of the invention are described in further detail below.

In embodiments described above, the present invention discloses compounds of Formula 1 as inhibitors of HCV protease, especially the HCV NS3/NS4a serine protease, or a pharmaceutically acceptable derivative thereof, where the various definitions are given above.

In another embodiment, this invention provides pharmaceutical compositions comprising the inventive peptides as an active ingredient. The pharmaceutical compositions generally additionally comprise a pharmaceutically acceptable carrier diluent, excipient or carrier (collectively referred to herein as carrier materials). Because of their HCV inhibitory activity, such pharmaceutical compositions possess utility in treating hepatitis C and related disorders. The HCV inhibitory activity can also lead to use of the inventive compounds and/or compositions for treating diseases (e.g., AIDS, etc) that are associated or connected with HCV.

In yet another embodiment, the present invention discloses methods for preparing pharmaceutical compositions comprising the inventive compounds as an active ingredient. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, i.e. oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Powders and tablets may be comprised of from about 5 to about 95 percent inventive composition.

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

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

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

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

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

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

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

The compounds of the invention may also be deliverable transdermally. The transdermal compositions may take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

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

The compounds of the invention may also comprise preparations which are in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active components, e.g., an effective amount to achieve the desired purpose.

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

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

Some useful terms are described below:

Capsule - refers to a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredients. Hard shell

capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

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

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

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

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

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

Binder - refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in

the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

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

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

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

oxide. The amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition, preferably from about 0.1 to about 1%.

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

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

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

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

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

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

Another embodiment of the invention discloses a method of making the compounds disclosed herein. The compounds may be prepared by several techniques known in the art. Representative illustrative procedures are outlined in the following reaction schemes. The invention disclosed herein is then further exemplified by preparative examples and example compounds which 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:

AcOH: Acetic acid

ADDP: 1,1'-(Azodicarbobyl)dipiperidine

Boc means t-butyloxy or tert-Butyloxycarbonyl

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

Cbz: Benzyloxycarbonyl

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

Bn or Bzl: Benzyl

Bz: Benzoyl

Chg: Cyclohexylglycine

Cp: Cylcopentyldienyl

DCM means dichloromethane;

DCC: 1,3-Dicyclohexylcarbodiimide

DEAD: Diethylazodicarboxylate

DMAP: 4-N,N-Dimethylaminopyridine

DMF means *N,N*-dimethylformamide;

DMSO means dimethyl sulfoxide;

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

Et: Ethyl;

EtOAc means ethyl acetate;

Et_2O: Diethyl ether;

HATU means O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium;

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

HOBt: N-Hydroxybenzotriazole;

iBoc: isobutoxycarbonyl;

iPr: isopropyl;

KHMDS means Potassium hexamethyl disilylamide;

LiHMDS means hexamethyldisilazide;

Me: Methyl;

MS means mass spectrum;

nBuLi means n-butyl lithium;

NMM means N-methyl morpholine;

NMR means nuclear magnetic resonance;

Phg: Phenylglycine;

Ph: Phenyl;

Pd/C means palladium on charcoal catalyst;

PyBrOP: Bromo-*tris*-pyrrolidinophosphonium hexafluorophosphate;

TBuNCO means t-butyl isocyanate;

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

THF means tetrahydrofuran;

THP means tetrahydrofuran;

TMSI means trimethyl silyl iodide;

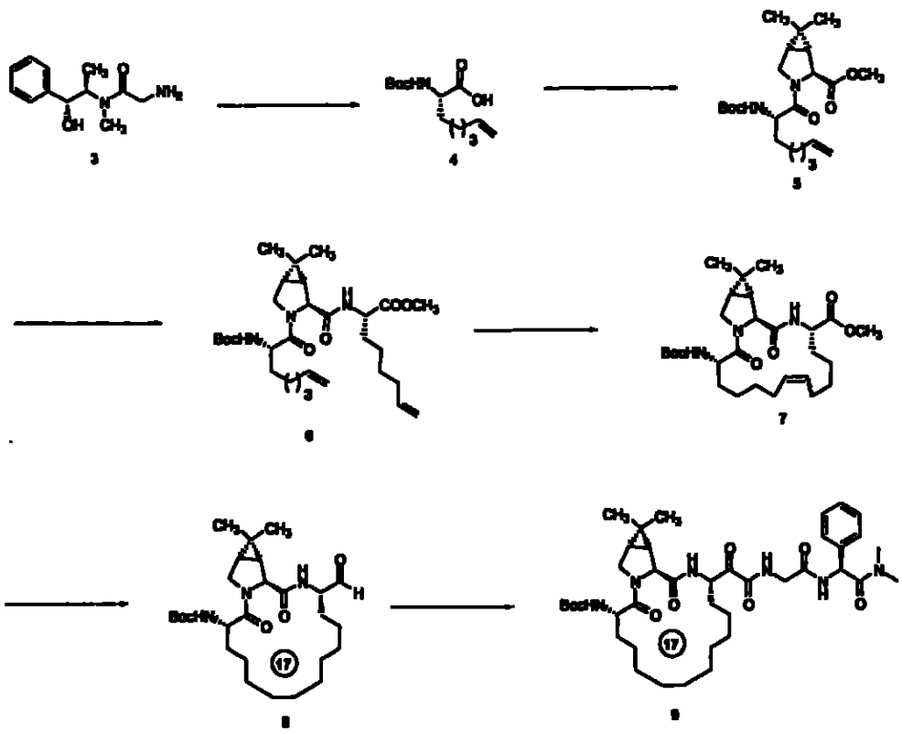
T_3N means triethylamine;

Ts: p-toluenesulfonyl.

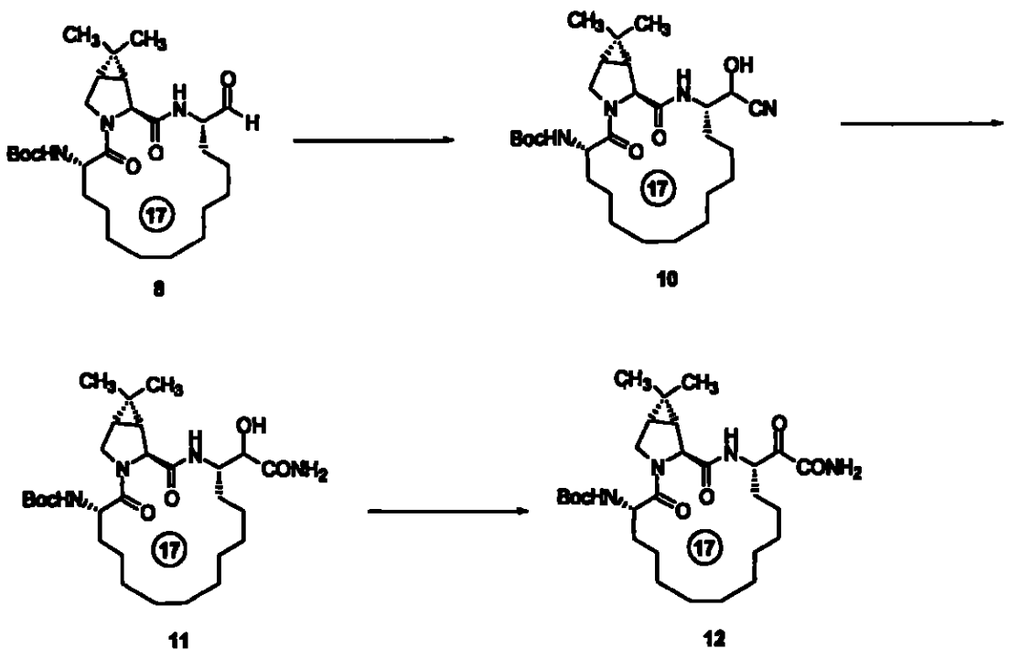
Several of the intermediates and/or preparative examples used in the following synthetic procedures have been disclosed in WO 01/77113; WO 01/081325; WO 02/08198; WO 02/08256; WO 02/08187; WO 02/08244; WO 02/48172; WO 02/08251; and pending U.S. patent application, Serial No. 10/052,386, filed January 18, 2002. The disclosures of those applications are incorporated herein by reference thereto.

General Preparative Schemes and Procedures for Preparative Examples

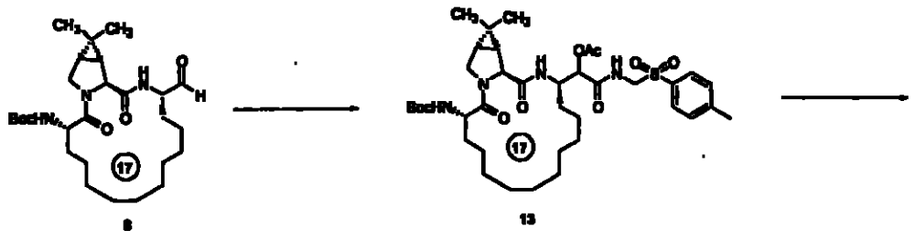
SCHEME 1



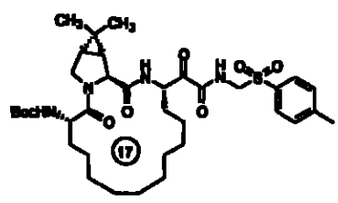
SCHEME 2



SCHEME 3



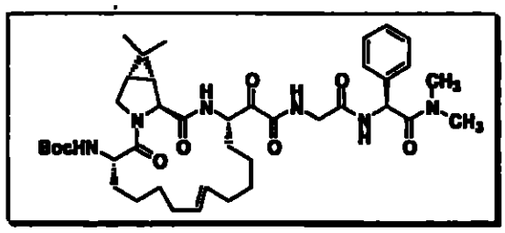
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Procedures For Preparative Examples

Preparative Example 1



1

Step A



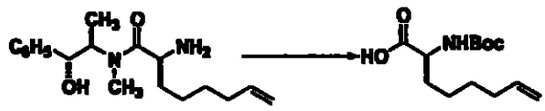
1a 1b

The synthesis of 1b can be accomplished using the procedure of (1) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W.; *J. Am. Chem. Soc* 1997, *119*, 656; (2) Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W.; *J. Org. Chem.*, 1999, 64, 3322.; or (3) Myers, A. G.; Gleason, J. L.; *Org. Synth.* 1998, *76*, 57.

A solution of amine 1a (24 g, 120 mmol) in THF (300 mL) was treated with anhydrous LiCl (16.80 g, 400 mmol) over 0.5 h and stirred till the reaction mixture turns homogeneous. The reaction mixture was cooled to 0° C

and treated with a THF solution of LiHMDS (66.80 g , 400 mmol in 300 ml of THF) over 20 min. The reaction mixture was stirred at 0° C for 0.5 h and treated with 6-bromohexene (19.44 g, 120 mmol) and stirred at rt. for 24 h. The reaction mixture was dissolved in aq. 1 M HCl and concentrated in *vacuo* to remove THF. The mostly aq. layer was further diluted with 3M aq HCl (300 mL) and extracted with ether (2x200 mL). The aqueous layer was basified to pH 14 using aq. NaOH (50%) and extracted with CH_2Cl_2 (3x 300 mL). The combined organic layers were dried with $MgSO_4$ filtered concentrated in *vacuo* to yield crude **1b** (15.1 g) that was used in next step without further purification.

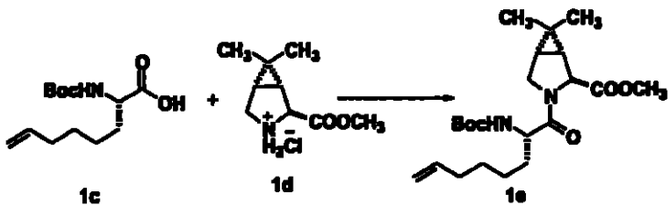
Step B



1b **1c**

A solution of **1b** (12.5 g, 41.2 mmol) was dissolved in aq. NaOH (1 M, 88.0 mL, 88 mmol) and heated at reflux for 3 h. The reaction mixture was cooled to rt. and extracted with CH2Cl2 (3x100 mL). The aq. layer was treated with 100 mL of dioxane followed by $NaHCO_3$ (8.00 g, 95.2 mmol) and di-tertbutyl dicarbonate (8.95 g, 41 mmol) and stirred at rt. for 5 h. The reaction mixture was extracted with ether (2x250 mL) and the aqueous layer was acidified to pH~2 with aq. HCl and extracted with CH_2Cl_2 (2x200 mL). The combined organic layers were dried with MgSO4, filtered concentrated in *vacuo* to yield acid **1c** (10.8 g) as a colorless oil.

Step C



1c **1d** **1e**

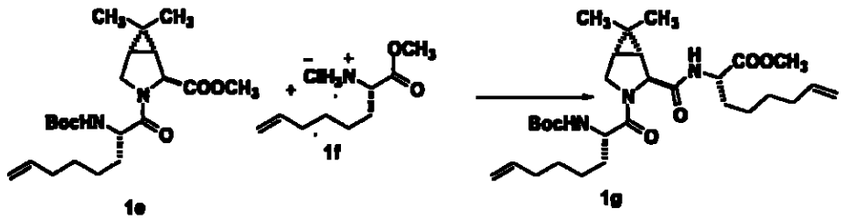
A solution of acid **1c** (5g, 19.44 mmol) and amine **1d** (3.98 g, 19.44 mmol) in CH_2Cl_2 (30 mL), DMF (30 mL) at 0° C was treated with HATU (8.87

g, 23.31 mmol) and NMM (4.91 g, 5.33 mL) and stirred overnight at 0° C. The reaction mixture was concentrated in *vacuo* and diluted with 650 mL of CH_2Cl_2. The aqueous layer was washed with aq. HCl (1M, 2x300 mL), aq. $NaHCO_3$ (1M, 2x300 mL). The organic layers were dried with $MgSO_4$, filtered concentrated in *vacuo* and purified by chromatography (SiO_2, Acetone/Hexanes 5:1) to yield **1e** as a colorless oil (5.5 g).

^{1}H NMR: (CD_3OD, 300 MHz) δ5.87-5.76 (m, 1 H), 4.97-4.92 (dd, 2 H), 4.26 (bt, 1 H, J=7.8 Hz), 3.98 (d, 1 H, J= 10.2 Hz), 3.61 (dd, 2 H, J=5.1, 5.1 Hz), 3.73 (s, 3 H), 2.14-2.07 (m, 2 H), 1.74-1.42 (m, 9 H), 1.41 (s, 9 H), 1.12 (s, 3 H), 0.92 (s, 3 H).

^{13}C NMR: (CD_3OD, 75 MHz), d 173.8, 173.2, 158.0, 139.8, 115.0, 80.4, 60.91, 53.42, 52.80, 34.7, 33.5, 32.3, 31.4, 29.8, 28.7, 26.4, 26.1, 20.6, 12.9.

Step D

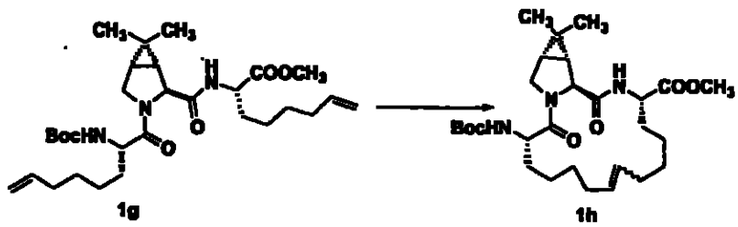


A solution of ester **1e** (4g, 9.79 mmol) in THF (20 mL), H_2O (20 mL) and MeOH (10 mL) was treated with $LiOH·H_2O$ (575 mg, 14 mmol) and stirred at rt. for 4h. The reaction mixture was concentrated in *vacuo* to remove THF and MeOH. The mostly aqueous layer was acidified with aq. HCl and extracted into CH_2Cl_2 (3x100 mL). The combined organic layers were dried with $MgSO_4$, filtered, concentrated in *vacuo* and used as it is.

A solution of acid obtained from hydrolysis of **1e**, amine segment **1f** (2.02 g, 9.79 mmol) in DMF (40 mL), CH_2Cl_2 (40 mL) at 0 °C was treated with HATU (4.46 g, 11.84 mmol) and NMM (3.5 g, 35 mmol) and stirred at 0° C for 24 h. The reaction mixture was concentrated in *vacuo* and diluted with aq. HCl (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3x75 mL). The combined organic layers were washed with aq saturated $NaHCO_3$ (3x100 mL), brine dried with $MgSO_4$, filtered concentrated in *vacuo* and purified by

silica gel chromatography (EtOAc/Hex 1:3) to yield 1g (4.5 g) as a colorless foam.

Step E

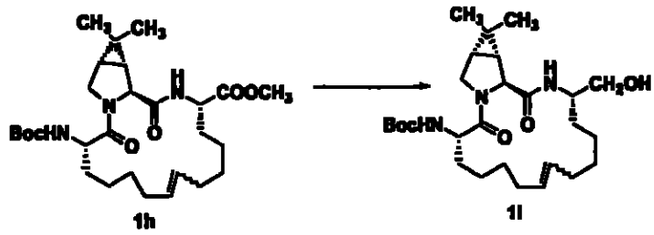


A solution of diene 1g (1.1 g, 2.0 mmol) in dry CH_2Cl_2 (20 mL) was treated with Grubbs catalyst [$(Cy)_3RuCl_2$=CHC_6H_5, 83.8 mg, 0.1 mmol) and stirred at rt. for 24 h. The reaction mixture was concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hex 1:3) to yield 1h (501 mg) as a colorless solid and mixture of *E/Z* isomers.

^{1}H NMR ($CDCl_3$, 300 MHz) δ, 7.38 (d, 1 H, J=8.1 Hz), 5.30-5.18 (m, 2 H), 4.55 (dt, 1 H, J= 2.4, 9.6 Hz), 3.92 (bs, 1 H), 3.77 (s, 3 H), 3.79-3.77 (bm, 1H), 2.06-2.1 (bm, 3 H). 1.95-1.81 (m, 2 H), 1.79-1.77 (m, 13 H), 1.31 (s, 9 H), 1.05 (s, 3 H), 0.85 (s, 3H).

MS (ESI), m/z, relative intensity 542 [$(M+Na)^+$ 45], 464 (20), 448 (25) 420 (100).

Step F

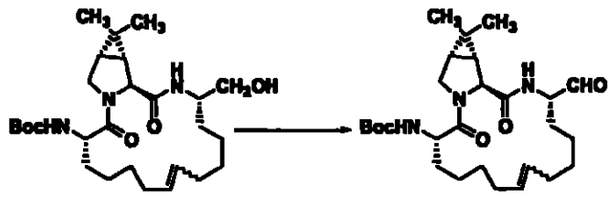


A solution of ester 1h (100 mg, 0.19 mmol) in dry THF (1 mL) was treated with $LiBH_4$ (2M soln. in THF, 0.2 mL) and stirred at rt. for 16 h. The reaction mixture was quenched with aqueous HCl (1M, 30 mL) and extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were washed with aq. $NaHCO_3$ (100 ml) brine, dried with $MgSO_4$ filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 1:3) to yield 1l (70 mg) as an amorphous solid.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.96 (d, 1 H, J=8.1 Hz), 5.32-5.21 (m, 2 H), 4.43-4.37 (m, 2 H) 4.01-3.93 (m, 1 H), 3.77 (dd, 1 H, J=5.7, 4.8 Hz), 3.65 (dd, 1 H, J= 3.9, 6.6 Hz), 3.53 (dd, 1 H, J= 6.0, 10.8 Hz), 2.11-1.77 (m, 6 H), 1.55-1.31 (m, 12 H), 1.45 (s, 9 H), 1.05 (s, 3 H), 0.87 (s, 3 H).

MS (ESI), m/z, relative intensity 530 [$(M+K)^+$, 10], 514 [$(M+Na)^+$, 70], 492 [$(M+1)^+$, 20], 392 (100).

Step H



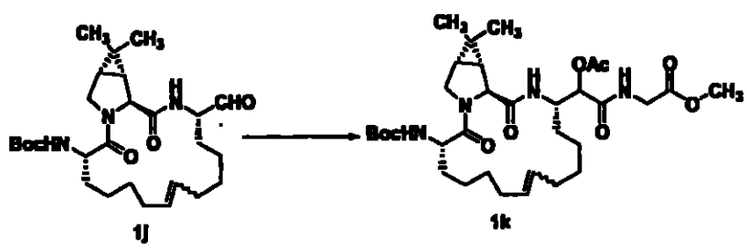
1I 1J

A solution of alcohol 1I (70 mg, 0.15 mmol), in CH_2Cl_2 (3 mL) was treated with Dess Martin reagent (85 mg, 0.2 mmol) and stirred at rt. for 2 h. The reaction mixture was quenched with $Na_2S_2O_3$ solution (10%, 10 mL) and saturated $NaHCO_3$ solution (10 mL) and stirred at rt. for 0.5 h. The reaction mixture was extracted with CH_2Cl_2 (50 mL). The organic layer was dried with $MgSO_4$, filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 4:1) to yield 1J (50 mg) as a colorless fluffy solid.

^{1}H NMR ($CDCl_3$, 300 MHz) δ9.54 (s, 1 H), 7.43 (d, 1 H, J = 7.8 Hz), 5.30-5.19 (m, 2 H), 4.55-4.40 (m, 2 H), 3.93 (d, 1 H, J=10.2 Hz), 3.77 (dd, 1 H, J=5.4, 5.1 Hz), 2.04-1.78 (m, 4 H), 1.55-1.27 (m, 14), 1.31 (s, 9 H), 1.02 (s, 3 H), 0.95 (s, 3 H).

MS (ESI), m/z, relative intensity 512 [$(M+Na)^+$, 80], 490 [$(M+1)^+$, 10], 434 (20), 390 (100).

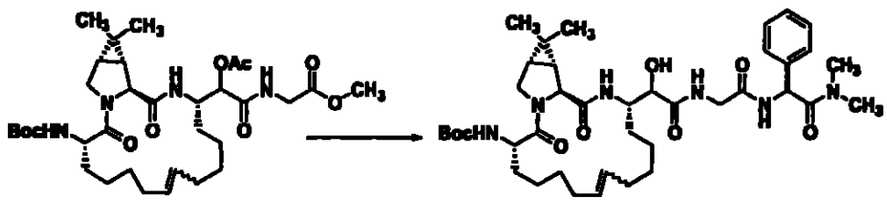
Step I



1J 1k

A solution of aldehyde 1j (50 mg, 0.11 mmol) in dry CH_2Cl_2 (2 mL) was treated with CH_3COOH (19 mg, 0.31 mmol) and methylisocyanoacetate (31 mg, 0.31 mmol). The reaction mixture was stirred at rt. for 48 h and concentrated in *vacuo*. The residue was purified by chromatography (SiO_2, acetone/hexanes 1:2) to yield 1k (50 mg) as a mixture of diastereomers. **MS** (ESI), m/z, relative intensity 671 [$(M+Na)^+$, 45], 649 [$(M+1)^+$, 30], 549 (100).

Step J

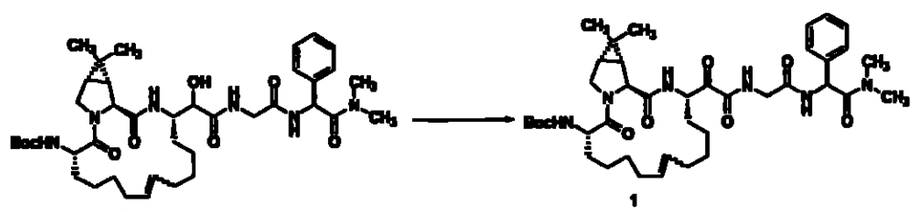


1k 1l

A solution of methyl ester 1k (50 mg, 0.078 mmol) in THF (2 mL), H_2O (2 mL) and CH_3OH (2 mL) was treated with $LiOH \cdot H_2O$ (20 mg, 0.5 mmol) and stirred at rt. for 2 h. After the completion of the reaction it was acidified with aq. HCl (2 mL) and concentrated in *vacuo*. The residue was dried in *vacuo* and used as it with out further purification.

The acid was dissolved in CH_2Cl_2 (2 mL), DMF (2 mL) and treated with H-Phg-$N(CH_3)_2 \cdot HCl$ (26 mg, 0.12 mmol), NMM (32 mg, 0.32 mmol) HATU (45 mg, 0.12 mmol) and stirred at 0 °C for 24 h. The yellow colored solution was concentrated in *vacuo* and diluted with CH_2Cl_2 (70 mL). The organic layers were washed with saturated aq. $NaHCO_3$, aq. HCl and brine. The reaction mixture was dried ($MgSO_4$) filtered concentrated in *vacuo* and used as it is in next step (47 mg).

Step K

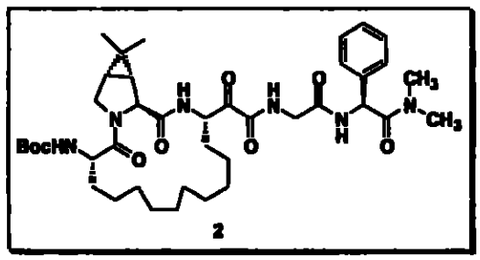


1l 1

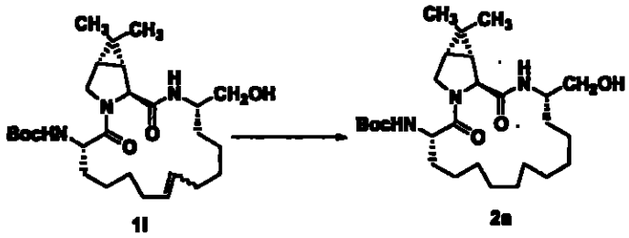
A solution of alcohol 1l (50 mg, 0.066 mmol) in CH_2Cl_2 (2 mL) was treated with Dess-Martin reagent (60 mg, 0.14 mmol) and stirred at rt. for 2 h. The reaction was diluted with aq Na2S2O3 solution and aq. $NaHCO_3$ solution (20 mL each) and extracted with CH_2Cl_2 (50 mL). The organic layer was washed with satd. $NaHCO_3$, brine, dried with $MgSO_4$ filtered concentrated in *vacuo* and purified by chromatography (acetone/hexanes 2:3) to yield 1 (22 mg) as a colorless solid.

MS (ESI), m/z, relative intensity 773 [$(M+Na)^+$, 80], 751 [$(M+1)^+$, 60], 651 (100).

Preparative Example 2

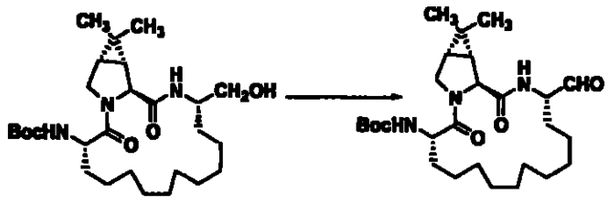


Step A



A solution of alcohol 1l (1.1g, 2.25 mmol) in methanol (30 mL) was treated with Pd/C (10% w/w, 100 mg) and hydrogenated at 60 psi for 3 h. The reaction mixture was filtered through a plug of celite, concentrated in *vacuo* to yield 2a which was used in the next step without further purification.

Step B

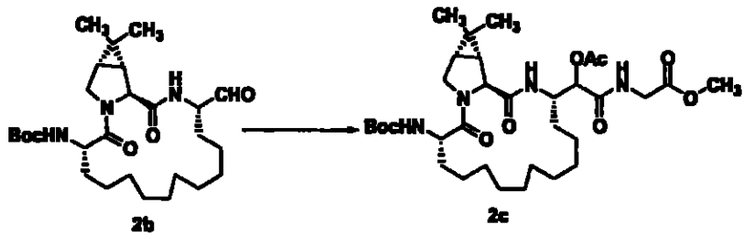


2a 2b

Crude **2a** from step A was oxidized using Dess-Martin reagent (1.14 g, 2.68 mmol) following the procedure similar to step H (preparative example 1) to yield **2b** (760 mg) as a colorless foam.

MS (ESI), m/z, relative intensity 1005 [$(2M+Na)^+$, 10], 530 [$(M+K)^+$, 20], 514 [$(M+Na)^+$, 90], 492 [$(M+1)^+$, 30], 436 (40), 392 (100).

Step C



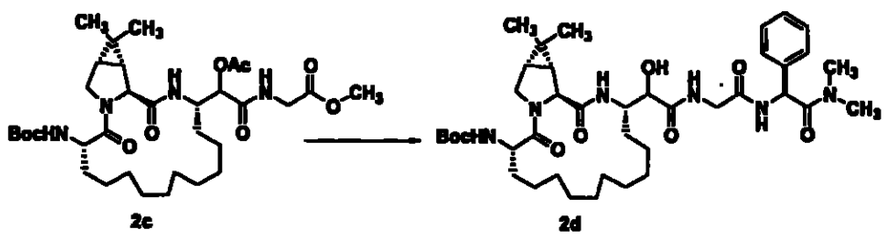
2b 2c

Compound **2b** (200 mg, 0.41 mmol) from step B was converted to **2c** (250 mg) using CH_3COOH (60 mg) and methylisocyanoacetate (99 mg, 1 mmol) following the procedure similar to step I (preparative example 1) as a mixture of diastereomers.

^{1}H NMR ($CDCl_3$, 300 MHz, mixture of diastereomers) 8.05, 7.93 (d, 1 H), 6.60 (d, 1 H, J=7.8 Hz), 5.20, 5.09 (d, 1 H), 4.58-4.49 (bt, 1 H), 4.34 (s, 1H), 4.34-4.31 (bt, 1H), 4.11-4.06 (m, 1H), 3.95-3.86 (m, 3 H), 3.73, 3.71 (s, 3 H), 2.21, 2.19 (s, 3H), 1.99-1.06 (m, 31 H), 0.99-0.94 (6 H).

MS (ESI), m/z, relative intensity 689 [$(M+K)^+$, 5], 673 [$(M+Na)^+$, 30], 651 [$(M+1)^+$, 35], 551 (100).

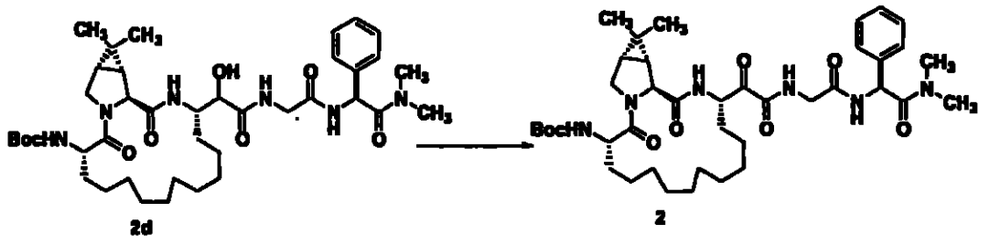
Step D



2c 2d

Methyl ester 2c (250 mg, 0.39 mmol) was hydrolyzed to acid using $LiOH \cdot H_2O$ (42 mg, 1 mmol) and coupled to H-Phg-$N(CH_3)_2 \cdot HCl$ (90 mg, 0.42 mmol) using NMM (126 mg, 1.26 mmol) and HATU (160 mg, 0.42 mmol) as outlined in preparative example 1, step J to yield crude 2d directly used for oxidation.

Step E

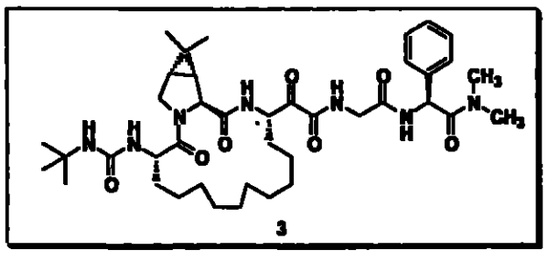


2d 2

Hydroxy amide 2d was oxidized using Dess-Martin reagent (200 mg, 0.48 mmol) which was purified by chromatography (SiO_2, acetone/CH_2Cl_2 1:4) to yield 2 (110 mg) as colorless solid.

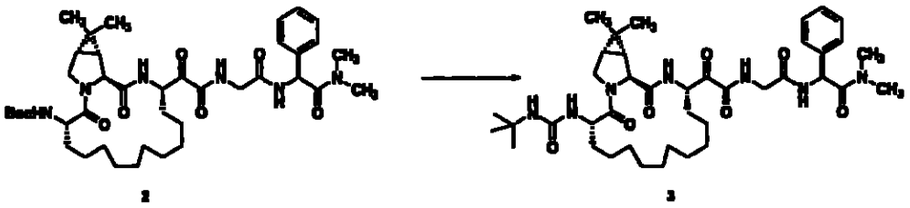
MS (ESI), m/z, relative intensity 775 [$(M+Na)^+$, 60], 753 [$(M+1)^+$, 50], 653 (100), 277 (80), 232 (60), 162 (30), 162 (40), 148 (80), 217 (95).

Preparative Example 3



3

Step A



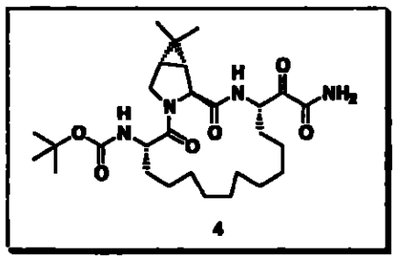
2 3

A solution of 2 (40 mg, 0.0053 mmol) in HCOOH (2 mL) was stirred at rt. for 2 h and concentrated in *vacuo*. The residue was repeatedly dissolved in toluene and dried in *vacuo* to remove residual formic acid. The residue was

dissolved in CH_2Cl_2/DMF (1 mL each) and treated with ^tBuNCO (10 µL) and NMM (15 µL) at 0° C and left in the refrigerator for 12 h. The reaction mixture was concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 1:2) to yield 3 (21 mg) as a colorless solid.

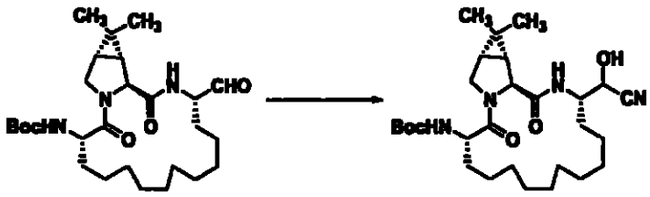
MS (ESI), m/z, relative intensity 774 [$(M+Na)^+$, 50], 752 [$(M+1)^+$, 70], 653 (90), 420 (30), 297 (30), 148 (100), 134 (40).

Preparative Example 4



4

Step A

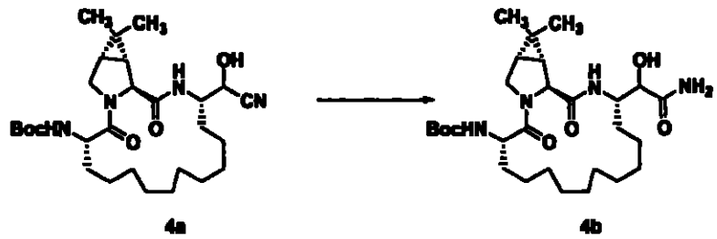


2b 4a

A solution of aldehyde **2b** (100 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was treated with Et_3N (50 mg, 0.5 mmol) and acetone cyanohydrin (43 mg, 0.5 mmol). The reaction mixture was stirred at rt. for 2 h and concentrated in *vacuo*. The residue was purified by chromatography (SIO2, acetone/hexanes 1:4) to yield **4a** (100 mg) as a colorless solid.

MS (ESI), m/z, relative intensity 541 [$(M+Na)^+$, 60], 519 [$(M+1)^+$, 10], 463 (30), 419 (100).

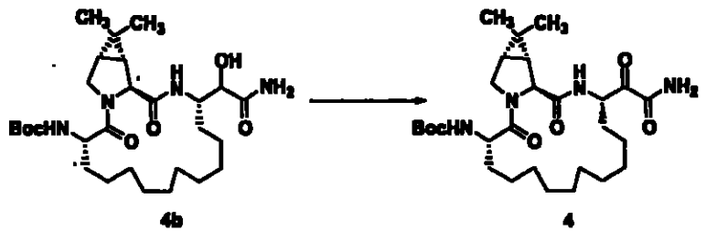
Step B



4a 4b

A solution of cyanohydrin 4a (100 mg, 0.2 mmol) in DMSO (3 mL) was treated with H_2O_2 (35%, 0.3 mL) and K_2CO_3 (43 mg, 0.3 mL) and stirred at rt. for 4 h. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with aq. $Na_2S_2O_3$ solution (10%, 30 mL) and brine (30 mL). The reaction mixture was dried (MgSO4) filtered concentrated in *vacuo* and directly used in step C without further purification.

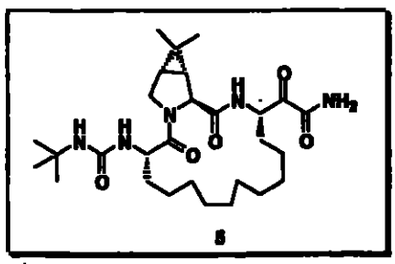
Step C



4b 4

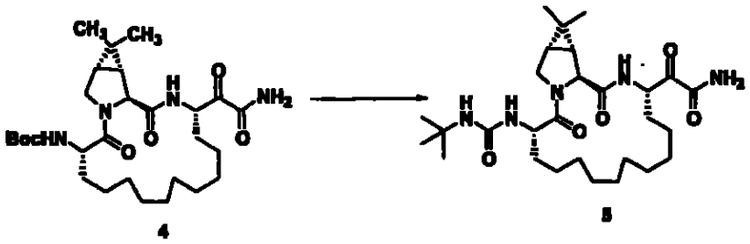
A solution of hydroxy amide 4b (100 mg, 0.18 mmol) in toluene/DMSO (1:1, 5 mL) at 0 °C was treated with EDCI (356 mg, 1.86 mmol) and $Cl_2CHCOOH$ (120 mg, 0.93 mmol) and stirred at 0 °C for 3 h. The reaction mixture was diluted with EtOAc (150 mL) and washed with satd. aq. $NaHCO_3$ (100 mL) and brine (100 mL). The ethyl acetate layer was dried ($MgSO_4$), concentrated and purified by chromatography (SiO_2, acetone/hexanes 2:3) to yield 4 (20 mg) as colorless solid MS (ESI), m/z, relative intensity 435 [$(M+1)^+$, 85], 390 (100).

Preparative Example 5



5

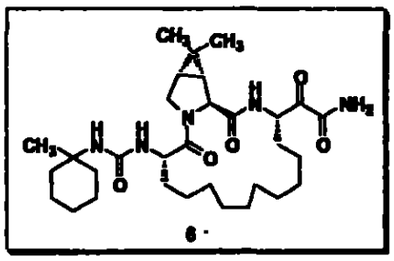
Step A



4 5

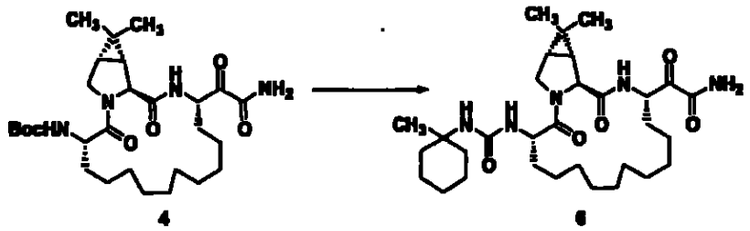
Carbamate 4 (40 mg, 0.1 mmol) was converted to urea 5 (7.5 mg) following the procedure similar to preparative example 3, Step A.

Preparative Example 6



6

Step A



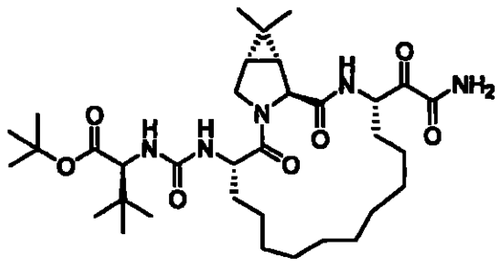
4 6

The synthesis of 6 was achieved using the similar procedure so synthesis of 5. A solution of 4 (180 mg 0.34 mmol) in HCOOH (3.0 mL) was stirred at rt. for 3 h an concentrated in *vacuo*. The residue was dried in *vacuo* and taken in CH_2Cl_2 (4 mL) and treated with methyl cyclohexylisocyanate (72 mg, 0.52 mmol) and Et_3N (52 mg, 0.52 mmol). The reaction mixture was stirred at 0 °C for 16 h and concentrated in *vacuo*. The residue was purified by chromatography (SiO_2, acetone/hexanes 1:3) to yield 6 (10 mg) as colorless solid

MS (ESI), m/z, relative intensity 574 [$(M+1)^+$, 20], 435 (100), 390 (50).

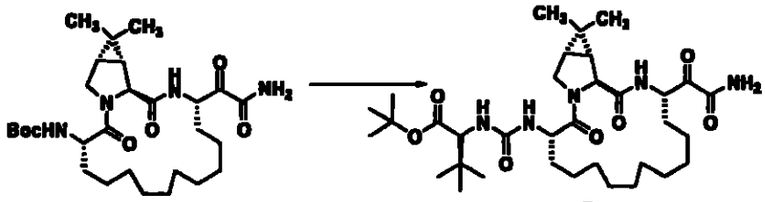
135 13/6

Preparative Example 7



7

Step A

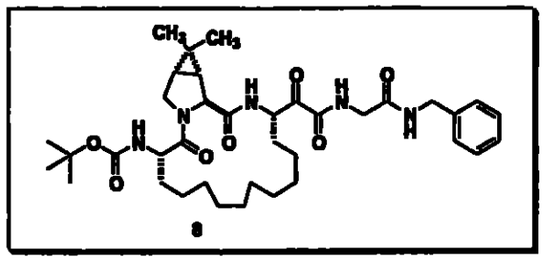


4 7

The synthesis of 7 was achieved using the similar procedure so synthesis of 5. A solution of 4 (180 mg 0.34 mmol) in HCOOH (3.0 mL) was stirred at rt. for 3 h and concentrated in *vacuo*. 50 mg (0.12 mmol) of this residue was dried in *vacuo* and taken in CH_2Cl_2 (4 mL) and treated with isocyanate of *tert*-butyl glycine *tert*butyl ester (74mg, 0.0.35 mmol) and Et_3N (35 mg, 0.0.35 mmol). The reaction mixture was stirred at 0 °C for 16 h and concentrated in *vacuo*. The residue was diluted with CH_2Cl_2 and washed with aq HCl, aq satd. $NaHCO_3$ and brine. The organic layers were dried ($MgSO_4$) and purified by chromatography (SiO_2, acetone/hexanes 1:3) to yield 7 (15 mg) as colorless solid.

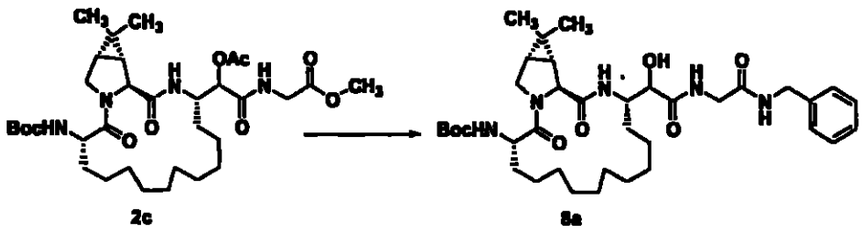
MS (ESI), m/z, relative intensity 648 [$(M+1)^+$, 45], 592 (25), 435 (100).

Preparative Example 8



8

Step A

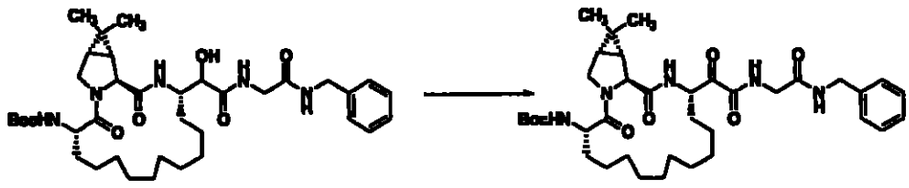


2c 8a

A solution of methyl ester 2c (100 mg, 0.15 mmol) in THF (2 mL), H_2O (2 mL) and CH_3OH (2 mL) was treated with $LiOH \cdot H_2O$ (41 mg, 1.0 mmol) and stirred at rt. for 2 h. After the completion of the reaction it was acidified with aq. HCl (2 mL) and concentrated in *vacuo*. The residue was dried in *vacuo* and used as it with out further purification.

The acid was dissolved in CH_2Cl_2 (2 mL), DMF (2 mL) and treated with benzyl amine (107 mg, 0.22 mmol), NMM (42 mg, 0.42 mmol) HATU (53 mg, 0.14 mmol) and stirred at 0 °C for 24 h. The yellow colored solution was concentrated in *vacuo* and diluted with CH_2Cl_2 (100 mL). The organic layers were washed with saturated aq. $NaHCO_3$, aq. HCl and brine. The reaction mixture was dried ($MgSO_4$) filtered concentrated in *vacuo* and used as it is in next step (63 mg).

Step B

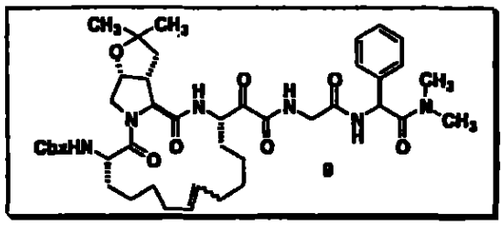


8a 8

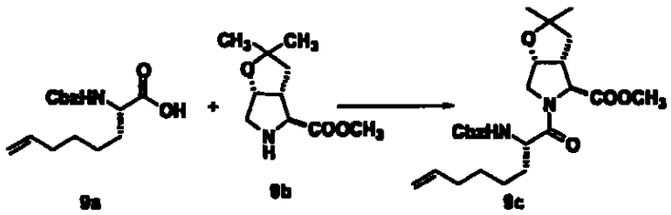
Hydroxyamide 8a (62 mg) in CH_2Cl_2 (3 mL) was treated with Dess-Martin reagent (62 mg, 0.15 mmol) and stirred at rt. for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and treated with aq. soln of $Na_2S_2O_3$ (10%, 25 mL) and satd. $NaHCO_3$ (25 mL) and stirred for 20 min. The aqueous layer was separated and extracted once again with CH2Cl2. The combined organic layers were dried ($MgSO_4$), filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 1:2) to yield 8 as a colorless solid (21 mg).

MS (ESI), m/z, relative intensity 704 [(M+Na)$^+$, 40], 682 [(M+1)$^+$, 20], 582 (100), 150 (70), 117 (30).

Preparative Example 9



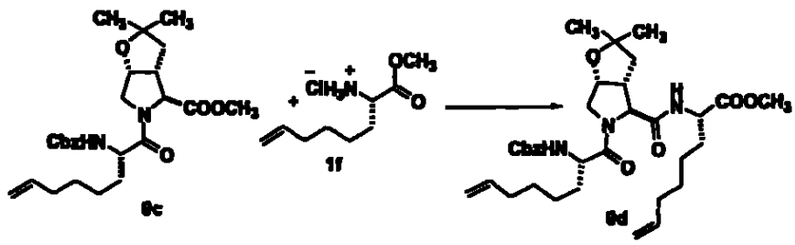
Step A



A solution of acid **9a** (3.6 g, 18.1 mmol), amine **9b** (5.53 g, 18.1 mmol) HATU (8.59 mmol, 22.62 mmol) and NMM in CH_2Cl_2 (50 mL), DMF (50 mL) was stirred at 0°C overnight. The reaction mixture was concentrated in *vacuo* and diluted with aq. HCl (1M, 500 mL) and extracted with CH_2Cl_2 (3x250 mL). The combined organic layers were washed with aq. HCl 500 ml), aqueous saturated $NaHCO_3$ (500 mL) brine (300 mL) and purified by chromatography (SiO_2, acetone/hexanes 1:4) to yield **9c** (6.7 g) as colorless solid.

MS (ESI), m/z, relative intensity 495 (M+Na)$^+$, 90], 473 [(M+1)$^+$, 60], 429 (70), 391 (40), 200 (100), 140 (30).

Step B

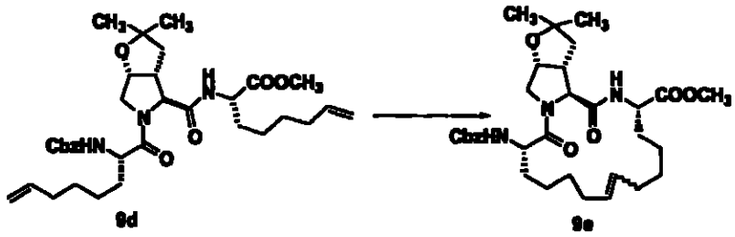


A solution of methyl ester **9c** (5.5 g, 11.59 mmol) in $CH_3OH/THF/H_2O$ (300 mL) was treated with $LiOH.H_2O$ (700 mg, 16.7 mmol) and stirred at rt. for 1.5 h. The reaction mixture was diluted with aq. HCl and extracted into CH_2Cl_2

(700 mL). The organic layer was dried with $MgSO_4$ filtered concentrated in *vacuo* and used as it is in subsequent steps.

A solution of crude acid in CH_2Cl_2 (50 mL), DMF (50 mL) was treated with HATU (5.5 g, 17.35 mmol), NMM (4.07 g, 40.32 mmol) and stirred at 0 °C for 24 h. The reaction mixture was concentrated in vacuo and taken in aq. HCl (300mL). The acidic layers was extracted into CH_2Cl_2 (2x200 mL) and the combined organic layers were washed with saturated NaHCO3, brine and purified by chromatography (SiO_2, acetone/hexanes 4:1) to yield **9d** (7.1 g) as a colorless solid.

Step c

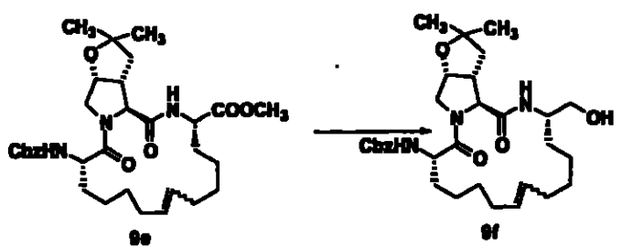


A solution of diene **9d** (2.0 g, 3.2 mmol) in CH2Cl2 (64 mL) was treated with Grubbs catalyst ($[(Cy)_3RuCl_2{=}CHC_6H_5$, 404 mg, 0.48 mmol) and stirred at rt. for 24 h. The reaction mixture was concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hex 1:3) to yield **9e** (1.1 g) as a brown solid and mixture of *E/Z* isomers.

^{1}H NMR ($CDCl_3$, 300 MHz) □, 7.36 (bm, 5 H), 7.13 (d, 1 H, 4.5 Hz), 5.73 (d, 1 H, J=8.1Hz), 5.28 (m, 2 H), 5.10 (s, 2 H), 4.75 (m, 1 H), 4.65 (m, 2 H), 4.52-4.46 (m, 1 H), 3.90 (bd, 1 H), 3.74 (s, 3 H), 3.61 (dd, 1 H, J= 15.6, 11.1 Hz), 3.44 (dd, 1 H, J=6.9, 7.2 Hz), 2.12-2.01 (m, 5 H), 1.79-1.67 (m, 3 H), 1.49-1.43 (m, 3 H), 1.36-1.34 (m, 4 H), 1.26 (bs, 5 H), 1.16 (bs, 3 H).

MS (ESI), m/z, relative intensity 606 [$(M+Na)^+$ 70], 584 (100), 540 (30).

Step D

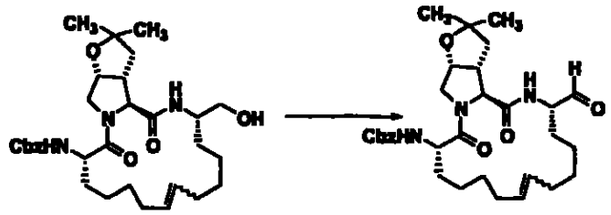


A solution of ester 9e (200 mg, 0.32 mmol) in dry THF (5 mL) was treated with $LiBH_4$ (2M soln. in THF, 0.32 mL) and stirred at rt. for 3 h. The reaction mixture was quenched with aqueous HCl (1M, 100 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were washed with aq. $NaHCO_3$ (100 ml) brine, dried with $MgSO_4$ filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 1:3) to yield 9f (2.1 g).

^{1}H NMR ($CDCl_3$, 300 MHz) δ.

MS (ESI), m/z, relative intensity 578 [$(M+Na)^+$, 40], 556 [$(M+1)^+$, 80], 512, (30), 295 (100).

Step E



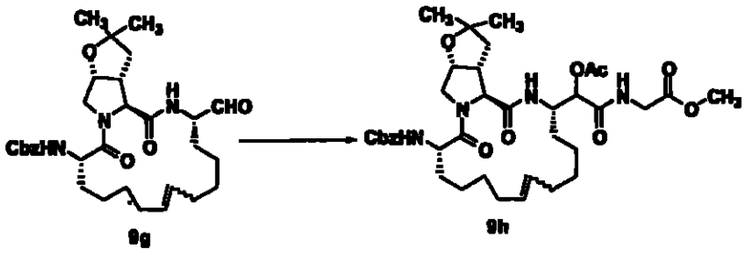
9f 9g

A solution of alcohol 9f (100 mg, 0.19 mmol), in CH_2Cl_2 (3 mL) was treated with Dess Martin reagent (106 mg, 0.25 mmol) and stirred at rt. for 2 h. The reaction mixture was quenched with $Na_2S_2O_3$ solution (10%, 10 mL) and saturated $NaHCO_3$ solution (10 mL) and stirred at rt. for 0.2 h. The reaction mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 3:1) to yield 9g (80 mg).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.52 (s, 1 H), 7.36 (bs, 5 H), 7.11 (d, 1 H, J=7.2 Hz), 5.67 (d, 1 H, J=7.8 Hz), 5.24-5.11 (m, 2 H), 5.11 (s, 2 H), 4.77-4.45 (m, 5 H), 3.92 (d, 1 H, J=12 Hz), 3.58 (dd, 1 H, J=6.6, 5.5 Hz), 3.51-3.46 (m, 1 H), 2.17-1.00 (m, 25 H).

MS (ESI), m/z, relative intensity 576 [$(M+Na)^+$, 15], 554 [$(M+1)^+$, 100], 510 (40).

Step F

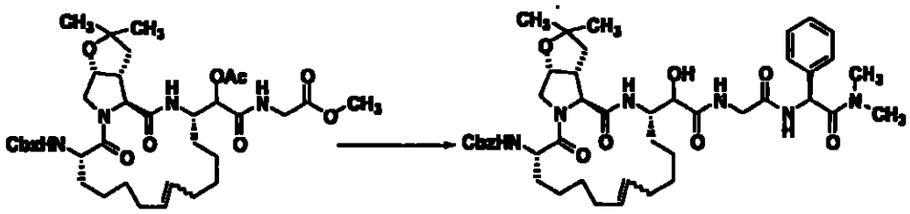


9g 9h

A solution of aldehyde.9g (80 mg, 0.15 mmol) in dry CH_2Cl_2 (2 mL) was treated with CH_3COOH (30 mg, 0.50 mmol) and methylisocyanoacetate (50 mg, 0.50 mmol). The reaction mixture was stirred at rt. for 24 h and concentrated in *vacuo*. The residue was purified by chromatography (SiO_2, acetone/hexanes 1:3) to yield **9h** as a mixture of diastereomers.

MS (ESI), m/z, relative intensity 735 [$(M+Na)^+$, 70], 713 [$(M+1)^+$, 100].

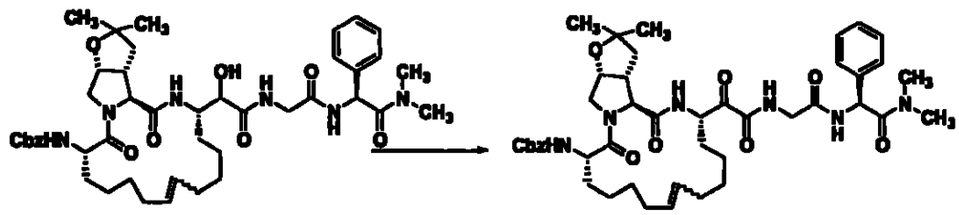
Step F



9h 9i

Methyl ester **9h** (600 mg, 0.92 mmol) was hydrolyzed to acid using $LiOH{\cdot}H_2O$ and coupled to H-Phg-$N(CH_3)_2$ ·HCl (235 mg, 1.09 mmol) using NMM (303 mg, 3.0 mmol) and HATU (437 mg, 1.15 mmol) as outlined in preparative example 1, step J to yield **9i** that was directly used for oxidation.

Step G

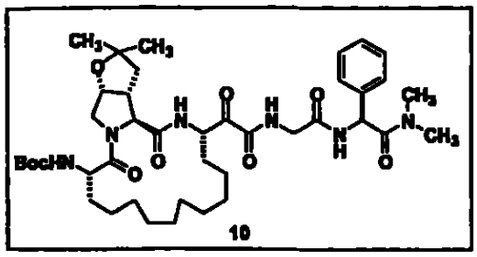


9i 9j

Crude **9j** (470 mg, 0.58 mmol) from step F was oxidized using Dess-Martin reagent (424 mg, 1.00 mmol) following the procedure similar to step H (preparative example 1) to yield **9j** (310 mg) as a colorless solid.

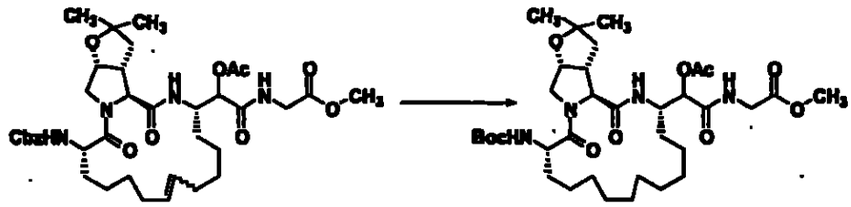
MS (ESI), m/z, relative intensity 869 [$(M+CH_3OH+Na)^+$, 100], 815 [$(M+1)^+$, 40], 770 (30).

Preparative Example 10



10

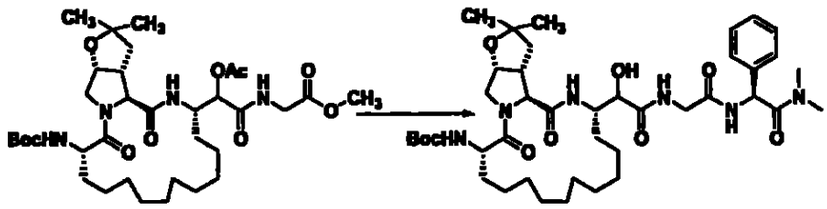
Step A



9h 10a

A solution of **9h** (200 mg, 0.3 mmol) in methanol (5 ml) was treated with Pd(OH)2/C (wet, 10%) and hydrogenated for 3h. The reaction mixture was filtered through a plug of celite and the filtrate was concentrated in vacuo. The residue was dissolved in methylene chloride and treated with ditertbutyldicarbonate (200 mg, 0.92 mmol). The reaction mixture was stirred at rt. for 24 h and purified by chromatography (SiO_2, acetone/Hexanes 1:2) to yield **10a** (85 mg) as a colorless solid.

Step B

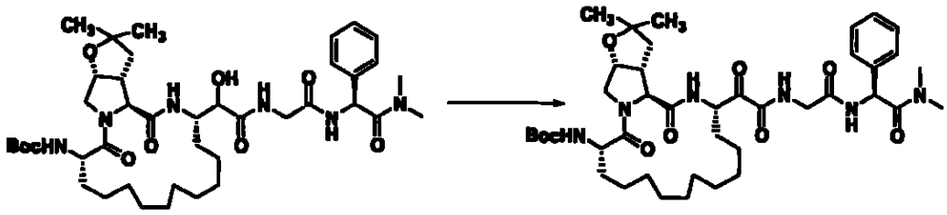


10a 10b

Methyl ester **10a** (80 mg, 0.15 mmol) was hydrolyzed to acid using $LiOH{\cdot}H_2O$ (41 mg, 1 mmol) and coupled to H-Phg-$N(CH_3)_2$ ·HCl (32 mg, 0.15 mmol) using NMM (40 mg, 0.40 mmol) and HATU (64.6 mg, 0.17 mmol) as

outlined in preparative example 1, step J to yield **10b** directly used for oxidation.

Step C

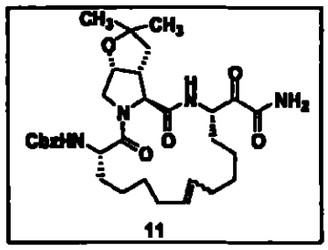


10b 10c

Hydroxy amide **10b** (60 mg, 0.08 mmol) was oxidized using Dess-Martin reagent (60 mg, 0.14 mmol) which was purified by chromatography (SiO_2, acetone/CH_2Cl_2 1:2) to yield **10c** (21 mg) as colorless solid.

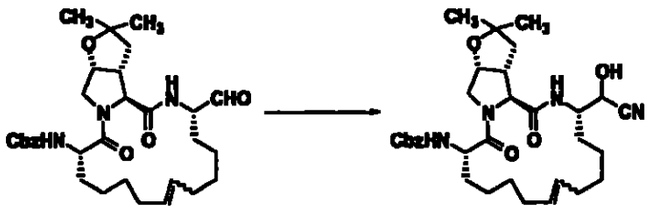
MS (ESI), m/z, relative intensity 805 [$(M+Na)^+$, 20], 783 [$(M+1)^+$, 20], 683 (30), 369 (40), 210 (70), 116 (100).

Preparative Example 11



11

Step A

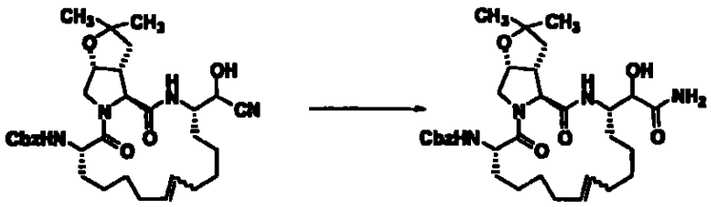


9g 11a

A solution of aldehyde **9g** (400 mg, 0.73 mmol) in CH_2Cl_2 was treated with Et_3N (150 mg, 1.5 mmol) and acetone cyanohydrin (170 mg, 1.5 mmol). The reaction mixture was stirred at rt. for 3 h and concentrated in *vacuo*. The residue was purified by chromatography (SiO_2, acetone/hexanes 1:4) to yield **4a** (286 mg) as a colorless solid.

MS (ESI), m/z, relative intensity 603 [(M+Na)$^+$, 60], 581 [(M+1)$^+$, 70], 464 (50), 420 (100).

Step B

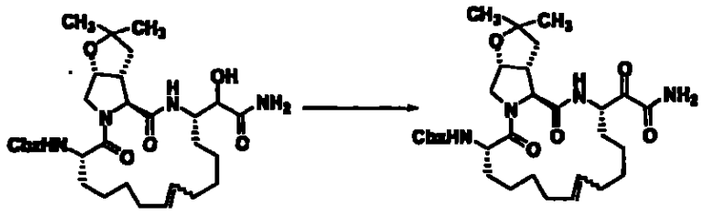


11a 11b

A solution of cyanohydrin **11a** (600 mg, 1.1 mmol) in DMSO (12 mL) was treated with H_2O_2 (35%, 1.0 mL) and K_2CO_3 (43 mg, 0.3 mL) and stirred at rt. for 8 h. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with aq. $Na_2S_2O_3$ solution (10%) and brine (30 mL). The reaction mixture was dried ($MgSO_4$) filtered concentrated in *vacuo* and directly used in step C without further purification.

MS (ESI), m/z, relative intensity 621 [(M+Na)$^+$, 70], 599 [(M+1)$^+$, 100], 554 (40).

Step C

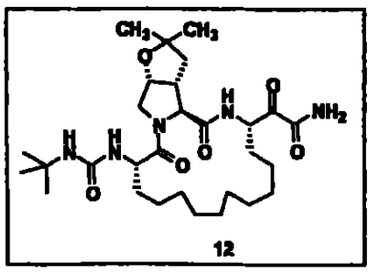


11b 11

A solution of hydroxy amide **11b** (320 mg, 0.54 mmol) in toluene/DMSO (1:1, 10 mL) at 0 °C was treated with EDCI (1.1 g, 5.40 mmol) and $Cl_2CHCOOH$ (350 mg, 2.7 mmol) and stirred at rt. for 4 h. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with satd. aq. $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), concentrated and purified by chromatography (SiO_2, acetone/hexanes 1:2) to yield **11** (173 mg) as colorless solid.

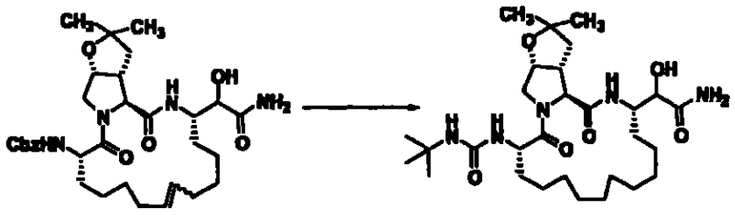
MS (ESI), m/z, relative intensity 619 [(M+1)$^+$, 20], 597 (100).

Preparative Example 12



12

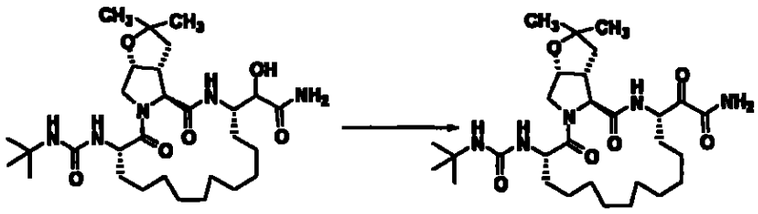
Step A



11a 11b

A solution of **11a** was hydrogenated using Pd/C and the amine obtained was dissolved in CH_2Cl_2 and treated with tert-butylisocyanide at 0 °C. The reaction mixture was stirred at rt. for 12 h and diluted with water. The reaction mixture was extracted with CH_2Cl_2 (30 mL) and combined organic layers were dried ($MgSO_4$) filtered concentrated in vacuo to obtain **11b** that was used in oxidation without further purification.

Step B



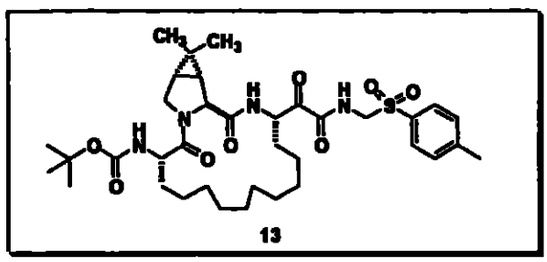
11b 12

A solution of hydroxy amide **11b** (320 mg, 0.54 mmol) in toluene/DMSO (1:1, 10 mL) at 0 °C was treated with EDCI (1.1 g, 5.40 mmol) and $Cl_2CHCOOH$ (350 mg, 2.7 mmol) and stirred at rt. for 4 h. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with satd. aq. $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), concentrated and purified by

chromatography (SiO_2, acetone/hexanes 1:2) to yield **11** (173 mg) as colorless solid.

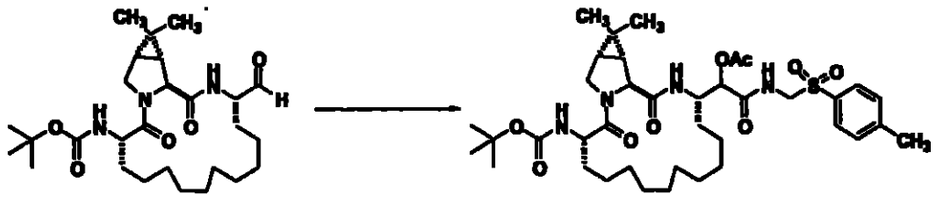
MS (ESI), m/z, relative intensity 619 [$(M+1)^+$, 20], 597 (100).

Preparative Example 13



13

Step A

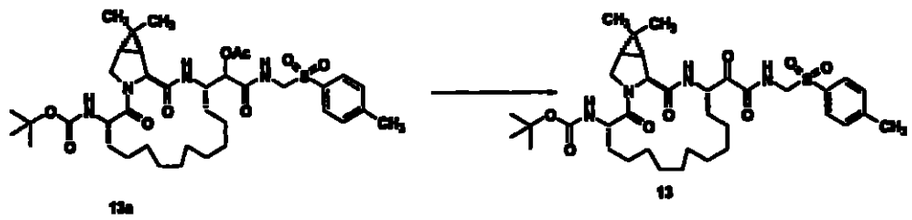


2b **13a**

A solution of aldehyde **2b** (50 mg, 0.1 mmol) in dry CH_2Cl_2 (5 mL) was treated with CH_3COOH (21 mg, 0.3 mmol) and TOSMIC (59 mg, 0.3 mmol, 3.0 eq.). The reaction mixture was stirred at rt. for 40 h and concentrated in *vacuo*. The residue was purified by chromatography (SiO_2, EtOAc/hexanes 2:3) to yield **1k** (60 mg) as a mixture of diastereomers.

MS (ESI), m/z, relative intensity 769 [$(M+Na)^+$, 30], 747 [$(M+1)^+$, 20], 647 (100).

Step B



13a **13**

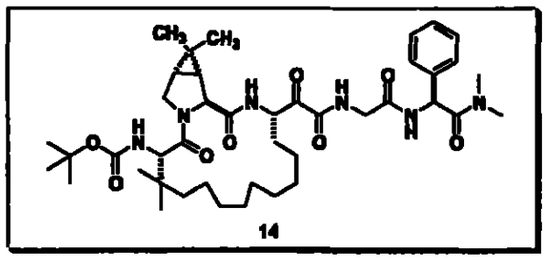
A solution of **13a** (60mg, 0.08 mmol) in methanol was treated with a 8 drops of concentrated HCl and stirred at rt for 12 h. The acetate ester was

hydrolyzed with partially deprotection of Boc group which was reprotected with ditertbutyldicarbonate (16 mg, 0.073 mmol).

The hydroxyamide (46 mg, 0.07 mmol) in CH_2Cl_2 was treated with Dess-Martin reagent (55 mg, 0.13 mmol) and stirred at rt for 10 min. Satd aq. $Na_2S_2O_3$ was added and reaction mixture was extracted into CH_2Cl_2 . The reaction mixture was dried ($MgSO_4$) filtered concentrated in vacuo and purified by chromatography to yield 13 (61 mg).

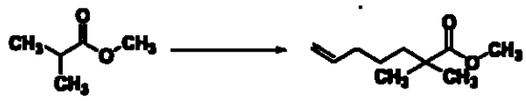
MS (ESI), m/z, relative intensity 703 [$(M+1)^+$, 11], 603 (100).

Preparative Example 14



14

Step A



14a

A solution of methylisobutyrate (2.0g, 19.5 mmol) in THF was added dropwise to a solution of KHMDS in THF (4.65 g, 23.5 mmol) at –78 °C and stirred for 0.5 h. The reaction mixture was treated with 5-bromo-1-pentene (3.5 g, 23.5 mmol) and shirred at rt. for 1 h. The reaction mixture was quenched with aq. HCl and extracted into ether (150 mL). The organic layer was dried ($MgSO_4$) filtered concentrated in vacuo and purified by chromatography (EtOAc/Hexane 1:19) to yield 2.1 g of **14b** as colorless liquid.

^{1}H NMR: ($CDCl_3$, 300 MHz) δ, 5.83-5.70 (m, 1 H), 5.00-4.91 (dd, 2 H), 3.65 (s, 3 H), 2.01 (dt, 2 H), 1.53-1.48 (m, 2 H), 1.35-1.30 (m, 2 H), 1.1 (s, 9 H).

Step B



14b 14c

A solution of ester (2. 6 g, 16 mmol) in ether (30 mL) was treated with $LiAlH_4$ (1M soln in THF, 20 mL) at –78 °C and warmed to rt. The reaction mixture was quenched with a solution of $KHSO_4$ and filtered through a plug of celite and $MgSO_4$. The filtrate was concentrated in vacuo and used as it is in the next step.

Step C



14c 14d

A solution of oxalyl chloride (1.48 g, 11.7 mmol) in dry CH_2Cl_2 was treated with DMSO (1.53 g, 19.5 mmol) at –78 °C and stirred for 15 min. To this mixture was added alcohol **14c** (1.1 g, 7.8 mmol) and stirred at –78 °C for 15 min. Triethyl amine (5.0 mL, 35.5 mmol) was added and the reaction mixture was warmed to rt. The reaction mixture was acidified and extracted with EtOAc (200 mL). The combined organic layers were washed with aq. HCl, dried (MgSO4) filtered, concentrated in vacuo and used in next reaction. ^{1}**H NMR** ($CDCl_3$, 300 MHz) δ 9.42 (s, 1 H), 5.82-5.68 (m, 1 H), 5.00-4.91 (m, 2 H), 2.03 (dt, 2 H), 1.48-1.23 (m, 4 H), 1.03 (s, 3 H).

Step D

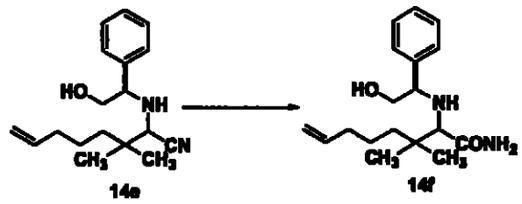


14d 14e

A solution of aldehyde **14d** (18g, 129 mmol) in CH_2Cl_2 (150 mL) was treated with (R)-phenyglycinol (20.33 g, 148.3 mmol) and stirred at 0 °C for 1 h. The reaction mixture was treated with TMS-CN (25.6g, 258 mmol) and stirred at rt. for 12 h. The reaction mixture was quenched with saturated aqueous NaHCO3 and extracted with EtOAc (3x150 mL). The combined organic layers were dried ($MgSO_4$) filtered concentrated in vacuo and the residue was dissolved in THF (100 mL) and treated with aq HCl (100 mL). The aqueous layer was basified with aq. NaOH (1 M) and extracted with (EtOAc, 450 mL). The combined organic layers were dried, filtered

concentrated in vacuo and purified with chromatography (SiO_2, EtOAc/Hexanes 6:1) to yield **14e** 21 g as a colorless oil.

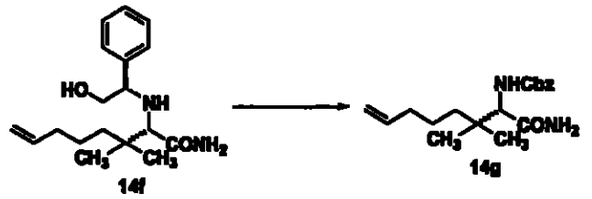
Step E



A solution of **14e** (20 g) in CH_3OH (200 mL) was treated with H_2O_2 (60 mL) and $LiOH.H_2O$ (5.88 g, 209.6 mmol) at 0 °C. The reaction mixture was stirred at rt. for 12 h and cooled to 0°C and carefully quenched with aq. $Na_2S_2O_3$ solution (10%). The reaction mixture was concentrated in vacuo and the aq. layer was extracted with EtOAc (600 mL). The combined organic layers were washed extensively with aq. $Na_2S_2O_3$, dried ($MgSO_4$) concentrated in vacuo and purified by crystallization (EtOAc/Hexanes) to yield pure diastereomer directly used in the next reaction.

^{1}**H NMR** ($CDCl_3$, 300 MHz) δ 7.30 (bs, 5 H), 6.25 (s, 1 H), 6.17 (s, 1 H), 5.79-5.66 (m, 2 H), 4.98-4.89 (m, 2 H), 3.71-3.60 (m, 3 H), 2.68 (bs, 1 H), 1.98-1.90 (3 H), 1.03 (s, 3 H), 0.99 (s, 3 H), 1.03-0.99 (m, 1 H).

Step F



A solution of amide **14f** (8.00g, 26.3 mmol) in CH_2Cl_2 (160 mL), CH3OH (80 mL) at 0°C was treated with $Pb(OAc)_4$ (13.45 mmol, 30.3 mmol), at 0° C for 1 h. the yellow solution was treated with aq. $NaHCO_3$ (250 mL, and stirred for 15 min. The reaction mixture was filtered and concentrated in vacuo. The mostly aqueous layer was extracted in CH_2Cl_2 (3x300 mL) concentrated in vacuo and directly used in further reaction.

A solution of the crude imine was taken in THF (200 mL) and treated with aq HCL (1 M, 200 mL) and stirred at rt. for 1 h. The reaction mixture was

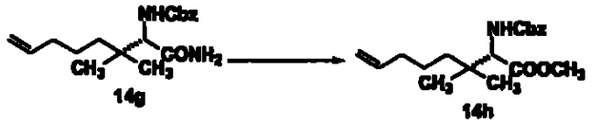
concentrated in vacuo and extracted with Ether (2x250 mL). The aqueous layer was basified with aq. NaOH (50%) at 0 °C and extracted with CH_2Cl_2 (600 mL). The combined organic layers were extracted with brine, dried (MgSO4) filtered concentrated in vacuo and directly used in the next reaction.

The residue was dissolved in CH_2Cl_2 (200 mL) and cooled to –78°C and treated with NMM (4.2 g, 40 mmol) and Cbz-Cl (5.4g, 31.58 mmol). The reaction mixture was stirred at rt. for 12 h and washed with aq. HCl . The organic layer was separated and the aq. layer was extracted with CH_2Cl_2 (200 mL) The combined organic layers were extracted with brine, dried and purified by chromatography (SiO_2, EtOAc/Hexanes 2:3) to yield **14g** (6.8 g) as a colorless solid.

^{1}**H NMR** ($CDCl_3$, 300 MHz) δ 7.37-7.30 (m, 5 H), 6.23 (bs, 1 H), 5.86 (bs, 1 H), 5.82- 5.64 (m, 1 H), 5.63 (d, 1 H, J= 9.3 Hz), 5.12-4.93 (m, 4 H), 4.07 (d, 1 H, J=9 Hz), 2.0-1.9(m, 2 H), 1.42- 1.30 (m, 4 H), 0.96 (s, 6 H).

MS (ESI), m/z, relative intensity 341[M+Na)$^+$, 100], 319 [(M+1)+, 30], 274 (50), 230 (70), 213 (30), 140 (30).

Step G



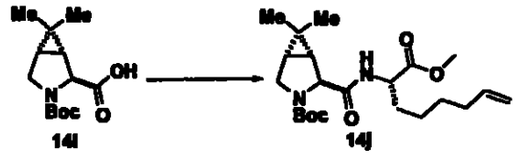
A solution of amide **14 g** (6.8 g, 21.4 mmol) in CH_2Cl_2 (200 mL) was treated with Me_3OBF_4 (10.36 g, 69.9 mmol) and K_3PO_4 (12.11 g, 69.52 mmol) and stirred at rt. for 12 h. The reaction mixture was concentrated in vacuo and dissolved in CH_3OH (280 mL) and aq. HCl (140 mL, 1 M) and heated at reflux for 1 h. The reaction mixture was concentrated and the aqueous layer was further extracted with CH_2Cl_2 (3x150 mL). The combined organic layers were dried ($MgSO_4$), filtered concentrated in vacuo and purified by chromatography (SiO_2, EtOAc/hexanes 1:19) to yield **14h** (5.6g) as colorless oil

^{1}**H NMR** ($CDCl_3$, 300 MHz) δ 7.36 (bs, 5 H), 5.85-5.71 (m, 1 H), 5.32 (d, 1 H, J=9.9 Hz), 5.10 (dd, 2 H, J= 12, 3.9 Hz), 5.03-4.93 (m, 2 H), 4.27 (d, 1 H, J=9.9 Hz), 3.72 (s, 3 H), 2.05—1.98 (m, 2 H), 1.47-1.24 (m, 4 H), 0.93 (s, 9 H).

150 155

MS (ESI), m/z, relative intensity 356 [M+Na)$^+$, 95], 334 [(M+1)+, 10], 290 (100), 230 (60), 213 (20).

Step H

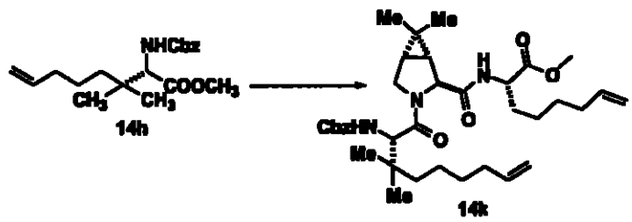


A solution of acid 14i (4.5g, 17.64 mmol) and amine 1f (3.66 g, 17.64 mmol) in CH_2Cl_2 (50 mL), DMF (50 mL) at 0° C was treated with HATU (8.39 g, 22.05 mmol) and NMM (5.35 g, 52.92 mmol) and stirred overnight at 0° C. The reaction mixture was concentrated in *vacuo* and diluted with 450 mL of CH_2Cl_2. The aqueous layer was washed with aq. HCl (1M, 2x300 mL), aq. $NaHCO_3$ (1M, 2x300 mL). The organic layers were dried with $MgSO_4$, filtered concentrated in *vacuo* and purified by chromatography (SiO_2, Acetone/Hexanes 5:1) to yield 14j as a colorless oil (5.8 g).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.03, 6.39 (d, 1 H, J = 7.5 Hz), 5.8-5.7 (m, 1 H), 4.99-4.90 (m, 2 H), 4.66 –4.54 (m, 1 H), 3.72 (s, 3 H), 3.62-3.42 (m, 2 H), 2.01 (bs, 2 H), 1.88-1.63 (m, 4 H), 1.61, 1.43 (s, 9 H), 1.6-1.3 (m, 4 H), 1.02 (s, 3 H), 0.90 (s, 3H).

MS (ESI), m/z, relative intensity 431 [(M+Na)$^+$, 60], 409 [(M+1)$^+$, 40], 353 (40), 309 (100), 110 (80).

Step I



A solution of ester 14h (5.4g, 16.2 mmol) in H_2O (30 mL), THF (30 mL) and CH_3OH (30 mL) was stirred with $LiOH·H_2O$ (1.36 g, 32.42 mmol) for 24 h and concentrated in vacuo. The aqueous layer was acidified with aq. HCl (1M) and extracted into CH_2Cl_2 (400 mL). The combined organic layers were dried ($MgSO_4$), filtered concentrated in vacuo and used as it is in further reactions.

151 152

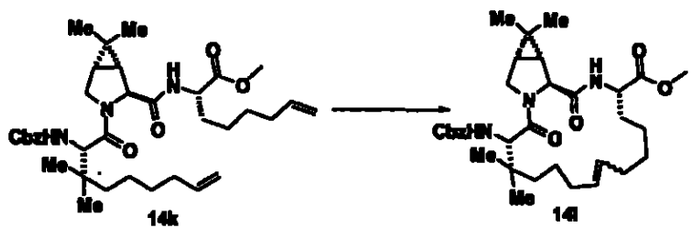
A solution of acid (4.0 g, 12.5 mmol) and deprotected amine* in CH_2Cl_2 (30 mL), DMF (30 mL) at 0° C was treated with HATU (7.15 g, 18.79 mmol) and NMM (4.5 g, 45.0 mmol) and stirred at 0° C for 48 h, and 25°C for 24 h. The reaction mixture was concentrated in *vacuo* and diluted with 300 mL of CH_2Cl_2. The aqueous layer was washed with aq. HCl (1M, 3x100 mL), aq. $NaHCO_3$ (satd, 3x100 mL). The organic layers were dried with $MgSO_4$, filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hexanes 3:1) to yield 14k as a colorless oil (4 g of pure 14k and 2 g of partially impure 14k).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.32 (bs, 5 H), 6.92 (d, 1H, J=7.5Hz), 5.48-5.69 (m, 2 H), 5.37 (d, 1 H, J=9.9 Hz), 5.08-4.92 (m, 6 H), 4.56-4.33 (M, 1 h), 3.97-3.93 (m, 2 H), 3.84-3.80 (m, 2 H), 3.74 (s, 3 H), 2.03-1.97 (m, 4 H), 1.86-1.87-1.39 (m, 12 H), 1.12 (s, 3 H), 0.98 (s, 6 H), 084 (s, 3 H)

MS (ESI), m/z, relative intensity 632 [$(M+Na)^+$, 20], 610 [$(M+1)^+$, 100], 309 (60).

* Amine was obtained by the deportation of 14j with 4 M HCl in dioxane.

Step J

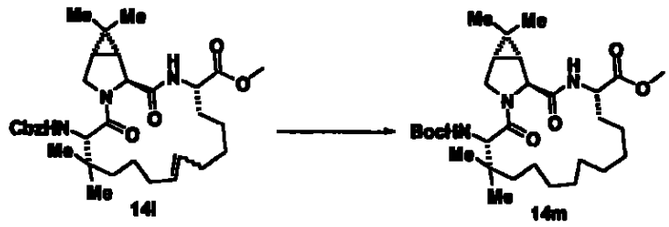


A solution of diene 14k (4.00 g, 6.57 mmol) in CH_2Cl_2 (65.0 mL) at rt. was saturated with N_2 and treated with Grubbs catalyst (551 mg, 0.657 mmol) and stirred for 24 h. The reaction mixture was concentrated in vacuo and purified by chromatography (SiO_2, EtOAc/hexanes 1:3) to yield 14l (1.7 g) as a tan colored solid.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.31 (bs, 5 H), 7.08 (d, 1 H, J = 7.8 Hz), 5.43 (d, 1 H, J = 10.2 Hz), 5.28 (m, 2 H), 5.13-5.02 (m, 2 H), 4.56-4.32 (m, 1 H), 4.49-4.28 (m, 2 H), 3.96-3.79 (m, 2 H), 3.74 (s, 9 H), 2.05-1.29 (m, 16 H), 1.0 (s, 3 H), 0.96 (s, 3 H), 0.94 (s, 3 H), 0.86 (s, 3 H).

MS (ESI), m/z, relative intensity 550 [$(M+1)^+$, 50], 450 (100).

Step K

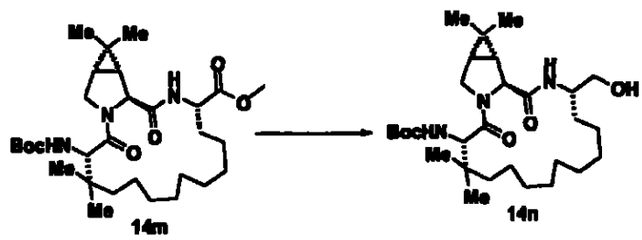


A solution of alkene **14l** (200 mg, 0.35 mmol) in CH3OH (2 0 mL) was treated with Pd/C (5%, 200 mg), ditertbutyldicarbonate (200 mg, 0.92 mmol) and hydrogenated at rt. for 12 h. The reaction mixture was filtered through a plug of celite and concentrated in vacuo. The reaction mixture was purified by chromatography (SiO_2, acetone/hexanes 1:5) to yield **14m** (81 mg).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.84 (d, 1 H, J=7.8 Hz), 5.14 (d, 1 H), 4.61-4.55 (m, 1 H), 4.31 (s, 1 H), 4.22 (d, 1 H, J=10 Hz), 4.03 (d, 1 H, J=10.5 Hz), 3.88-3.85 (m, 1 H), 3.75(s, 3 H), 1.89-1.76 (m, 1 H), 1.59-1.76 (m, 28 H), 1.02 (s, 3 H), 0.97 (s, 3 H), 0.94 (s, 3 H), 0.86 (s, 3 H).

MS (ESI), m/z, relative intensity 610 [$(M+AcOH+1)^+$, 40], 550 [$(M+1)^+$, 50], 450 (100), 309 (20).

Step L

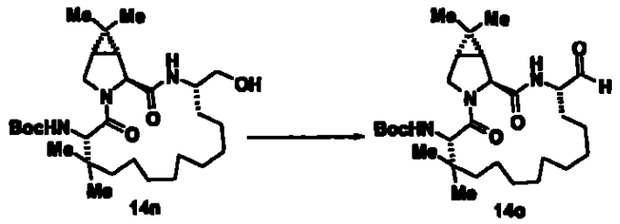


A solution of ester **14m** (80 mg, 0.15 mmol) in dry THF (2 mL) was treated with $LiBH_4$ (2M soln. in THF, 0.1 mL) and stirred at rt. for 4 h. The reaction mixture was quenched with aqueous HCl (1M, drops) and extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were washed with aq. $NaHCO_3$ (100 ml) brine, dried with $MgSO_4$ filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 1:3) to yield **14n** (70 mg) as an amorphous solid.

153 154

MS (ESI), m/z, relative intensity 544 [(M+Na)$^+$, 30], 522 [(M+1)$^+$, 40], 422 (100).

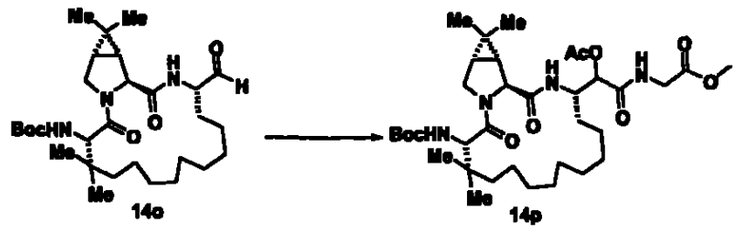
Step M



A solution of alcohol **14n** (30 mg, 0.05 mmol), in CH_2Cl_2 (2 mL) was treated with Dess Martin reagent (30 mg, 0.07 mmol) and stirred at rt. for 2 h. The reaction mixture was quenched with $Na_2S_2O_3$ solution (10%, 10 mL) and saturated $NaHCO_3$ solution (10 mL) and stirred at rt. for 0.5 h. The reaction mixture was extracted with CH_2Cl_2 (3x10 mL). The organic layer was dried with $MgSO_4$, filtered concentrated in *vacuo* and used as it is in further reaction.

MS (ESI), m/z, relative intensity 552 [(M+1)$^+$, 100], 248 (40).

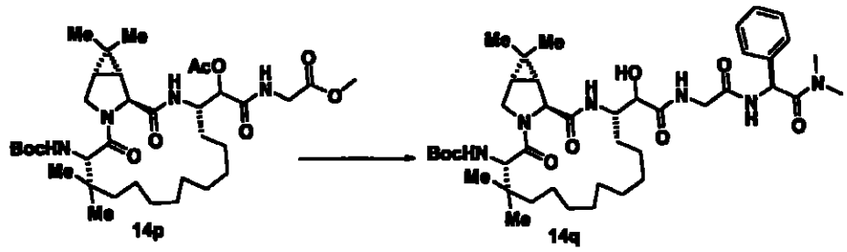
Step N



Compound **14o** from step M was converted to **14p** (40 mg) using CH_3COOH (20 □L) and methylisocyanoacetate (20 □L) following the procedure similar to step I (preparative example 1) as a mixture of diastereomers..

MS (ESI), m/z, relative intensity 711 [(M+1)$^+$, 100], 240 (20).

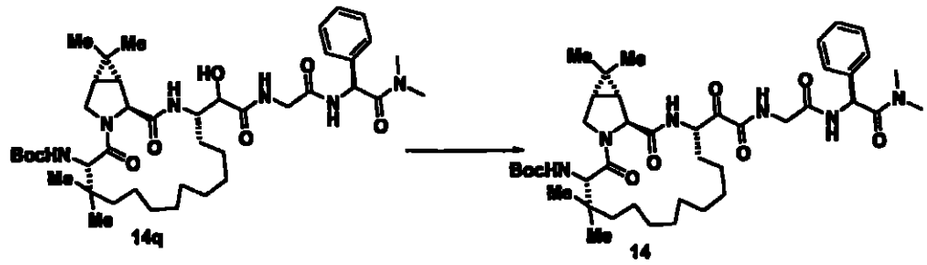
Step O



A solution of methyl ester **14p** (80 mg, 0.12 mmol) in THF (3 mL), H_2O (3 mL) and CH_3OH (3 mL) was treated with $LiOH \cdot H_2O$ (41 mg, 1 mmol) and stirred at rt. for 2 h. After the completion of the reaction it was acidified with aq. HCl (15 mL) and extracted with CH2Cl2 (3x30 mL). The combined organic layers were dried (MgSO4), filtered and concentrated in *vacuo*. The residue was dried in *vacuo* and used as it with out further purification.

The acid was dissolved in CH_2Cl_2 (2 mL), DMF (2 mL) and treated with H-Phg-N$(CH)_2$ ·HCl (40 mg, 0.2 mmol), NMM (40 mg, 0.4 mmol) HATU (68 mg, 0.16 mmol) and stirred at 0 °C for 24 h. The yellow colored solution was concentrated in *vacuo* and diluted with CH_2Cl_2 (75 mL). The organic layers were washed with saturated aq. $NaHCO_3$, aq. HCl and brine. The reaction mixture was dried ($MgSO_4$) filtered concentrated in *vacuo* and used as it is in next step (90 mg).

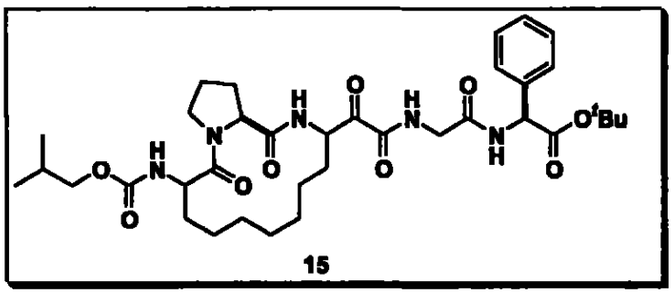
Step P



A solution of alcohol **14q** (90 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) was treated with Dess-Martin reagent (100 mg, 0.24 mmol) and stirred at rt. for 2 h. The reaction was diluted with aq $Na_2S_2O_3$ solution (30 mL) and aq. $NaHCO_3$ solution (30 mL each) and extracted with CH_2Cl_2 (50 mL). The organic layer was washed with satd. $NaHCO_3$, brine, dried with $MgSO_4$ filtered concentrated in *vacuo* and purified by chromatography (acetone/hexanes 2:3) to yield **14** (22 mg) as a colorless solid.

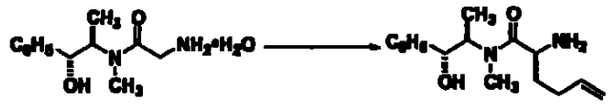
MS (ESI), m/z, relative intensity 813 [(M+1)$^+$, 100], 768 (20).

Preparative Example 15



15

Step A



1a 15a

To 45 mL THF, diisopropylamine (4.70 mL, 33.51 mmol, 2 eq.) and LiCl (4.26 g, 6 eq) at –78 ^{0}C was added nBuLi (20.4mL, 1.95 eq) under nitrogen atmosphere. 10 min later, the solution of 1a/30 mL THF was transferred to the above solution over 10 min. After 20 min, the brownish yellow mixture was warmed up to 0 ^{0}C. Another 20 min later, the solution became opaque bright yellow and 4-Iodo-1-butene (3.35 g, 1.1 eq) was added in dropwise. The solution became even brighter and 60 min later 115 mL 1 M HCl was added to quench the reaction. The THF was removed and 150 mL EtOAc was added in for extraction. The organic layer was further washed with 115 mL 1M HCl. The aqueous layers were combined and adjusted to pH 14 by 6M NaOH at 0^{0}C. Extraction was done with dichloromethane 110 mL x 4. The organic layer was dried over sodium carbonate. Filtration through celite and removal of the solvent afforded 4 g of the oil which upon standing, became solid. Flash chromatography with 5:5:90 Et_3N/MeOH/DCM provided 2.63 g pure **15a** in 57 % yield. (R_f = 0.64, 5:5:90 Et_3N/MeOH/DCM)

^{1}H NMR (4: 1 rotamer ratio. * denotes minor rotamer peaks. $CDCl_3$): δ 0.96* (d, 3H, J = 6.7 Hz) 1.15 (d, 3H, J = 6.9 Hz) 1.45-1.55 (m, 2H) 2.05-2.20 (m, 2H) 2.80 (s, 3H) 2.92* (s, 3H) 3.55-3.60 (m, 2H) 4.00* (m, 1H) 4.35-4.45*

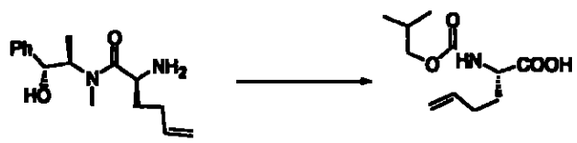
(m, 1H) 4.60-4.65 (m, 2H) 4.92-5.02 (m, 2H) 5.68-5.80 (m, 1H) 7.20-7.40 (m, 5H).

^{13}C NMR($CDCl_3$): δ 11.26 15.68 31.11 35.67 47.17 52.22 76.92 116.46 127.50 128.67 129.34 138.60 143.19 178.08.

MS: $C_{18}H_{24}N_2O_2$: 277 $(M+H)^+$;

HRMS: calcd: 277.1916; found: 277.1917.

Step B



15a 15b

1.9 g of 15a (6.88 mmol, 1 eq) was treated with 2N NaOH (7.0 mL, 2 eq), 7 mL of water and refluxed at 100 ^{0}C for 3 h. The mixture was cooled to room temperature. 20 mL of DCM, 10 mL of water was added and the organic layer was separated. The aqueous layer was washed with 20 mL of DCM. The combined organic layers were further washed with 10 mL of water. The combined aqueous layer was treated with 1.3 mL 12 N HCl. 20 mL of dioxane was added and the solution was adjusted to pH 8-9 by adding saturated $NaHCO_3$. 1.48 g of iBOC-OSU (1 eq) was added and the mixture was stirred for overnight. After decreasing the solvent volume to one half, 10 mL of water and 10 mL DCM was added for extraction. The aqueous layer was then treated with 12 N HCl dropwise until it precipitated (pH 2). Extraction with EtOAc 40 mL x 2 followed by $MgSO_4$ drying and cellte filtration afforded 1.52 g colorless oil 15b in 90 % yield.

^{1}H NMR($CDCl_3$): δ 0.88 (d, 6 H, J = 6.6 Hz) 1.78-2.00 (m, 3 H) 2.10-2.20 (m, 2 H) 3.80-3.82 (m, 2 H) 4.40 (m, 1 H) 5.00-5.06 (m, 2 H) 5.10 (m, 1 H) 5.80 (m, 1 H).

^{13}C NMR($CDCl_3$): δ 20.0 26.2 29.0 32.8 54.2 72.8 117.0 138.0 157.8 177.6.

MS for $C_{11}H_{19}NO_4$: 230 $(M+H)^+$.

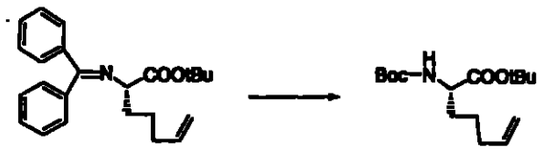
Step C



15c 15d

Imine 15c (9.42 g, 31.88 mmol, 1 eq) was mixed with the Corey's catalyst (*J. Am. Chem. Soc.*, 1997, *119*, 12414) (1.93 g, 0.1 eq), cesium hydroxide monohydrate (53.55 g, 10 eq) in 150 mL DCM. The solution was cooled down to –60 ^{0}C followed by addition of 5-iodo-1-pentene (25 g, 4 eq) under nitrogen. The crude was stirred for 60 h when 100 mL ethyl ether was added in. After washing with water 100 mL x 2 and brine 70 mL x 1, the organic layer was dried over $MgSO_4$. Celite filtration and removal of the solvent afforded the crude 28.56 g. 5.1 g of the crude was chromatographed with pure hexane first and then 1 : 40 to 1:20 EtOAc/hexane. A 2.56 g of a mixture of 15d, 5-iodo-1-pentene and benzophenone (1 : 2.5 : 0.8) was obtained. (15d: R_f = 0.39, 1 : 20 EtOAc/hexane.)

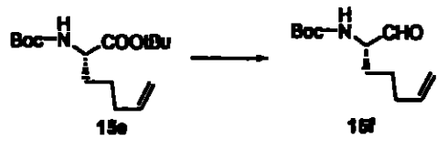
Step D



15d 15e

0.5 g of the above crude 15 d (2.56 g) was treated with 4 mL HOAc/THF/water 1 : 1 : 1 for 90 min when TLC shows disappearance of the starting material. Two pipetful of saturated $NaHCO_3$ was added. 10 mL water and 20 mL hexane was added for extraction. The aqueous layer was then further basified to pH 9-10. $(Boc)_2O$ (0.15 g) and dioxane 4 mL were added and after 2.5 h, the solvent was removed and the pH of the solution was adjusted to 3-4. Extraction with ether followed by chromatography with 1: 10 EtOAc/hexane afforded 0.16 g of 15e in 48 % overall yield from 15c. (R_f = 0.44, 1 : 10 EtOAc/hexane.)

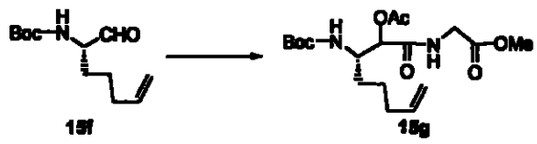
Step E



15e 15f

4.88 g of 15e (13.87 mmol) was dissolved in 20 mL of toluene at –78 ^{0}C and was treated with 21 mL $LiAlH_4$ (1 M in Et_2O, 1.6 eq) for 40 min. The mixture was warmed up to 0^{0}C and was quenched by EtOAc and 20 mL 5 % $NaHSO_4$. Extraction with ether, filtration through celite and removal of solvent afforded the residue which was chromatographed with 1/5 EtOAc/hexane. 2.8 g of the desired aldehyde 15f (R_f = 0.4) along with the alcohol (1.43 g, R_f = 0.04) were obtained. The latter could be converted to the aldehyde by Dess-Martin reaction.

Step F



15f 15g

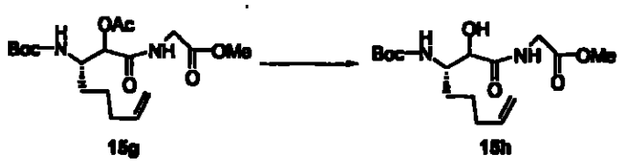
1.26 g of 15f (5.55 mmol, 1 eq), methyl isocyanoacetate (0.50 mL, 1 eq), acetic acid (0.32 mL, 1 eq) were mixed in 20 mL DCM and stirred for 80 h. Removal of the solvent and flash chromatography provided 1.10 g of 15g in 51 % yield. (R_f = 0.29, 1:1 EtOAc/hexane).

^{1}H NMR($CDCl_3$): δ 1.42 (s, 9 H) 1.50-1.60 (m, 2 H) 1.99-2.20 (m, 4 H) 2.18 (s, 3 H) 3.76 and 3.78 (two singlets, 3 H, 1 : 1 diastereomers) 3.90-4.20 (m, 4 H) 4.90-5.00 (m, 2 H) 5.20 (br s, 1 H) 5.70 (m, 1 H) 6.62 (br s, 1 H).

^{13}C NMR($CDCl_3$): δ 21.93 26.26 29.46 31.25 34.41 41.99 52.53 53.50 75.57 80.41 115.74 139.14 156.28 168.91 169.38 170.79.

HRMS for $C_{18}H_{30}N_2O_7$: calcd: 387.2131 $(M+H)^+$; found 387.2133.

Step G



15g 15h

Compound 15g (1.08 g, 2.8 mmol, 1 eq), 60 mg K_2CO_3 (0.15 eq) in 6 mL MeOH were stirred at room temperature for 1 h and then another 2 h at

40°C. Removal of solid followed by flash chromatography afforded the desired product **15h** as white solid (0.65 g, 68 % yield).

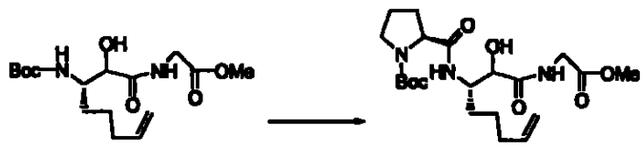
^{1}H NMR($CDCl_3$): δ 1.40 (s, 9 H) 1.40-1.70 (m, 4 H) 1.99-2.10 (m, 2 H) 3.70(s, 3 H) 3.80 (br, 1 H) 4.00-4.25 (m, 4 H) 4.90-5.00 (m, 2 H) 5.10 (br s, 1 H) 5.30 (m, 1 H) 5.78 (m, 1 H) 7.40 (br s, 1 H).

^{13}C NMR($CDCl_3$): δ 26.83 29.48 30.76 34.53 42.03 53.51 54.95 75.05 81.07 115.76 139.30 157.92 170.84 174.16.

$C_{16}H_{28}N_2O_6$: 345 $(M+H)^+$.

HRMS: calcd: 345.2026; found: 345.2033.

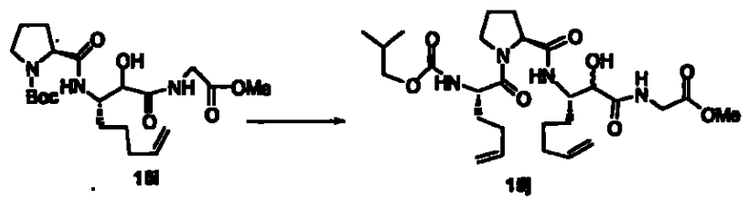
Step H



15h 15i

Compound **15h** (0.39 g, 1.13 mmol) was stirred with 4 M HCl in dioxane (4 mL) at room temperature for 2 h when solid precipitates formed. The solvent was removed and 20 mL DCM was added. The pH was adjusted to 7 by using Hunig's base. The solvent was then removed and the residue was treated with 10 mL THF, Boc-Pro-OH (0.73 g, 3 eq), HATU (1.29 g, 3 eq), Hunig's base (1.18 mL, 6 eq) and 1 mL DMF. After stirring at room temperature for 7 h, the solvent was removed in vacuo. The residue was dissolved in 20 mL EtOAc and washed with 10 mL saturated $NaHCO_3$, 10 mL 0.5 M HCl twice, water 20 mL and brine 5 mL. Chromatography provided 0.68 g **15i** (Rf = 0.31, 5 % MeOH in DCM).

Step I



15i 15j

15i was treated with 2 mL DCM, 3 mL 4 M HCl in dioxane for 1 h. 30mL DCM was added followed by neutralization with Hunig's base at 0 °C. The solvent was removed and the crude was dissolved in 5 mL DCM, 10 mL

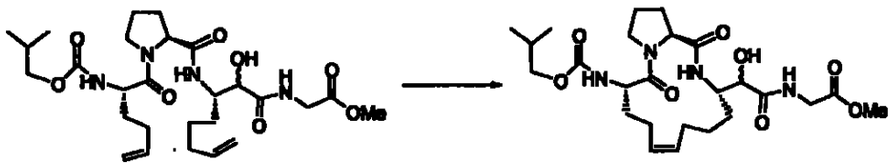
THF. After addition of 15b (0.26 g, 1 eq), HATU (0.43 g, 1 eq) and Hunig's base (0.41 mL, 2.1 eq) and stirred for 4 h, the solvent was removed and 30 mL EtOAc was added. The solution was then washed with 10 mL saturated $NaHCO_3$, 10 mL 1 M HCl, 10 mL 0.5 M HCl, water 20 mL, brine 5 mL. Chromatography gave the desired product 15j (0.3 g, 48 % from 15h).

^{13}C NMR($CDCl_3$): δ 20.20 26.26 26.72 29.18 29.55 30.58 33.25 34.60 41.95 48.57 52.90 53.00 53.40 54.68 61.56 72.34 75.68 115.64 116.73 138.07 139.33 157.47 171.04 171.15 173.06 174.23

$C_{27}H_{44}N_4O_8$: 553 $(M+H)^+$.

HRMS: calcd: 553.3237; found: 553.3259.

Step J



15j 15k

Compound 15j (0.37 g, 0.67 mmol) was treated with 0.138 g Grubbs' catalyst (0.25 eq) in 223 mL DCM under argon. After stirring at room temperature for 65 h, NMR shows the mixture contained the S.M. 15j, the desired product 15k (about 20 % yield) and $PO(C_6H_{11})_3$. The R_f for these three are 0.34, 0.24, 0.74, respectively in 5 % HOAc/EtOAc. Repeated flash chromatography could provide the pure sample of 15k.

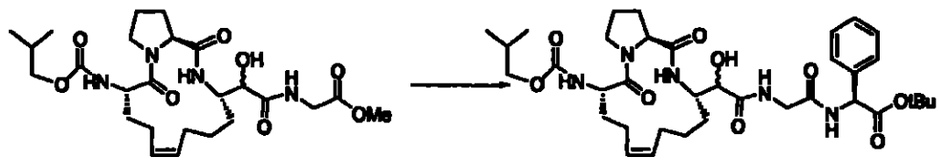
^1H NMR($CDCl_3$): δ 0.90 (d, 6 H, J = 6.6 Hz) 1.40-2.00 (m, 14 H) 2.05-2.50 (m, 3 H) 3.60(m, 1 H) 3.70 (s, 3 H) 3.75-4.00 (m, 3 H) 4.00-4.20 (m, 2 H) 4.50 (m, 1 H) 4.70 (d, 1 H, J = 7.5 Hz, diastereomer) 4.81 (d, 1 H, J = 7.9 Hz, another diastereomer) 5.38 (m, 1 H) 5.58 (m, 1 H) 5.65 (br s, 1 H) 7.20 (d, 1 H J = 7.0 Hz) 7.38 (d, 1 H, J = 7.1 Hz).

^{13}C NMR($CDCl_3$): δ 20.26 23.05 26.54 27.02 27.67 27.73 29.21 31.06 34.03 41.97 48.71 52.40 52.80 53..53 60.54 72.43 75.08 130.44 130.56 157.02 171.13 172.01 173.13 173.38.

LC/MS: Tr = 5.11min (gradient A (acetonitrile)/B (water with 0.1 % TFA): from 5% A/B to 95 % A/B in 10 min.) $C_{25}H_{40}N_4O_8$: 525 $(M+1)^+$

HRMS: calcd: 525.2924; found: 525.2908.

Step K



15k 15l

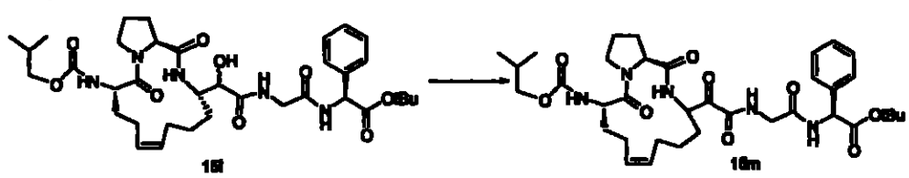
Compound 15k (92 mg, 0.18 mmol, 1 eq), 60 mg K_2CO_3 (2.5 eq) in 5 mL MeOH were stirred at 40°C for 2 h when TLC shows complete disappearance of S.M. After removal of the solvent, 44 mL 0.01 M HCl in DCM (2.5 eq) was added to neutralize the solution. The solvent was removed followed by addition of 10 mL THF, 1 mL DMF, PhG-O-tBu (HCl salt, 51 mg, 1.2 eq), 80 mg of HATU (1.2 eq), 0.11 mL of Hunig's base (3.5 eq). The mixture was stirred for 12 h. After removal of solvent, direct chromatography provided the product 15l (97 mg, 79 % yield from 15j. Rf = 0.32, 5 % MeOH/DCM).

^{1}H NMR($CDCl_3$): δ 0.90 (d, 6 H, J = 6.6 Hz) 1.30 (s, 9 H) 1.40-2.00 (m, 14 H) 2.15-2.20 (m, 1 H) 3.60(m, 1 H) 3.75-3.90 (m, 3 H) 4.00-4.09 (m, 1 H) 4.10-4.35 (m, 2 H) 4.50 (m, 1 H) 4.62 (d, 1 H, J = 7.5 Hz, diastereomer) 4.72 (d, 1 H, J = 7.9 Hz, another diastereomer) 5.20-5.38 (m, 1 H) 5.44 (d, 1 H, J = 6.6 Hz) 5.50 (m, 1 H) 5.98 (m, 1 H) 7.30 (m, 5 H) 7.45 (d, 1H, J = 7.0 Hz) 7.55 (d, 1 H, J = 7.1 Hz) 7.70 (br s, 1 H).

^{13}C NMR($CDCl_3$): δ 20.30 23.35 26.38 26.78 27.29 28.02 29.18 31.42 34.89 43.97 48.70 51.90 52.93 58.22 60.40 72.44 74.96 75.93 83.80 120.88 128.10 128.12 129.63 129.70 130.33 137.74 157.20 169.32 170.69 173.70 174.47.

LC/MS: Tr = 6.61min (gradient A (acetonitrile)/B (water with 0.1 % TFA): from 5% A/B to 95 % A/B in 10 min.) MS: $C_{36}H_{53}N_5O_8$: 700 $(M+H)^+$.

Step L



15l 15m

Compound 15l (90 mg, 0.13 mmol) was treated with 109 mg of Dess-Martin reagent (2 eq) in 10 mL DCM at room temperature for 12 h. After removal of the solvent, direct chromatography with 7:3 EtOAc/hexane provided 15m (40 %) as white solid.

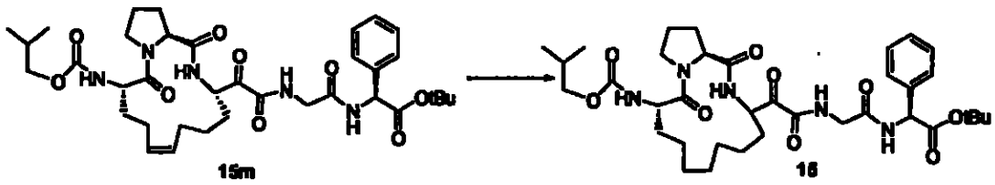
^{1}H NMR($CDCl_3$): δ 0.95 (d, 6 H, J = 6.6 Hz) 1.40 (s, 9 H) 1.50-2.10 (m, 14 H) 2.20-2.30 (m, 1 H) 3.60(m, 1 H) 3.75-3.90 (m, 3 H) 3.93 (dd, 1 H, J = 5.9, 16.8 Hz) 4.10 (m, 1 H) 4.50 (dd, 1 H, J = 8.0, 13.9 Hz) 4.80 (d, 1 H, J = 6.6 Hz) 5.20-5.40 (m, 3 H) 5.41 (d, 1 H, J = 6.6 Hz) 5.60 (dd, 1 H, J = 7.3, 10 Hz) 6.82 (d, 1 H, J = 7.3 Hz) 7.30 (m, 5 H) 7.50 (m, 1H) 7.80 (d, 1 H, J = 6.7 Hz).

^{13}C NMR($CDCl_3$): δ 20.29 23.65 26.34 26.75 29.02 29.20 30.37 30.95 31.56 35.07 43.71 48.83 52.95 54.20 58.14 60.23 72.54 84.15 128.03 129.41 129.68 129.87 130.62 137.60 156.99 160.33 167.41 171.37 173.84 187.26 196.36.

LC/MS: Tr = 6.81 min (gradient A (acetonitrile)/B (water with 0.1 % TFA): from 5% A/B to 95 % A/B in 10 min.) MS: $C_{36}H_{51}N_5O_9$: 698 $(M+H)^+$

HRMS: calcd 698.3765 found 698.3762.

Step M

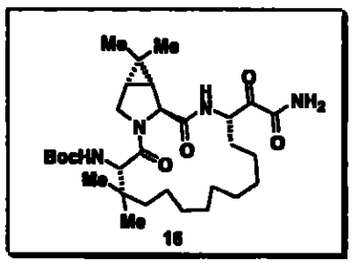


Compound 15m (4 mg) was treated with 5 mL MeOH, 2 mg of Pd-C under hydrogen balloon for 1.5 h. The solution was filtered through celite. The filtrate was dried in vacuo and the NMR shows exclusive formation of 15.

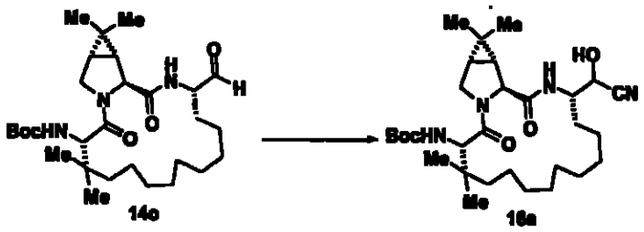
^{1}H NMR($CDCl_3$): δ 0.95 (d, 6 H, J = 6.6 Hz) 1.40 (s, 9 H) 1.50-2.10 (m, 16 H) 2.20-2.30 (m, 1 H) 3.60(m, 1 H) 3.75-3.90 (m, 3 H) 3.93 (dd, 1 H, J = 5.9, 16.8 Hz) 4.10 (m, 1 H) 4.50 (dd, 1 H, J = 8.0, 13.9 Hz) 4.80 (d, 1 H, J = 6.6 Hz) 5.30 (m, 1 H) 5.41 (d, 1 H, J = 6.6 Hz) 5.55 (d, 1 H, J = 7.0 Hz) 6.82 (d, 1 H, J = 7.3 Hz) 7.30 (m, 5 H) 7.50 (m, 1H) 7.80 (d, 1 H, J = 6.7 Hz).

LC/MS: Tr = 5.26 min (gradient A (acetonitrile)/B (water with 0.1 % TFA): from 5% A/B to 95 % A/B in 10 min.) MS: $C_{36}H_{53}N_5O_9$: 700 $(M+H)^+$.
HRMS: calcd: 700.3922; found: 700.3925.

Preparative Example 16

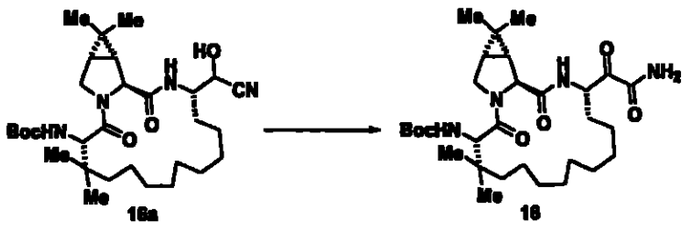


Step A



A solution of aldehyde 14o (590 mg, 1.15 mmol) in CH_2Cl_2 (10 mL) was treated with Et_3N (240 mg, 2.4 mmol) and acetone cyanohydrin (240 mg, 2.82 mmol). The reaction mixture was stirred at rt for 2 h and concentrated in *vacuo*. The residue was purified by chromatography (SiO_2, acetone/hexanes 1:4) to yield 16a (600 mg) as a colorless solid.
MS (ESI), m/z, relative intensity 569 $[(M+Na)^+$, 20], 547 $[(M+1)^+$, 40], 447 (100).

Step B

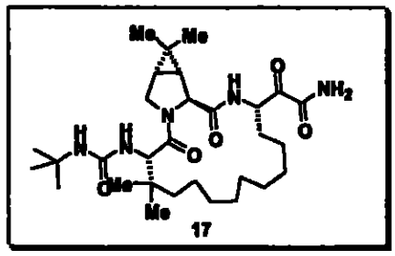


A solution of cyanohydrin 16a (600 mg, 1.1 mmol) in DMSO (10 mL) was treated with H_2O_2 (35%, 1.5 mL) and K_2CO_3 (252 mg, 1.83 mmol) and stirred at rt. for 15 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL)

and washed with aq. $Na_2S_2O_3$ solution (10%, 50 mL) and brine (30 mL). The reaction mixture was dried ($MgSO_4$) filtered concentrated in *vacuo* and directly used in oxidation without further purification.

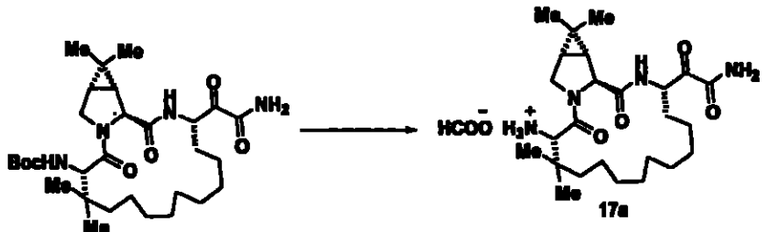
A solution of hydroxy amide in toluene/DMSO (2:1, 15 mL) was treated with EDCI (1.9 g, 10.00 mmol) and $Cl_2CHCOOH$ (317 mg, 2.49 mmol) and stirred at 0 °C for 3 h. The reaction mixture was diluted with CH_2Cl_2 (300 mL) and washed with satd. aq. $NaHCO_3$ (2x100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$), concentrated and purified by chromatography (SiO_2, acetone/hexanes 1:5) to yield **16** as colorless solid. **MS** (ESI), m/z, relative intensity 617 [$(M+CH_3OH+Na)^+$, 20], 595 [$(M+CH_3OH+1)^+$, 40], 507 [$(M+1)^+$, 20], 463 (100).

Preparative Example 17



17

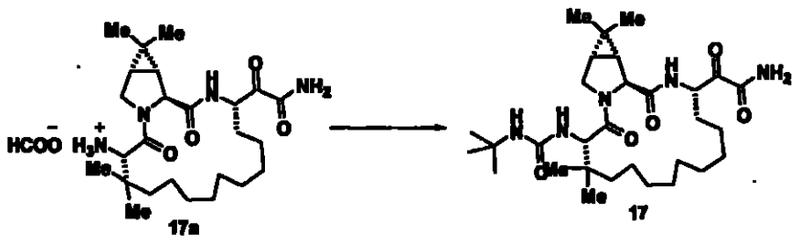
Step A



16 17a

A solution of **16** (300 mg 0.54 mmol) in HCOOH (10.0 mL) was stirred at rt for 2 h and concentrated in *vacuo*. The residue was dried in *vacuo* and used in further reactions without further purification.

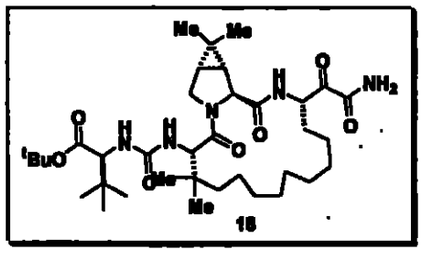
Step B



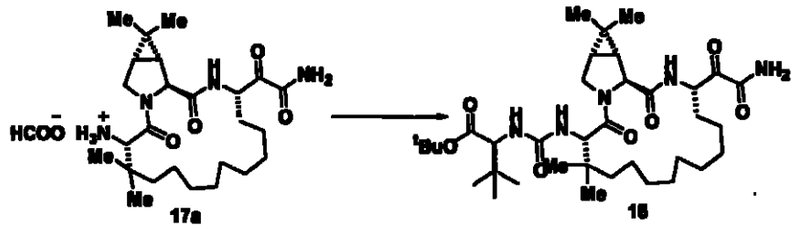
A solution of 17a (100 mg) in DMF/CH_2Cl_2 (1:1, 3 mL) was treated with ^{t}BuNCO (50 □L and NMM (52 mg, 0.52 mmol). The reaction mixture was stirred at rt for 16 h and concentrated in *vacuo*. and diluted with CH_2Cl_2 (60 mL) and washed with aq. HCl (1M, 2x30 mL), dried, concentrated in vacuo. The residue was purified by chromatography (SiO_2, acetone/hexanes 1:2) to yield 17 (34 mg) as colorless solid.

MS (ESI), m/z, relative intensity 584 [$(M+1)^+$, 30], 463 (100).

Preparative Example 18



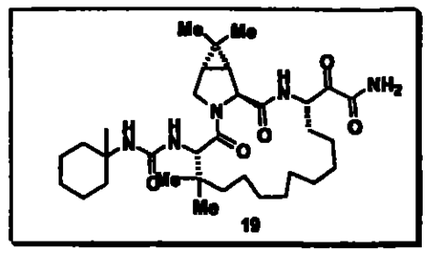
Step A



A solution of 17a (100 mg) in DMF/CH_2Cl_2 (1:1, 3 mL) was treated with isocyanate of tertbutylester of tert-butylglycine (100 mg, 0.46 mmol) and NMM (52 mg, 0.52 mmol). The reaction mixture was stirred at rt for 16 h and concentrated in *vacuo*. and diluted with CH_2Cl_2 (60 mL) and washed with aq. HCl (1M, 2x30 mL), dried, concentrated in vacuo. The residue was purified by chromatography (SiO_2, acetone/hexanes 1:2) to yield 18 (42 mg) as colorless solid.

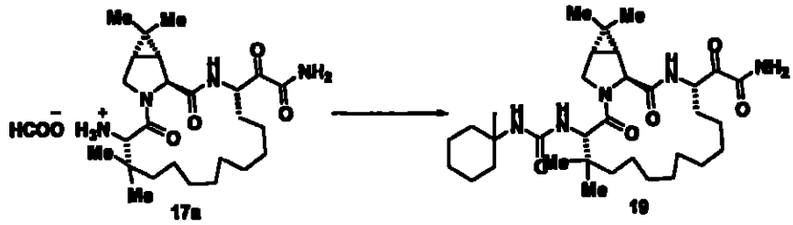
MS (ESI), m/z, relative intensity 698 [(M+Na)$^+$, 40], 676 [(M+1)$^+$, 100], 463 (20).

Preparative Example 19



19

Step A

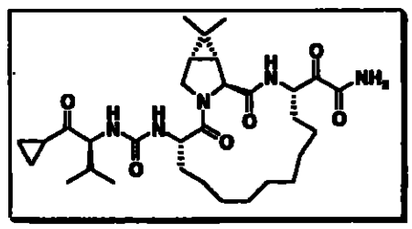


17a 19

A solution of **17a** (100 mg) in DMF/CH_2Cl_2 (1:1, 3 mL) was treated with isocyanate of α-methyl-cyclohexylamine (100 □L) and NMM (52 mg, 0.52 mmol). The reaction mixture was stirred at rt for 16 h and concentrated in *vacuo*. and diluted with CH_2Cl_2 (60 mL) and washed with aq. HCl (1M, 2x30 mL), dried, concentrated in vacuo. The residue was purified by chromatography (SiO_2, acetone/hexanes 1:2) to yield **20** (21 mg) as colorless solid.

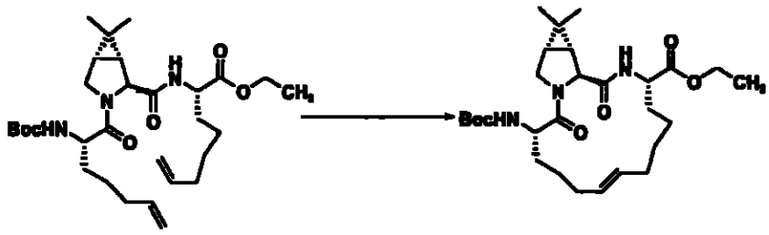
MS (ESI), m/z, relative intensity 624 [(M+Na)$^+$, 30], 602 [(M+1)$^+$, 15], 463 (100), 449 (20), 129 (30).

Preparative Example 20



20

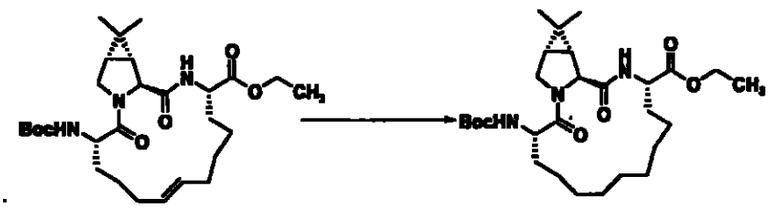
Step A



20a 20b

A solution of acyclic diene **20a** (6.00 g, 10.954 mmol) in dry toluene (500 mL), degassed with Argon for 0.5 h, was treated with Grubbs catalyst (1.35 g, 1.643 mmol) and heated at 60° C for 12 h. The reaction mixture was concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/hexanes 1:3) to yield **20b** as a brown foam.

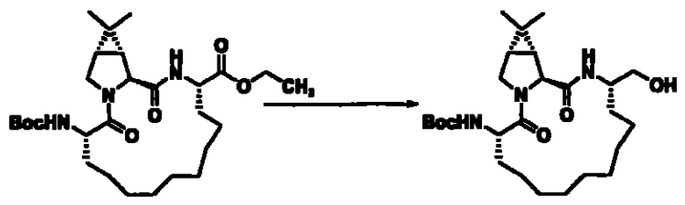
Step B



20b 20c

A solution of alkene **20b** (5.00g mg, 0.865 mmol) in methanol (100 mL) was treated with Pd/C (1.2g, 5% w/w) and hydrogenated at 50 psi for 3 h. The reaction was filtered through a plug of celite and concentrated in *vacuo*. The residue was purified by chromatography using THF/hexanes gradient from 10-40% to isolated **20c** (3.00 g) as a colorless solid.

Step C

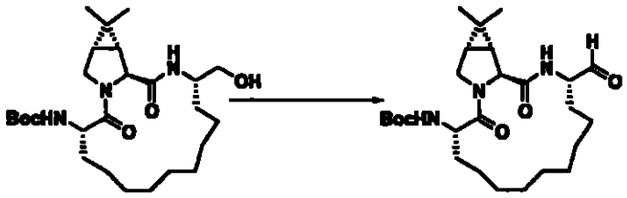


20c 20d

A solution of ester **20c** (3.00 g, 5.75 mmol) in dry THF (50 mL) was treated with $LiBH_4$ (2M soln in THF, 3.5 mL, 6.90 mmol) and stirred at rt for 3 h. The reaction was followed by TLC (EtOAc/Hexanes 1:2). The reaction was

quenched with methanol (2 mL) and diluted with aq. HCl (1 M, 30 mL) and extracted into CH_2Cl_2 (3x100 mL). The combined organic layers were washed with aq. saturated $NaHCO_3$ (30 mL), brine, dried ($MgSO_4$), filtered concentrated in *vacuo* and purified by chromatography (SiO_2, Acetone/Hexanes 1:2) to yield **20d** (2.21 g) as colorless solid. MS (*m/z*, relative Intensity) 518 [$(M+K)^+$, 15], 480 [$(M+H)^+$, 75], 380(100).

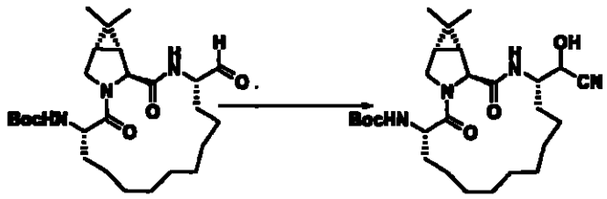
Step D



20d **20e**

A solution of alcohol **20d** (2.2 g, 4.58 mmol) in dry CH_2Cl_2 (50 mL) was treated with Dess-Martin reagent (2.91 g, 6.880 mmol) and stirred at rt for 2 h. The reaction mixture was diluted with aq. $Na_2S_2O_3$ (5%, 50 mL) and aq. saturated $NaHCO_3$ (50 mL) and stirred at rt. for 15 min. The reaction mixture was extracted with CH_2Cl_2 (500 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated in *vacuo* to yield crude 20e (1.9 g) that was used in the next reaction without further purification.

Step E

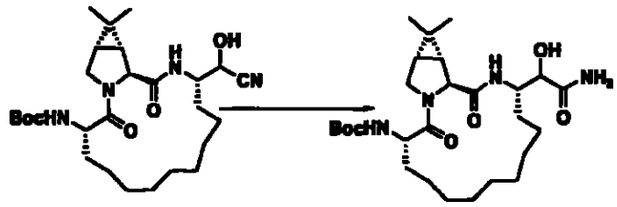


20e **20f**

A solution of crude **20e** (1.00 g, 2.094 mmol) in CH_2Cl_2 (15 ml) was cooled to 0° C and treated with acetone cyanohydrin (356 mg, 4.187 mmol) and triethylamine (424 mg, 4.187 mmol). The reaction mixture was stirred at 0° C for 12 h and concentrated in *vacuo*. The residue was purified by chromatography (SiO_2, EtOAc/Hexanes 1:5–>1:1) to yield 20f (500 mg) as a colorless oil.

Step F

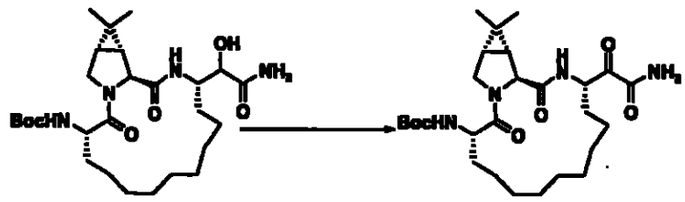
169



20f 20g

A solution of cyanohydrin 20f (500 mg, ~1.00 mmol) in DMSO (5 mL) was treated with H_2O_2 (5 mL), K_2CO_3 (276 mg, 2.00 mmol) and stirred at rt. for 12 h. The reaction mixture was diluted with aq. $Na_2S_2O_3$ (5%, 100 mL) and extracted with CH_2Cl_2 (2x100 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated in *vacuo* to yield 20g that was used as it is for further oxidation without purification.

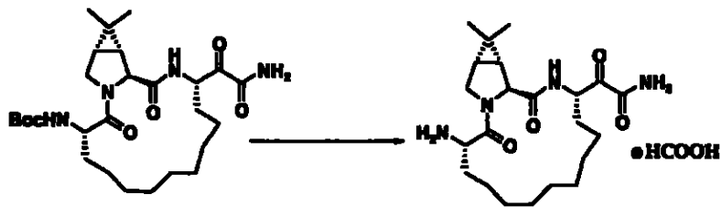
Step G:



20g 20h

A solution of hydroxylamine 20g (850 mg, 1.626 mmol) in toluene (5 mL) and DMSO (5 mL) was treated with EDCI (3.117 g, 16.26 mmol), and dichloroacetic acid (1.048 g, 8.13mmol, 698µL) and stirred at rt. for 3 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with aq. saturated $NaHCO_3$ (200 mL), aq. HCl (1 M,200 mL), brine (30 mL), dried ($MgSO_4$) filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/Hexanes 1:2) to yield 20h (300 mg) as a colorless solid.

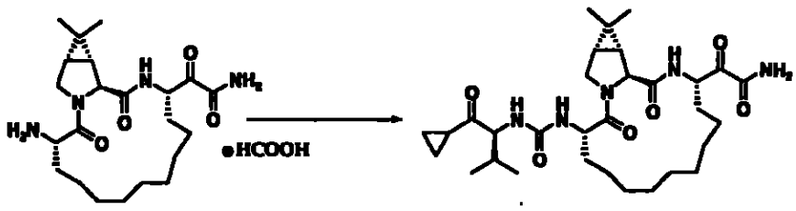
Step H:



20h 20i

170

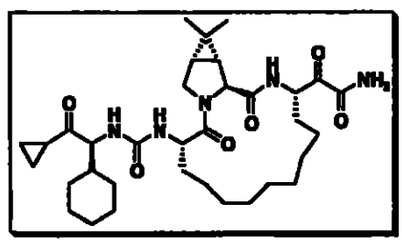
A solution of Boc protected ketoamide **20h** in formic acid (5 mL) was stirred at rt for 3 h and concentrated in *vacuo* and used as it is in the next step without further purification.



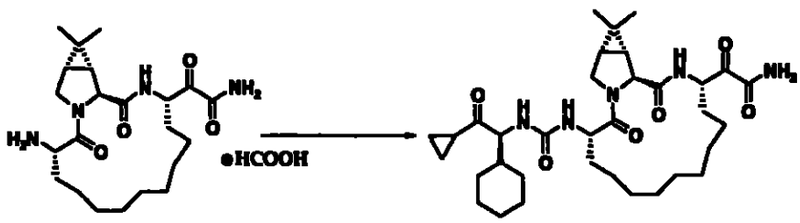
20I **20**

A solution of amine **20I** (40 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of isocyanate in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20→50%) to yield ***20*** as a colorless solid. MS (*m/z*, relative intensity) 588 [$(M+H)^+$, 100], 421 (40). HRMS (ESI) Calcd. for $C_{31}H_{50}N_5O_6$: 588.3761 $(M+H)^+$; Found: 588.3751.

Preparative Example 21:



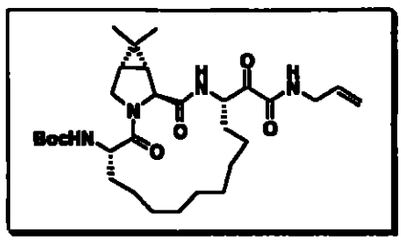
21



20I **21**

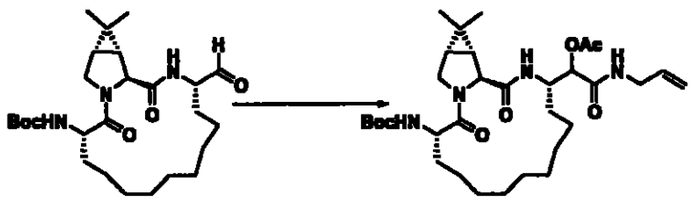
A solution of amine **20l** (40 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of 2-cyclohexyl-1-cyclopropyl-2-isocyanato ethanone (0.15 mmol) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20 → 50%) to yield **21** as colorless solid.

Preparative Example 22



22

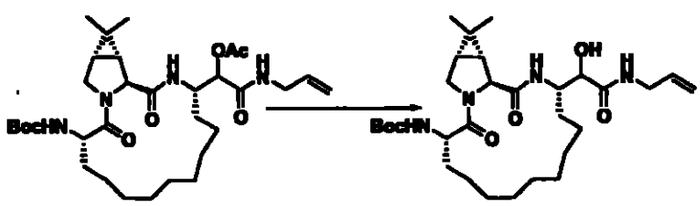
Step A:



20e **22a**

A solution of aldehyde **20e** (100 mg, 0.210 mmol) in methylene chloride (4 mL) was treated with allyl isocyanide (28.01 mg, 0.411 mmol) and acetic acid and stirred at rt. for 12 h. The reaction was concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 1:4→1:1) to obtain **22a** (75 mg) as colorless solid. MS (*m/z*, relative intensity) 605 [$(M+H)^+$, 100], 505 (98).

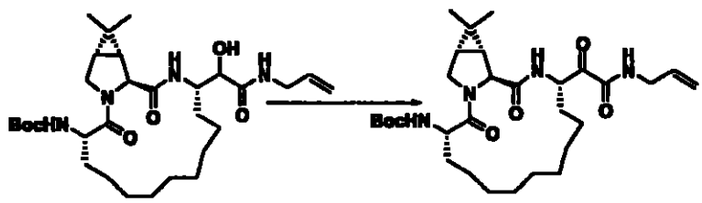
Step B:



22a 22b

A solution of **22b** (275 mg, 0.454 mmol) in methanol (4 mL), THF(4.0 mL) and water (4.0 mL) was treated with $LiOH \cdot H_2O$ (22 mg, 0.55 mmol) and stirred at rt. for 2 h. The reaction mixture was diluted with aq. HCl (1 M, 30 mL) and extracted in CH_2Cl_2 (2x40 mL). The combined organic layer were dried ($MgSO_4$), filtered, concentrated in *vacuo*, and used as it is in next step without further purification.

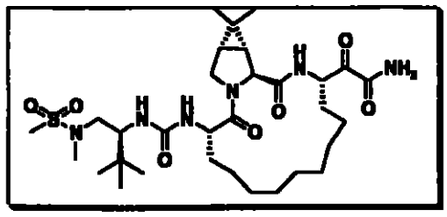
Step C:



22b 22

A solution of alcohol **22b** (300 mg, 0.534 mmol) in dry CH_2Cl_2 (15 mL) was treated with Dess-Martin reagent (453 mg, 1.06 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 (3x50 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 0:1→1:1) to yield **22** as a colorless solid. MS (*m/z*, relative intensity) 561 [$(M+H)^+$, 100], 461 (99). HRMS (ESI) Calcd. for $C_{31}H_{50}N_5O_6$: 588.3761 $(M+H)^+$; Found: 588.3751.

Preparative Example 23



23

Step A:



23a 23b

A solution of amine **23a** (900 mg, 3.40 mmol) in CH_2Cl_2 at 0 °C was treated with NMM (511 mg, 5.10 mmol) and methanesulfonyl chloride (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 methylsulfonamide **23b** (1.00 g).

Step B:

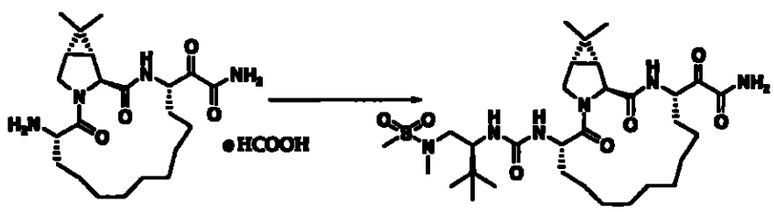


23b 23c

A solution methanesulfonamide **23b** (1.0 g, 2.9 mmol) in methanol (30 mL) was treated with palladium (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 further purification.

A solution of deprotected amine in CH_2Cl_2 (10 mL) aq. saturated $NaHCO_3$ (10 mL) at 0°C was treated with phosgene (5 mL, 15% soln. in toluene) and stirred at 0 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with cold aq $NaHCO_3$. The organic layer was dried ($MgSO_4$) filtered and further diluted with 10 mL toluene, concentrated the methylene chloride layer and used as a solution of **23c**.

Step C:

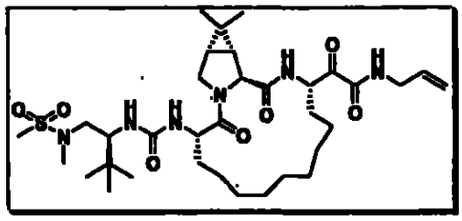


179 175

20I 23

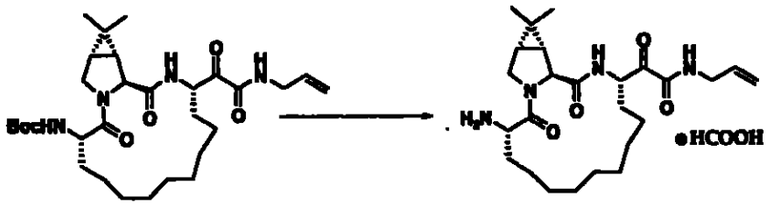
A solution of amine 20I (40 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of isocyanate 23 in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20→50%) to yield 23. MS (*m/z*, relative intensity) 693 [$(M+K)^+$, 10], 677 [$(M+Na)^+$, 20], 655 [$(M+H)^+$, 100], 449 (30), 421 (30); HRMS (ESI) Calcd. for $C_{31}H_{54}N_6O_7SNa$ 677.3672 $(M+Na)^+$; Found: 677.3685.

Preparative Example 24



24

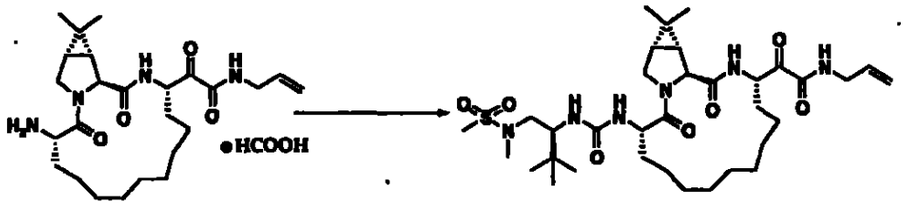
Step A:



22 24a

A solution of Boc protected ketoamide 22 (220 mg, 0.39 mmol) in formic acid (5 mL) was stirred at rt. for 3 h and concentrated in *vacuo* and used as it is in the next step without further purification.

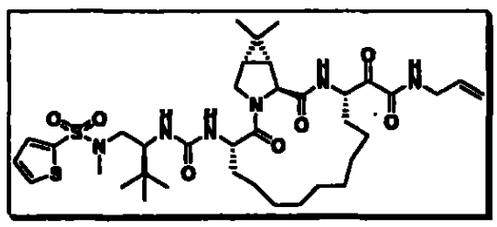
Step B:



24a 24

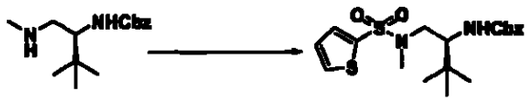
A solution of amine **24a** (40 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of isocyanate in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20→50%) to yield **24** (27 mg) MS (*m/z*, relative intensity) 734 [$(M+K)^+$, 10], 695 [$(M+H)^+$, 100], 461 (20), 443 (20); HRMS (FAB) Calcd. for $C_{34}H_{59}N_6O_7S$ 695.4166 $(M+H)^+$; Found: 695.4161.

Preparative Example 25



25

Step A:



23a 25a

A solution of amine **23a** (900 mg, 3.40 mmol) in CH_2Cl_2 at 0 °C was treated with NMM (511 mg, 5.10 mmol) and thiophene sulfonyl chloride (928 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 sulfonamide 25a (1.00 g) of colorless solid.

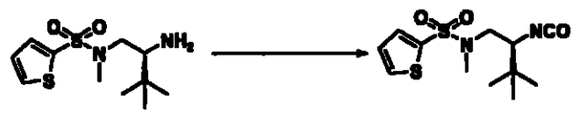
Step B:



25a 25b

A solution of Cbz-protected compound **25a** (1.00 g, 2.118 mmol) was treated with TFA (30 mL) and dimethylsulfide (7.78 mL) at 0° C and stirred at rt. for 3 h. The reaction mixture was concentrated in *vacuo* and diluted with aq. NaOH (100 mL). The amine was extracted with methylene chloride (2x100 mL) and the combined organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and to yield **25b** (800 mg) that was used in further reaction without purification. MS (*m/z*, relative intensity) 277 [$(M+H)^+$, 100], 190 (50).

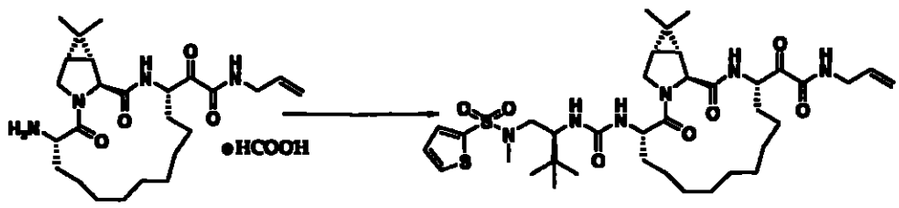
Step C:



25b 25c

A solution of deprotected amine **25b** (800 mg, 2.9 mmol) in CH_2Cl_2 (10 mL) aq. saturated $NaHCO_3$ (10 mL) at 0° C was treated with phosgene (5 mL, 15% soln. in toluene) and stirred at 0 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with cold aq $NaHCO_3$. The organic layer was dried ($MgSO_4$) filtered and further diluted with 10 mL toluene, concentrated the methylene chloride layer and used as a solution of 25c.

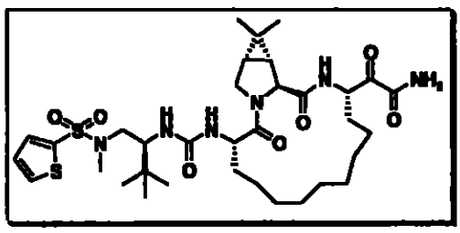
Step D:



24a 25

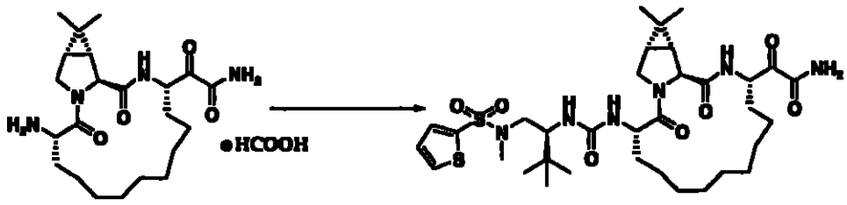
A solution of amine **24a** (40 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of isocyanate in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20→ 50%) to yield **25** (39 mg) as a colorless solid. MS (*m/z*, relative intensity) 801 [$(M+K)^+$, 10], 763 [$(M+H)^+$, 100], 461 (15), 277 (20); HRMS (ESI) Calcd. for $C_{37}H_{58}N_6O_7S_2Na$ 785.3706 $(M+Na)^+$; Found: 785.3706.

Preparative Example 26



26

Step A:



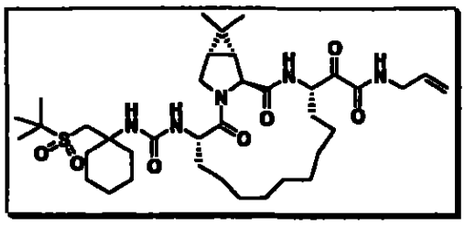
20i **26**

A solution of amine **20I** (40 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of isocyanate in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20→ 50%) to yield **26** as colorless solid (31 mg). MS (*m/z*,

178.

relative intensity) 761 [(M+K)$^+$, 10], 720 [(M+H)$^+$, 100], 421 (20); HRMS (ESI) Calcd. for $C_{34}H_{54}N_6O_7S_2Na$ 745.3393 (M+Na)$^+$; Found: 745.3396.

Preparative Example 27



27

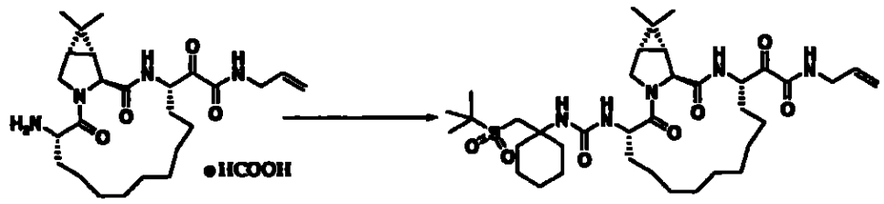
Step A:



27a 27b

A solution of acid **27a** (100 mg, 0.385 mmol) in toluene (5 mL) was treated with DPPA (116.5 mg, 0.425 mmol) and Et_3N (42.5 mg, 0.425 mmol) and stirred at reflux for 1.5 h. The reaction mixture was diluted with saturated $NaHCO_3$ (30 mL) and extracted into CH_2Cl_2 (2x20 mL). The combined organic layers were washed with aq. $NaHCO_3$ (30 mL), brine (30 mL), dried ($MgSO_4$), filtered, concentrated in *vacuo*, and used as a solution of isocyanate in toluene.

Step B:

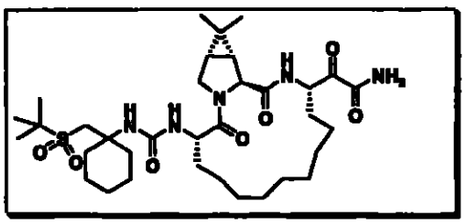


24a 27

A solution of amine **24a** (40 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of isocyanate **27b** (3 equiv) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by

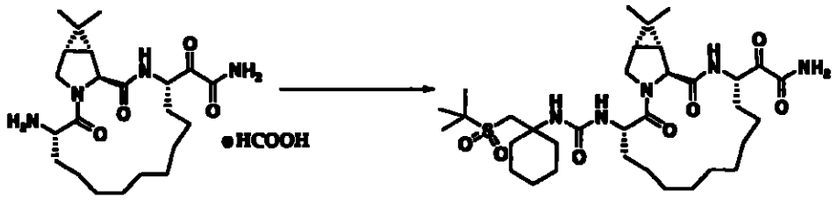
chromatography (SiO_2, acetone/hexanes 20→50%) to yield 27 as a colorless solid. MS (*m/z*, relative intensity) 720 [$(M+H)^+$, 85], 461(100); HRMS (ESI) Calcd. for $C_{37}H_{61}N_5O_7SNa$ 742.4189 $(M+Na)^+$; Found: 742.4200.

Preparative Example 28



28

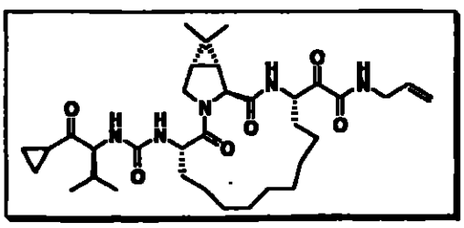
Step A:



20I 28

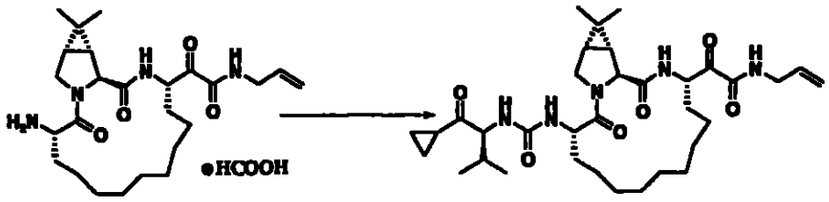
A solution of amine 20I (40 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of Isocyanate 27b (3.00 equiv) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20→ 60%) to yield 28 (29 mg) as a colorless solid. MS (*m/z*, relative intensity) 718 [$(M+K)^+$, 10], 702 [$(M+Na)^+$, 20], 680 [$(M+H)^+$, 80], 421 (100); HRMS (ESI) Calcd. for $C_{34}H_{57}N_5O_7SNa$ 702.3876 $(M+Na)^+$; Found: 702.3889.

Preparative Example 29



29

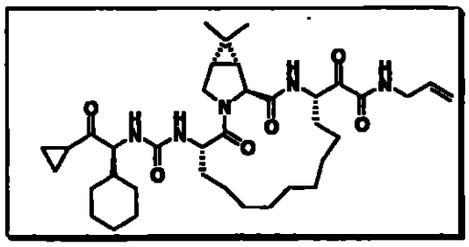
Step A:



24a 29

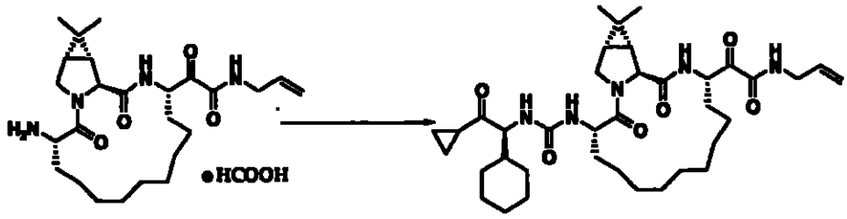
A solution of amine **24a** (50 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of isocyanate in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20 → 50%) to yield **29** as a colorless solid (41 mg). MS (*m/z*, relative intensity) 628 [$(M+H)^+$, 100], 129 (35).

Preparative Example 30



30

Step A:

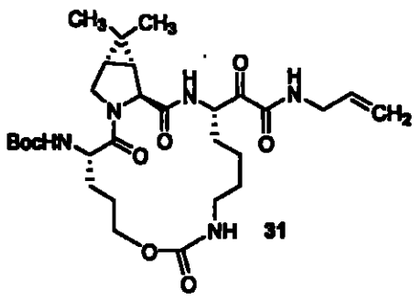


24a 30

A solution of amine **24a** (50 mg, 0.1 mmol) in methylene chloride (3.0 mL) was treated with NMM (30 mg, 0.3 mmol) and cooled to 0 °C. A solution of isocyanate (3.0 equiv.) in CH_2Cl_2 was added and the reaction mixture was

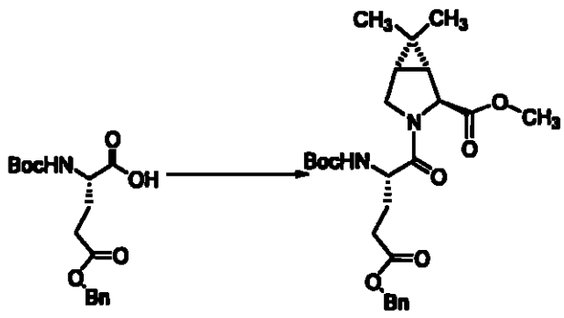
stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (60 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 20→ 50%) to yield 30 as a colorless solid. MS (*m/z*, relative intensity) 668 [$(M+H)^+$, 100], 169 (50), 128 (80).

Preparative Example 31: Preparation of:



31

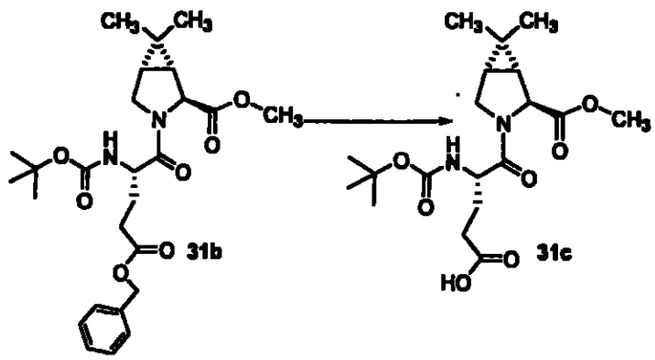
Step A:



31a 31b

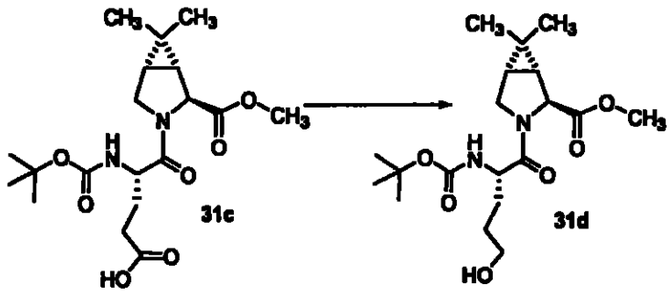
A solution of Boc-Glu-OBn **31a** (1.8 g, 5.36 mmol) and amine **1d** (1 g, 4.87 mmol) was reacted as in preparative example 1, step C and purified by silica gel chromatography (10% to 25% EtOAc/hexanes) to give **31b** (1.28 g).

Step B:



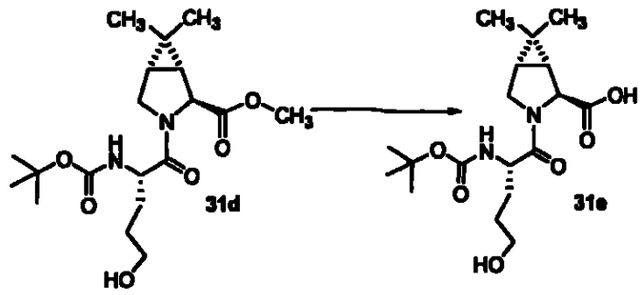
A solution of benzyl ester **31b** (1.25 g, 2.56 mmol) was treated with 10% Pd/C in EtOH and hydrogenated (1 atm., rt.) for 12 hours. The reaction mixture was filtered through a plug of celite and concentrated under vacuum to give **31c** (997 mg) which was used in the next reaction without further purification.

Step C



A solution of acid **31c** (20.4 g, 48.7 mmol) in THF (300 ml) was cooled to 0°C and treated with Et_3N (7.47 ml, 53.6 mmol) and ethyl chloroformate (4.89 ml, 51.2 mmol) and stirred for 2 hours. The white precipitate formed was filtered and washed with cold THF. The filtrate was cooled to 0°C and $NaBH_4$ (2.39 g, 63.4 mmol) was added. MeOH (20ml) was added dropwise over 1 hour and stirred for an additional 2.5 hours. Solvent was removed under vacuum, CH_2Cl_2 added and washed with water, brine and dried over Na_2SO_4. Na_2SO_4 was filtered and solvent removed to dryness. The residue was purified by silica gel chromatography (50% to 90% EtOAc/hexanes) to give **31d** (8.15 g).

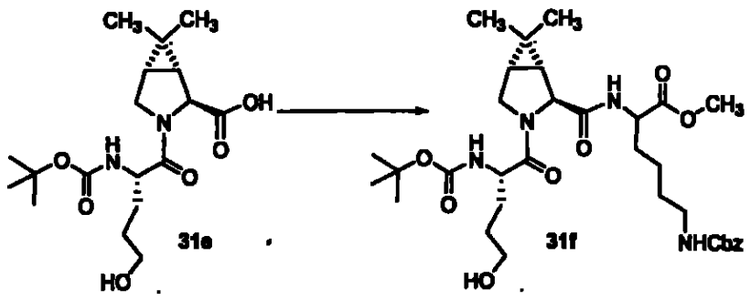
Step D:



31d 31e

A solution of ester **31d** (8 g, 20.8 mmol) in MeOH (120 ml) and H_2O (24 ml) was treated with $LiOH \cdot H_2O$ (2.62 g, 62.5 mmol) at room temperature for 12 hours. Solvent was removed under vacuum to dryness. CH_2Cl_2 was added and stirred for 5 minutes with 1N. HCl (72.9 mmol). CH_2Cl_2 layer was separated, washed with brine and dried over Na_2SO_4. Na_2SO_4 was filtered and solvent was removed to dryness to give white solid **31e** (7.65 g).

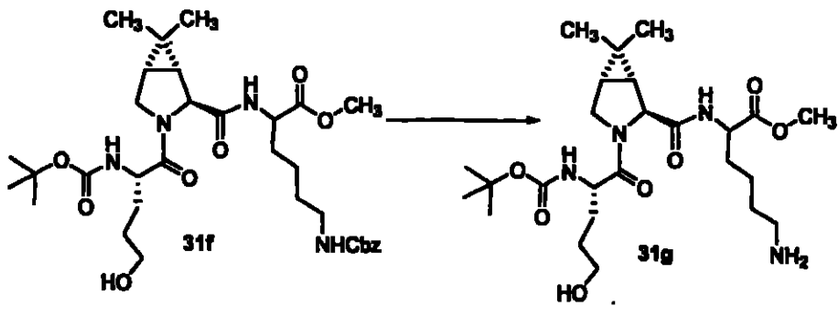
Step E:



31e 31f NHCbz

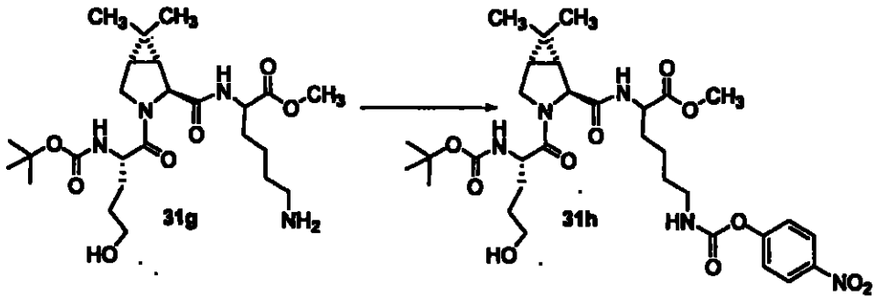
A solution of acid **31e** in anhydrous DMF (75 ml) and anhydrous CH_2Cl_2 (75 ml) was cooled to 0 °C and stirred with HOOBt (3.68 g, 22.5 mmol), NMM (6.77 ml, 61.6 mmol) and EDCI (5.11 g, 26.7 mmol) for 5 minutes. H-Lys(Z)-OMe•HCl (7.13 g, 21.5 mmol) was added and stirred for 3.5 hours at 0 °C. Reaction was held 12 hours at 5 °C after which CH_2Cl_2 was removed, EtOAc added and washed with sat. $NaHCO_3$, 5% H_3PO_4, Brine and filtered through Na_2SO_4. Solvent was removed under vacuum to dryness to give **31f** (12.7g).

Step F



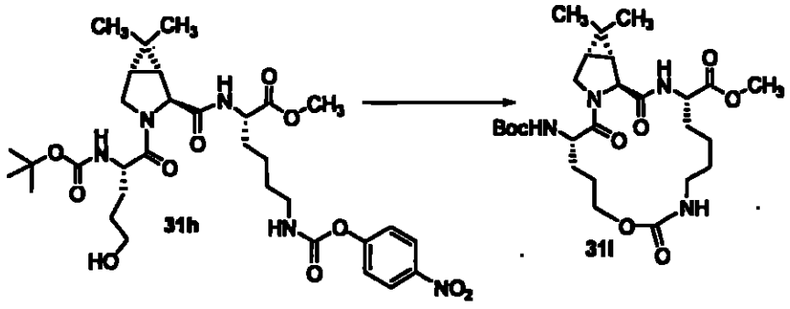
A solution of 31f (5.5 g, 8.51 mmol) was treated with 10% Pd/C in EtOH (100 ml) and hydrogenated (1atm., rt.) for 12 hours. The reaction mixture was filtered through a plug of celite and concentrated under vacuum to give 31g (4.25 g).

Step G:



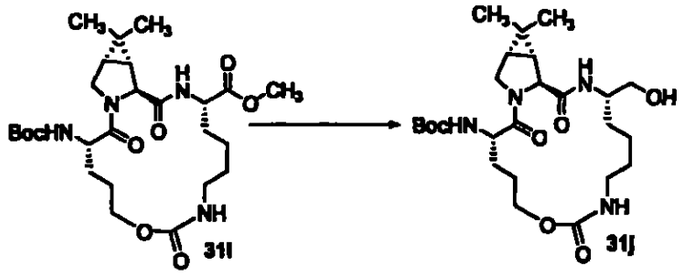
A solution of amine 31g (4.25 g, 8.3 mmol) in anhydrous CH_2Cl_2 (750 ml) was stirred with triethylamine (1.5 ml, 10.7 mmol) and 4-nitrophenyl chloroformate (2.0 g, 9.96 mmol) at room temperature for 5 hours. Solvent was removed under vacuum to ~200 ml, then washed with sat. $NaHCO_3$, water, 5% H_3PO_4, brine and filtered through Na_2SO_4. Na_2SO_4 was filtered and solvent was removed to give 31h (5.82 g).

Step H:



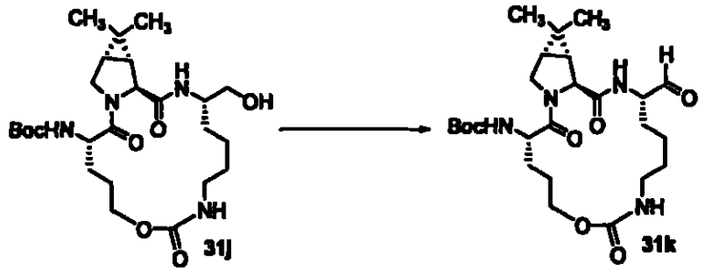
A solution of **31h** (5.8 g, 8.3 mmol) in anhydrous THF (600 ml) was treated with 60% NaH (996 mg, 24.9 mmol) at room temperature for 22 hours. Reaction was quenched by adding H_2O (5 ml) then 1N. HCl (50 ml) over 3 minutes. Solvent was removed under vacuum, CH_2Cl_2 was added and washed with 5% H_3PO_4, Brine and filtered through Na_2SO_4. Na_2SO_4 was filtered, solvent was removed and the residue was chromatographed on silica gel column with 0.25% to 3% MeOH/CH_2Cl_2 to give **31I** (2.86 g, 64 % yield).

Step I:



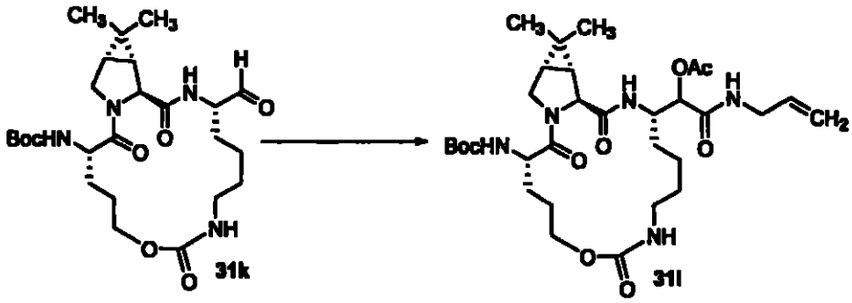
A solution of **31I** (613 mg, 1.13 mmol) was reacted as in preparative example 1, step F and purified by silica gel chromatography (3% to 6% MeOH/CH_2Cl_2) to give alcohol **31J** (500 mg).

Step J:



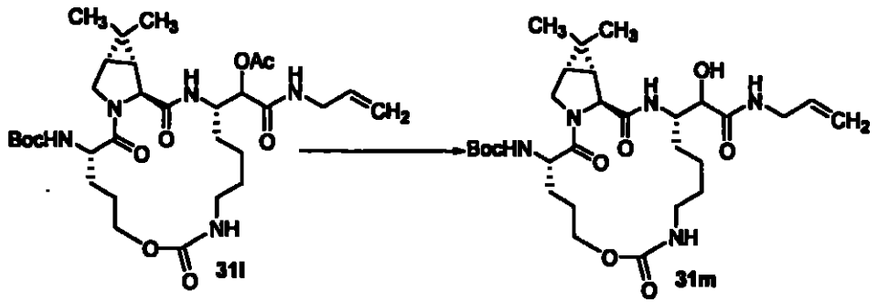
A solution of alcohol **31J** (480 mg, 0.94 mmol) was reacted as in preparative example 1, step H and purified by silica gel chromatography (30% to 60% acetone/hexanes) to give aldehyde **31k** (383 mg).

Step K:



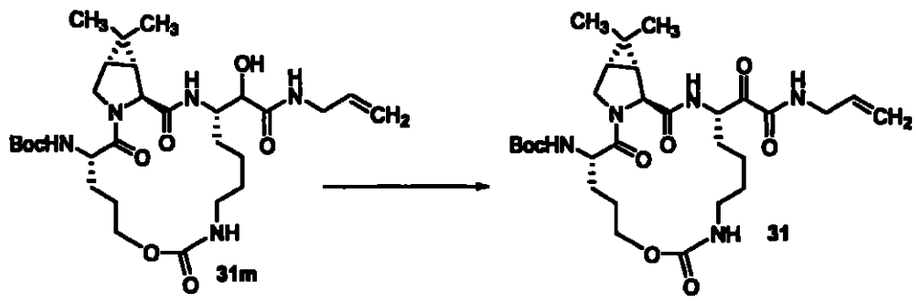
A solution of aldehyde 31J (365 mg, 0.71 mmol) was reacted as in preparative example 22, step A and purified by silica gel chromatography (30% to 50% acetone/hexanes) to give 31k (426 mg).

Step L:



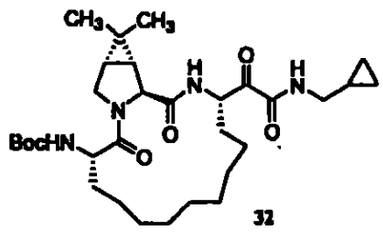
A solution of 31l (357 mg, 0.56 mmol) was reacted as in preparative example 22, step B to give 31m (426 mg).

Step M:



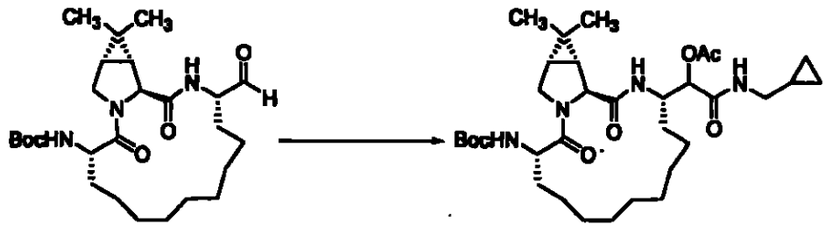
A solution of 31m (350 mg, 0.59 mmol) was reacted as in preparative example 22, step C and purified by silica gel chromatography (30% to 50% acetone/hexanes) to give 31 (335 mg). MS (ES) *m/z* relative intensity 492 [(M-BOC+1)$^+$, 80]; 592 [(M+1)$^+$, 100]. Calcd. for $C_{28}H_{46}N_5O_8$ [M+1]$^+$: 592.3346; Found 592.3359.

Preparative Example 32: Preparation of:



32

Step A:

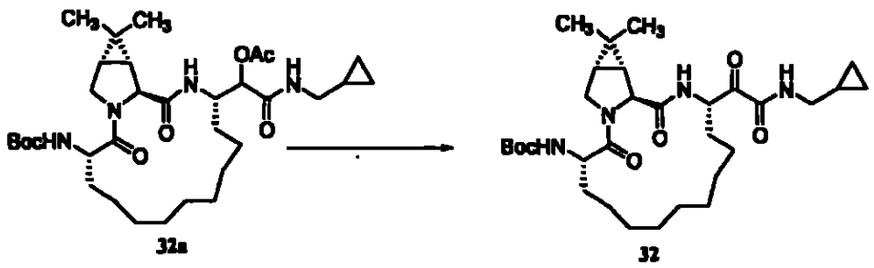


20e 32a

A solution of aldehyde **20e** (200 mg, 0.42 mmol) in methylene chloride (10 mL) was treated with cyclopropylmethylisocyanide (66.5 mg, 4.11 mmol) and acetic acid (50 mg, 0.82 mmol) and stirred at rt. for 12 h. The reaction was concentrated in *vacuo* and residue was purified by chromatography (SiO_2, acetone/hexanes 1:901:1) to obtain **32a** (230 mg).

MS (ES) *m/z* relative intensity 641 [$(M+Na)^+$, 70]; 619 [$(M+1)^+$, 100], 519 (50).

Step B:



32a 32

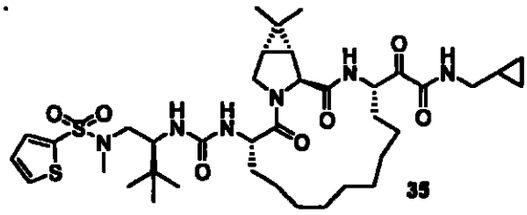
A solution of acetate **32a** (230 mg, 0.371 mmol) in methanol (5.0 mL), THF (5.0 mL) and water (5.0 mL) was treated with $LiOH \cdot H_2O$ (25 mg, 0.55 mmol) and stirred at rt. for 1 h. The reaction mixture was diluted with aq. HCl (1 M, 30 mL) and extracted in CH_2Cl_2 (2 x 50 mL). The combined organic layer were dried ($MgSO_4$), filtered, concentrated in *vacuo*, and used as it is in next step without further purification.

A solution of alcohol in dry CH_2Cl_2 (15 mL) was treated with Dess-Martin reagent (237 mg, 0.558 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 (3x50 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 0:1→1:1) to yield 32 as a colorless solid (275 mg) MS (ES) *m/z* relative intensity 629 [(M+isobutene)$^+$, 40], 575 [(M+1)$^+$, 100], 475 (90).

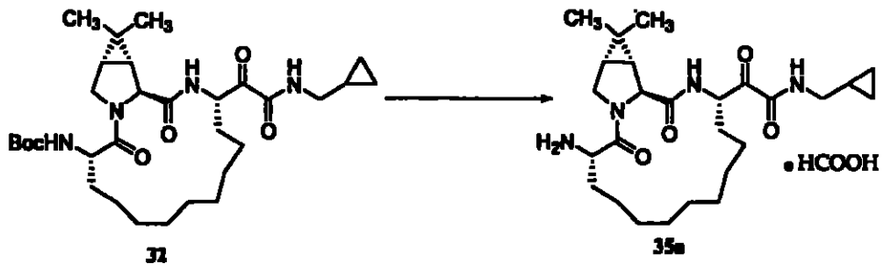
Similar procedures were used to synthesize compounds: 33 and 34 using cyclopropyl and ethyl isocyanide for Step A: preparative example 32:

Preparative Example 35: Preparation of:



35

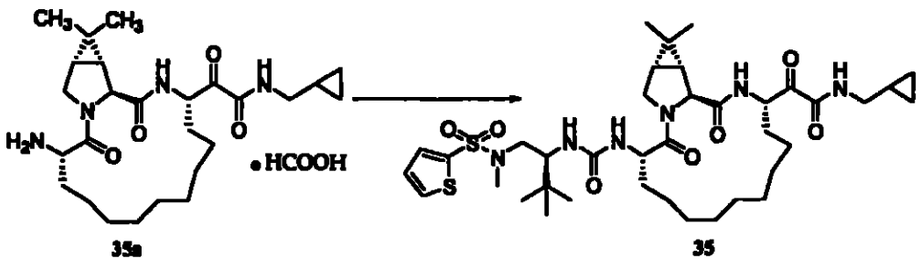
Step A:



32 35a

32 (200 mg, 0.39 mmol) was deprotected by dissolving in formic acid 20 mL and standing for 2 h. The reaction mixture was concentrated in *vacuo* to yield 35a and used in further reactions without purification.

Step B:

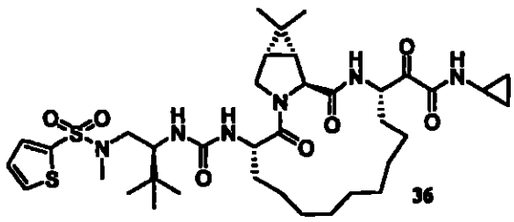


35a 35

A solution of amine **35a** (70 mg, 0.13 mmol) in methylene chloride (3.0 mL) was treated with NMM (50 mg, 0.5 mmol) and cooled to 0 °C. A solution of isocyanate **25c** (1 ml, 0.25 mmol) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (150 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/CH_2Cl_2 50□ 100%) to yield ***35*** as a colorless solid.

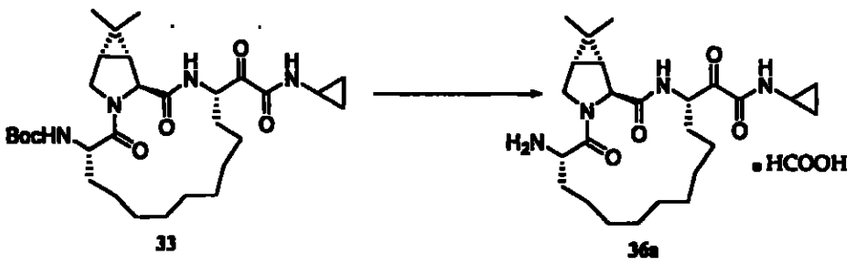
MS (ES) *m/z* relative intensity 799 [$(M+Na)^+$, 60]; 777 [$(M+1)^+$, 100].

Preparative Example 36: Preparation of:



36

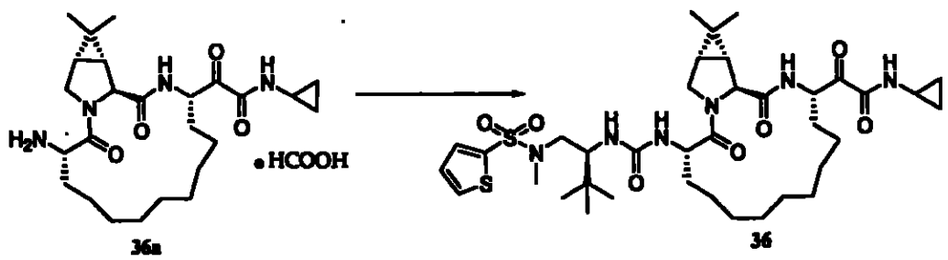
Step A:



33 36a

33 (200 mg, 0.39 mmol) was deprotected by dissolving in formic acid 20 mL and standing for 2 h. The reaction mixture was concentrated in *vacuo* to yield **36a** and used in further reactions without purification.

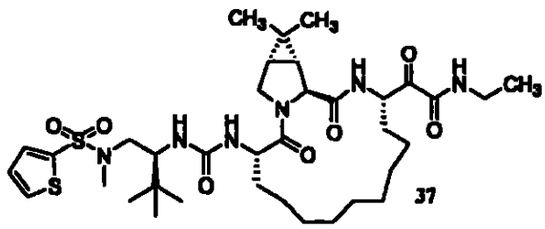
Step B:



36a 36

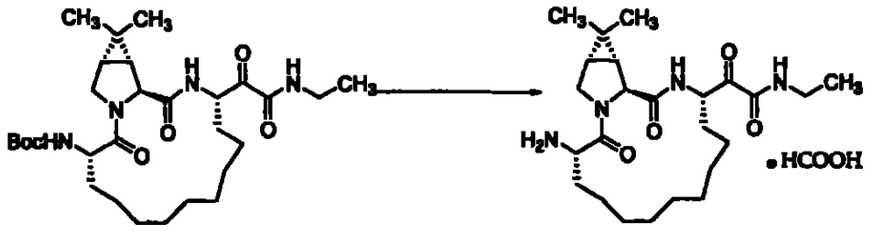
A solution of amine **36a** (70 mg, 0.13 mmol) in methylene chloride (3.0 mL) was treated with NMM (50 mg, 0.5 mmol) and cooled to 0 °C. A solution of isocyanate **25c** (1 ml, 0.25 mmol) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (150 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/CH_2Cl_2 0→100%) to yield **36** as a colorless solid. MS (ES) *m/z* relative intensity 785 [$(M+Na)^+$, 50]; 763 [$(M+1)^+$, 100]; 593 (60).

Preparative Example 37: Preparation of:



37

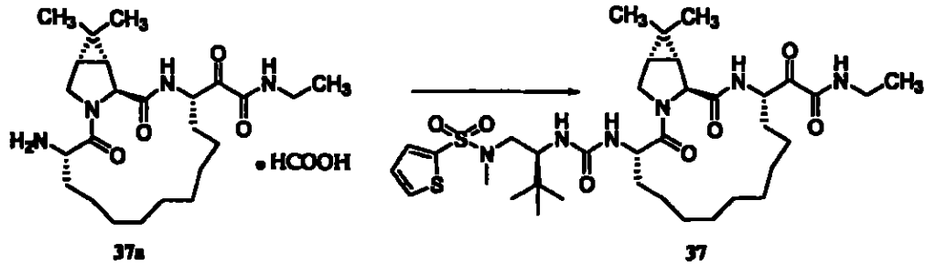
Step A:



34 **37a**

34 (200 mg, 0.39 mmol) was deprotected by dissolving in formic acid 20 mL and standing for 2 h. The reaction mixture was concentrated in *vacuo* to yield **37a** and used in further reactions without purification.

Step B:

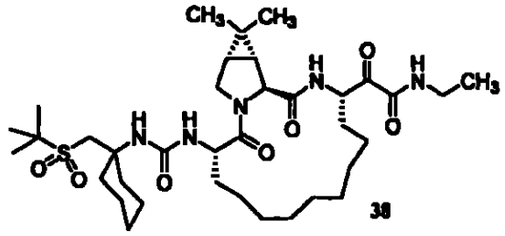


37a **37**

A solution of deprotected amine **37a** (70 mg, 0.13 mmol) in methylene chloride (3.0 mL) was treated with NMM (50 mg, 0.5 mmol) and cooled to 0 °C. A solution of isocyanate **25c** (1 ml, 0.25 mmol) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (150 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/CH_2Cl_2 50□ 100%) to yield **37**.

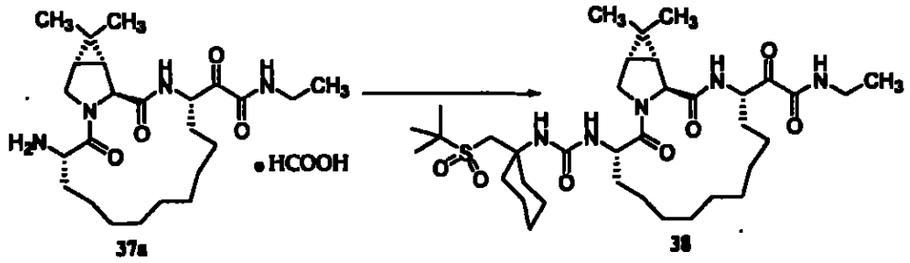
MS (ES) *m/z* relative intensity 773 [(M+Na)$^+$, 100]; 751 [(M+1)$^+$, 70].

Preparative Example 38: Preparation of:



38

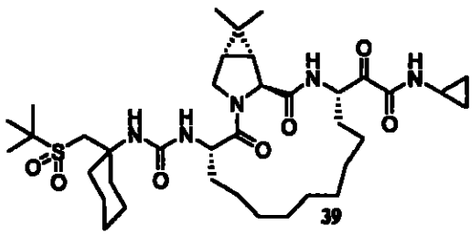
Step A:



37a **38**

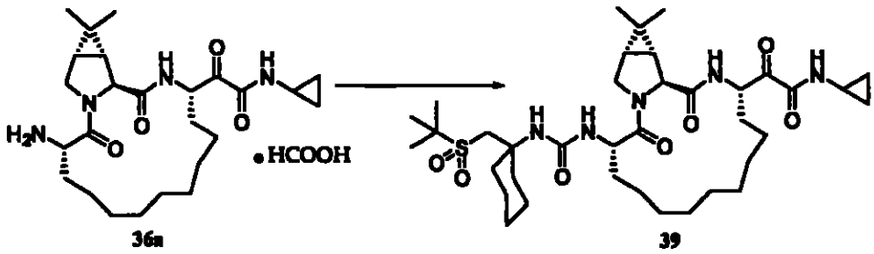
A solution of deprotected amine **37a** (70 mg, 0.13 mmol) in methylene chloride (3.0 mL) was treated with NMM (50 mg, 0.5 mmol) and cooled to 0 °C. A solution of isocyanate **27b** (1.5 ml, 0.25 mmol) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (150 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/CH_2Cl_2 50◊ 100%) to yield ***38*** as colorless solid. MS (ES) *m/z* relative intensity 730 [(M+Na)$^+$, 30]; 708 [(M+1)$^+$, 100]; 409 (30).

Preparative Example 39: Preparation of:



39

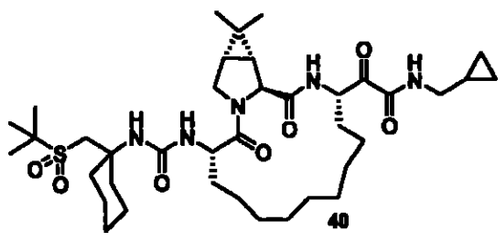
Step A:



36a 39

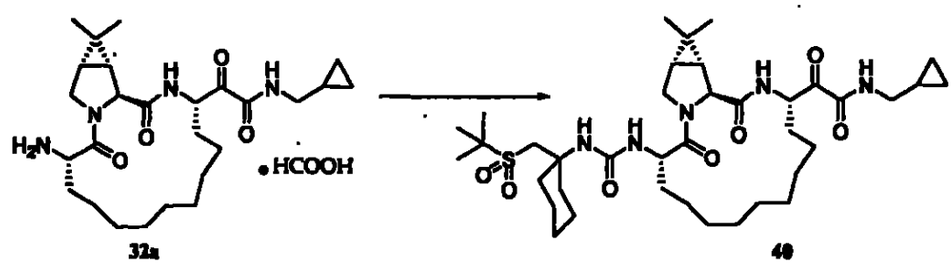
A solution of amine **36a** (70 mg, 0.13 mmol) in methylene chloride (3.0 mL) was treated with NMM (50 mg, 0.5 mmol) and cooled to 0 °C. A solution of isocyanate **27b** (1 mL, 0.25 mmol) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (150 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/CH_2Cl_2 50□ 100%) to yield **39**. MS (ES) *m/z* relative intensity 742 [$(M+Na)^+$, 70]; 720 [$(M+1)^+$, 100]; 461 (40). HRMS Calcd. for $C_{37}H_{62}N_5O_7S$ [$M+1]^+$: 720.4370; Found 720.4350.

Preparative Example 40: Preparation of:



40

Step A:

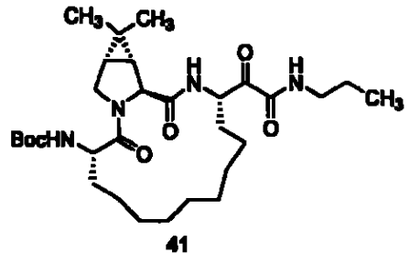


32a 40

A solution of amine **32a** (70 mg, 0.13 mmol) in methylene chloride (3.0 mL) was treated with NMM (50 mg, 0.5 mmol) and cooled to 0 °C. A solution of isocyanate **27b** (1 mL, 0.25 mmol) in CH_2Cl_2 was added and the reaction mixture was stirred at rt. for 1.5 h. The reaction mixture was diluted with methylene chloride (150 mL) and washed with aq. HCl (1 M, 30 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/CH_2Cl_2 50□ 100%) to yield **40**. ^{1}H NMR(dmso, 500 MHz), δ, 8.80 (t, 1 H, *J*=6.0 Hz), 8.37 (d, 1 H, *J*=9.5 Hz), 6.22 (d, 1 H, *J*=8.8 Hz), 5.88 (s, 1 H), 5.31 (dt, 1 H, *J*=2.8 & 9.5 Hz), 4.35 (s, 1 H), 4.28-4.22 (m, 1 H), 3.85 (d, 1 H, *J*=10 Hz), 3.76 (q, 1 H, *J*=5.4 Hz), 3.59 (t, 1 H, *J*=13.5 Hz), 3.41 (d, 1 H, *J*=13.9 Hz), 3.07-2.95 (m, 2 H), 2.22-2.15 (m, 2 H), 1.69-1.00 (b, 23 H), 1.25 (s, 9 H), 0.99 (s, 3 H), 0.99-0.70 (m, 1 H), 0.88 (s, 3 H), 0.42-0.38 (m, 2 H), 0.21-0.18 (m, 2 H).

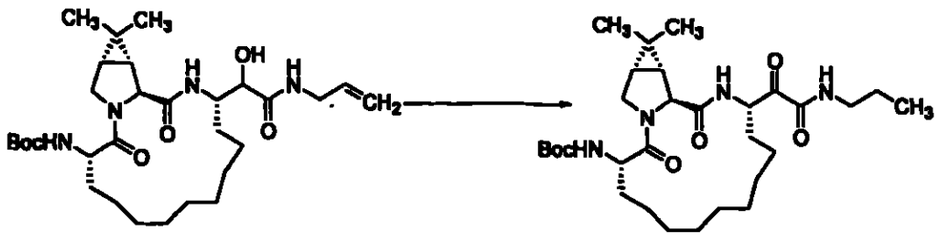
^{13}C NMR (dmso, 125 MHz) δ, 198.5, 172.1, 171.3, 162.0, 157.3, 60.5, 60.1, 54.4, 52.8, 51.5, 47.6, 43.8, 35.4, 35.1, 34.8, 32.3, 31.6, 31.4, 28.3, 28.0, 27.9, 27.3, 26.9, 26.6, 25.8, 25.6, 24.6, 23.4, 22.4, 21.5, 19.5, 13.7, 11.5. MS (ES) *m/z* relative intensity 756 [$(M+Na)^+$, 45]; 734 [$(M+1)^+$, 100]; 475 (20). HRMS calcd. for $C_{38}H_{64}N_5O_7S$ [$M+1]^+$: 734.4526; Found 734.4535.

Preparative Example 41: Preparation of:



41

Step A:

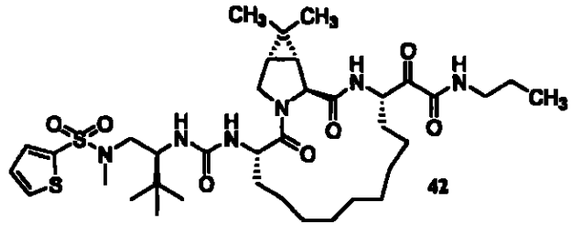


22b 41

A solution of intermediate 22b (300 mg, 0.54 mmol) was taken in methanol (25 mL) and treated with 10% Pearlman's catalyst and hydrogenated at 50 psi for 4 h. The reaction mixture was filtered through a plug of celite® and concentrated in vacuo to yield reduced product that was used in further reaction without purification.

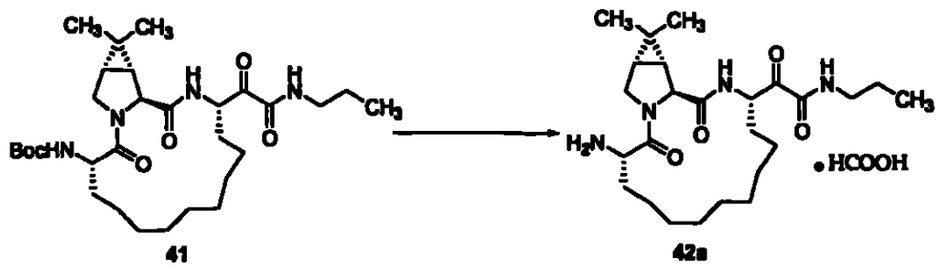
A solution of reduced alcohol in dry CH_2Cl_2 (5 mL) was treated with Dess-Martin reagent (350 mg, 0.82 mmol) and stirred at rt. for 2 h. The reaction mixture was diluted with aq. $Na_2S_2O_3$ (5%, 30 mL) and aq. saturated $NaHCO_3$ (30 mL) and stirred at rt. for 15 min. The reaction mixture was extracted with CH_2Cl_2 (3x75 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/hexanes 0:1 →1:1) to yield 41 (270 mg) as a colorless solid.

Preparative Example 42: Preparation of:



42

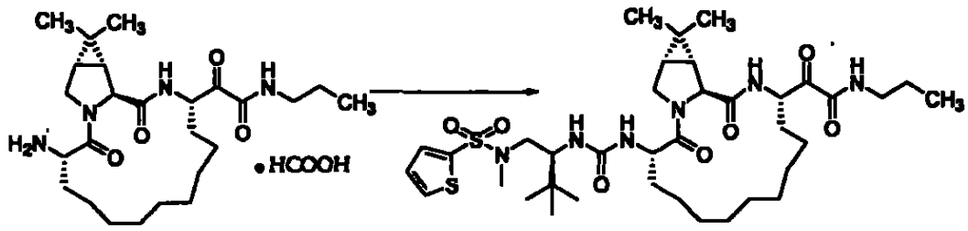
Step A:



41 42a

41 was deprotected by dissolving in formic acid 20 mL and standing for 2 h. The reaction mixture was concentrated in *vacuo* to yield **42a** and used in further reactions without purification.

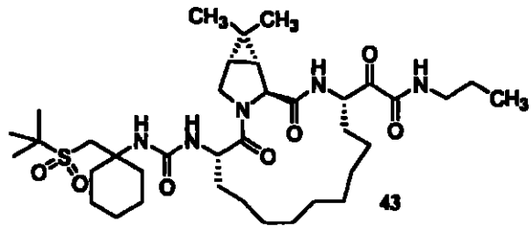
Step B:



42a **42**

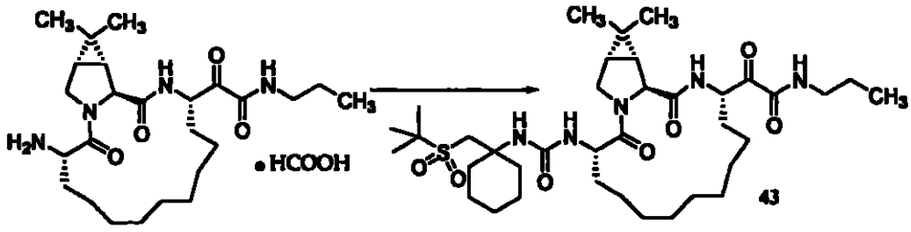
A solution of amine **42a** (100 mg, 0.196 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0 °C. A solution of isocyanate **25c** (1.5 mL, 0.25 mmol, 0.38 mmol) in toluene was added and the reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted with methylene chloride (100 mL) and washed with aq. HCl (1 M, 50 mL). The organic layers were dried with ($MgSO_4$) filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, Ethyl acetate/hexanes 1:1□ 1:0) yield **42** (65 mg) as a colorless solid. ^1H NMR (dmso, 500 MHz), δ, 8.71 (t, 1 H, *J*=6.3 Hz), 8.36 (d, 1 H, *J*=9 Hz), 8.00 (dd, 1 H, *J*=1.3 & 5.0 Hz), 7.65 (dd, 1 H, *J*=1.3 & 2.5 Hz), 7.25 (dd, 1 H, *J*= 3.8 &1.3 Hz), 6.15 (d, 1 H, *J*=9.0 Hz), 5.88 (d, 1 H, *J*=10 Hz), 5.31 (m, 1 H), 4.34 (s, 1 H), 4.30 (m, 1 H), 3.93 (d, 1 H, *J*=10.5 Hz), 3.79-3.75 (q, 1 H, *J*=5.0 Hz), 3.67-3.62 (dt, 1 H, *J*= 4.1 & 5.6 Hz), 3.12-3.05 (m, 2 H), 2.95-2.91 (m, 2 H), 2.67 (s, 3 H), 1.70-1.61 (m, 2 H) 1.40-1.00 (b, 20 H), 0.99 (s, 3 H), 0.85 (s, 3 H), 0.83 (s, 9 H), 0.83 (t, 3 H).^{13}C NMR (dmso, 125 MHz) □, 198.5, 172.0, 171.7, 162.2, 158.3, 137.7, 133.9, 133.1, 129.0, 60.5, 55.8, 55.7, 52.7, 51.6, 51.5, 47.6, 36.0, 35.0, 32.2, 31.6, 31.3, 28.5, 27.9, 27.4, 27.1, 26.9, 26.7, 26.3, 24.4, 22.8, 22.3, 19.5, 13.7, 12.1. MS (ES) *m/z* relative intensity 788 [$(M+Na)^+$, 50]; 765 [$(M+1)^+$, 100].

Preparative Example 43: Preparation of:



43

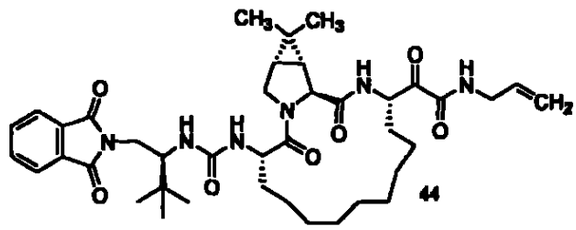
Step A:



42a 43

A solution of amine **42a** (100 mg, 0.196 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0 °C. A solution of isocyanate **27b** (3 mL, 0.1 M soln., 0.3 mmol) in toluene was added and the reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted with methylene chloride (100 mL) and washed with aq. HCl (1 M, 50 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hexanes 1:1→ 1:0) yield **43** (42 mg) as a colorless solid.^{1}H NMR (dmso, 500 MHz) δ, 8.71 (t, 1 H, *J*=6.0 Hz), 8.36 (d, 1 H, *J*=9.0 Hz), 6.22 (d, 1 H, *J*=8.5 Hz), 5.88 (s, 1 H), 5.29 (dt, 1 H, *J*=9.5 & 2.5 Hz), 4.34 (s, 1 H), 4.23 (t, 1 H, *J*=9.0 Hz), 3.86 (d, 1 H, *J*=10.5 Hz), 3.76 (dd, 1 H, *J*=5.0 & 5.5 Hz), 3.60 (d, 1 H, *J*=13.5 Hz), 3.41 (d, 1 H, *J*=13.5 Hz), 3.13-3.04 (m, 2 H), 2.23-2.15 (m, 2 H), 1.67-0.9 (bm, 30 H), 1.25 (s, 9 H), 0.99 (s, 3 H), 0.88 (s, 3 H), 0.83 (t, 3 H, *J*=7.0 Hz). ^{13}C NMR (dmso, 125 MHz) δ, 198.5, 172.1, 171.3, 162.1, 157.3, 60.5, 60.1, 55.8, 54.3, 52.8, 51.0, 47.6, 35.4, 35.1, 32.3, 31.7, 31.3, 28.3, 28.0, 27.9, 27.3, 26.9, 26.6, 26.2, 25.8, 24.6, 23.3, 22.8, 21.5, 19.5, 13.7, 12.2. MS (ES) *m/z* relative intensity 744 [$(M+Na)^+$, 40]; 722 [$(M+1)^+$, 100].

Preparative Example 44: Preparation of:



44

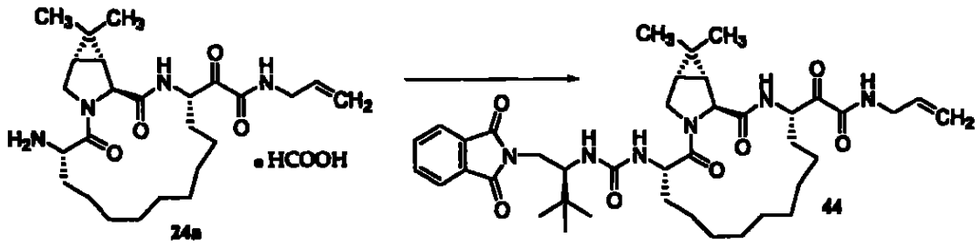
Step A:



44a 44b

A solution of deprotected amine **44a** (Busacca, C. A.; Grossbach, D.; Spinelli, E. *Tetrahedron: Asymmetry*, **2000**, *9*, 1907) in CH_2Cl_2 (10 mL) aq. saturated $NaHCO_3$ (10 mL) at 0° C was treated with phosgene (5 mL, 15% soln. in toluene) and stirred at 0 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with cold aq $NaHCO_3$. The organic layer was dried ($MgSO_4$) filtered and further diluted with 10 mL toluene, concentrated the methylene chloride layer and used as a solution

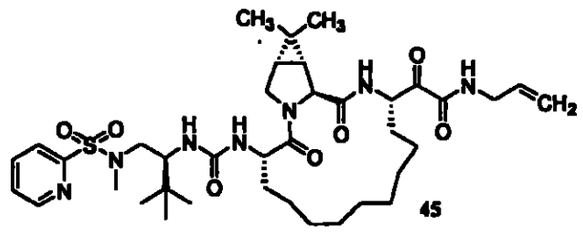
Step B:



24a 44

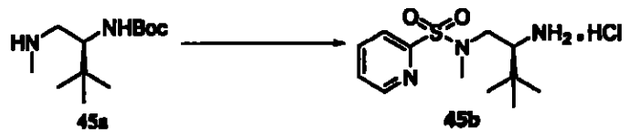
A solution of amine **24a** (100 mg, 0.196 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0 °C. A solution of isocyanate **44b** (2.5 mL, 0.25 mmol,) in toluene was added and the reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted with methylene chloride (100 mL) and washed with aq. HCl (1 M, 50 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, ethyl acetate/hexanes 1:1□ 1:0) yield **44** (31 mg) as a colorless solid. MS (ES) *m/z* relative intensity 755 [$(M+Na)^+$, 40]; 733 [$(M+1)^+$, 100].

Preparative Example 45: Preparation of:



45

Step A:



45a 45b

A solution of amine 45a* (2.00 g, 9.20 mmol) in CH_2Cl_2 at 0 °C was treated with $(C_2H_5)_3N$ (3.7 g, 37 mmol) and 2-pyridinesulfonyl chloride (2.4 g, 11.2 and stirred at rt. for 12 h. The reaction mixture was diluted with CH_2Cl_2 (300 mL) and washed with excess aq. $NaHCO_3$ (1M, 500 mL). The organic layer was dried ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, Acetone/Hexanes 0:1→1:1) to yield sulfonamide (2.3 g). A solution of Boc-protected amine was deprotected by dissolving (2.1 g, 5.7 mmol) in 4M soln. of HCl in dioxane and stirred at rt. for 2 h. The reaction mixture was concentrated in *vacuo* and used as it is in next step without further purification.

* obtained by the protection of *tert*-leucine-N-methylamide (TCI-Jpn) with ditertbutyldicarbonate and subsequent reduction with BH_3•DMS in THF (reflux, 2 h).

Step B:

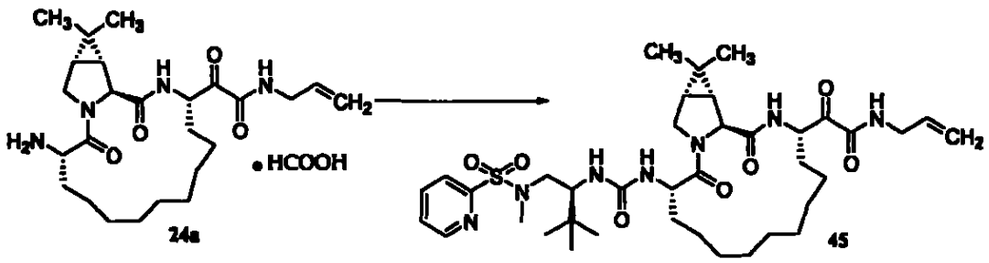


45b 45c

A solution of amine 45b (300 mg, 1 mmol) in CH_2Cl_2 (3 mL) aq. saturated $NaHCO_3$ (3 mL) at 0°C was treated with phosgene (2.5 mL, 15% soln. in toluene) and stirred at 0 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and the organic layer was washed with cold aq $NaHCO_3$.

The organic layer was dried ($MgSO_4$) filtered and further diluted with 3 mL toluene, concentrated the methylene chloride layer and used as a solution.

Step C.



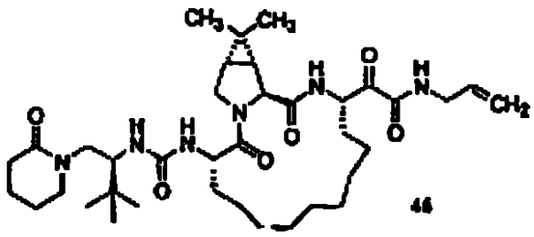
24a 45

A solution of amine **24a** (100 mg, 0.197 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0 °C. A solution of Isocyanate **45c** (2.5 mL, 0.25 mmol,) in toluene was added and the *reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted* with methylene chloride (100 mL) and washed with aq. HCl (1 M, 50 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, ethyl acetate/hexanes 1:1→ 1:0) yield product **45** as a colorless solid. The crude mixture was further purified using HPLC to yield pure product **45** (27 mg). ^1H NMR (dmso, 500 MHz) δ 8.89 (t, 1 H, *J*=7.0 Hz), 8.72 (d, 1 H, *J*=6.0 Hz), 8.37 (d, 1 H, *J*=10.5 Hz), 8.07 (t, 1 H, *J*=9.0 Hz), 7.88 (d, 1 H, *J*=9.0 Hz), 7.66 (dd, 1 H, *J*=6.5 &3.5 Hz), 6.12 (d, 1 H, *J*=11 Hz), 5.84-5.75 (m, 2 H), 4.27 (s, 1 H), 4.22 (bt, 1 H, *J*=11.5 Hz), 3.92 (d, 1 H, *J*=13 Hz), 3.77-3.60 (m, 4 H), 3.33 (bd, 1 H), 3.06 (bt, 1 H, *J*=12.5 Hz), 2.75 (s, 3 H), 1.68-1.59 (m, 2 H), 1.44-1.12 (m, 18 H), 0.98 (s, 3 H), 0.83 (s, 3 H), 0.78 (s, 9 H). ^{13}C NMR (dmso, 125 MHz) δ, 198.3, 172.1, 171.7, 162.1, 158.3, 157.1, 151.0, 139.6, 135.0, 127.9, 123.3, 116.4, 60.5, 55.8, 52.8, 52.2, 51.5, 36.4, 35.0, 28.0, 27.1, 26.9, 26.3, 19.5, 13.7.MS (ES) *m/z* relative Intensity 780 [$(M+Na)^+$, 50]; 758 [$(M+1)^+$, 100].

Preparative Example 46: Preparation of:

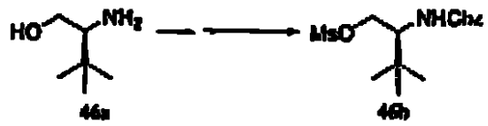
46b 46c

A solution of **46b** (3.1g, 9.9 mmol) in toluene (72 mL) containing water (400 µL) was treated with $(C_4H_9)_4NBr$ (582 mg, 1.8 mmol), K_2CO_3(2.72 g, 1.97 mmol) and 2-hydroxypyridine (937 mg, 9.85 mmol). The reaction mixture



46

Step A:



46a 46b

A solution of (S) –*tert*-leucinol (5.0 g, 42.7 mmol, Aldrich) 46a at 0 °C in CH_2Cl_2 (100.0 mL) was treated with benzyl chloroformate (6.7 mL, 47.0 mmol), followed by Hunig's base (9.3 mL, 53.3 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with ethyl acetate (500 mL), washed with 10 % KH_2PO_4, followed by saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated to yield protected leucinol (10.7 g, 100%) that was used in further reaction without any purification.

To a solution of protected leucinol (crude) (10.7 g, 42.7 mmol) in CH_2Cl_2 (100.0 mL) at 0 °C was added pyridine (20.0 mL) and methanesulfonyl chloride (3.63 mL, 47.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight, concentrated, redissolved in ethyl acetate (500 mL), washed with saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), concentrated and purified by flash chromatography over SiO_2 using ethyl acetate/hexane (1:4) to yield 46b (14.0 g, 100 %).

Step B:

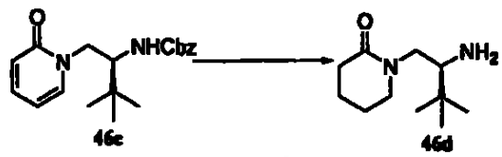


46b 46c

A solution of 46b (3.1g, 0.9 mmol) in toluene (72 mL) containing water (400 µL) was treated with $(C_4H_9)_4NBr$ (582 mg, 1.8 mmol), K_2CO_3(2.72 g, 1.97 mmol) and 2-hydroxypyridine (937 mg, 9.85 mmol). The reaction mixture

was refluxed overnight with stirring, filtered and the filtrate was concentrated in *vacuo*. The residue was purified by flash chromatography over SiO_2 using ethyl acetate/CH_2Cl_2 (1:9 to 1:1) to yield **46c** (1.15 g, 35 %) as a colorless oil.

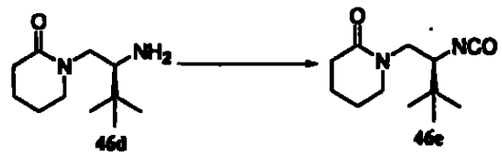
Step C:



46c 46d

A solution of pyridone **46c** (1.15 g) in MeOH (50 mL) was treated with Pd/C (10% w/w, 450 mg) and placed in a Parr® shaker and hydrogenated at 40 psi for 4 h. The reaction mixture was filtered through a plug of celite® and concentrated in *vacuo* to yield **46d** that was used in the next step without further purification.

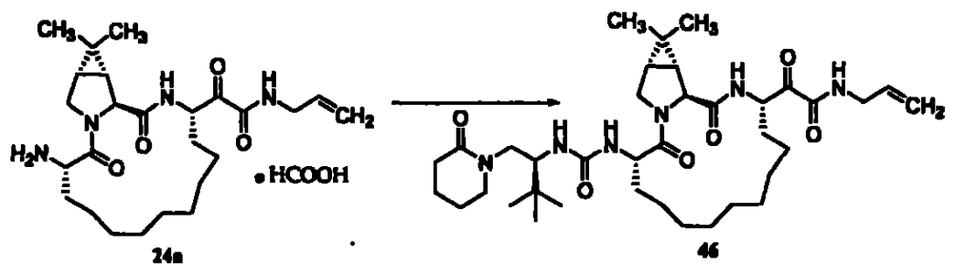
Step D:



46d 46e

A solution of amine **46d** (600 mg, 3.03 mmol) in CH_2Cl_2 (10 mL) aq. saturated $NaHCO_3$ (10 mL) at 0° C was treated with phosgene (5 mL, 15% soln. in toluene) and stirred at 0° C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with cold aq $NaHCO_3$. The organic layer was dried ($MgSO_4$) filtered and further diluted with 3 mL toluene, concentrated the methylene chloride layer and used as a solution in toluene.

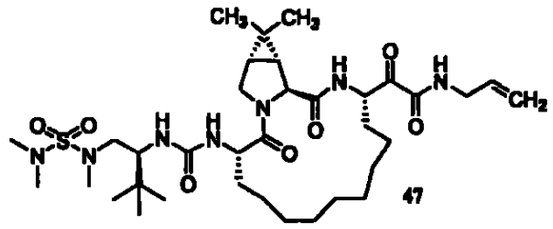
Step E:



24a 46

A solution of amine **24a** (100 mg, 0.197 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0 °C. A solution of isocyanate **46e** (1.5 mL, 0.25 mmol) in toluene was added and the reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted with methylene chloride (100 mL) and washed with aq. HCl (1 M, 50 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, ethyl acetate/hexanes 1:10 1:0) and 100% ethyl acetate to yield **46** (30 mg) as a colorless solid. ^1H NMR (dmso, 500 MHz) δ, 8.92 (t, 1 H, *J*=6.5 Hz), 8.39 (d, 1 H, *J*=9.0 Hz), 6.17 (d, 1 H, *J*=9.0 Hz), 5.81 (m, 1 H), 5.69 (d, 1 H, *J*=10.5 Hz), 5.29 (bt, 1 H, *J*=10.0 Hz), 5.13-5.10 (m, 2 H), 4.33 (s, 1H), 4.30-4.26 (m, 1 H), 3.86-3.65 (m, 6 H), 3.50 (bt, 1 H, *J*=12 Hz), 3.15-3.08 (m, 2 H), 2.21-2.05 (m, 2 H), 1.74-1.54 (bm, 6 H), 1.46-1.11 (bm, 18 H), 0.99 (s, 3 H), 0.84 (s, 3 H), 0.82 (s, 9 H). ^{13}C NMR (dmso, 125 MHz) δ, 198.2, 172.1, 171.3, 169.3, 162.1, 158.2, 135.0, 116.4, 60.5, 55.8, 55.1, 52.8, 51.5, 48.3, 47.6, 47.0, 41.7. 34.6, 33.0, 32.4, 31.5, 28.3, 28.0, 27.8, 27.2, 26.9, 26.2, 24.5, 23.7, 22.4, 21.9, 19.5, 13.7.

Preparative Example 47: Preparation of:



47

Step A:



47a 47b

The amine, **47a**, (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 rise 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 **47b**. ^{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).

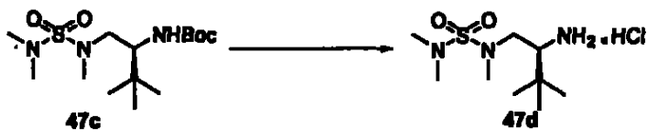
Step B:



47b 47c

To the Boc protected sulfonyl urea **47b** (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 were dried over anhydrous sodium sulfate, filtered and evaporated off the solvent to afford 420 mg (91%) of **47c** that was used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) □ 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:

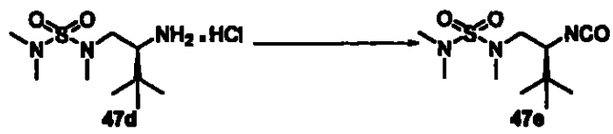


47c 47d

To the Boc-protected sulfonyl urea **47c** (890 mg, 1 equiv.) was added 4 M solution of HCl in dioxane (25 mL) at room temperature 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.

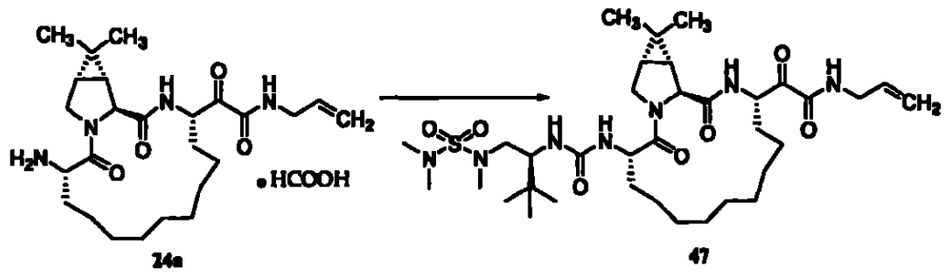
Step D:



47d 47e

To the amine hydrochloride salt **47d** (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:



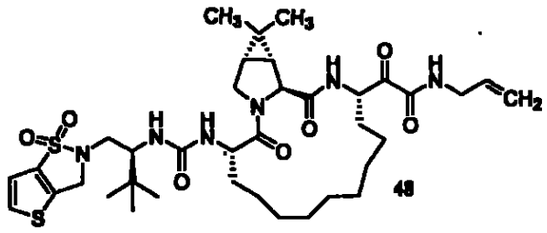
24a 47

A solution of amine **24a** (100 mg, 0.197 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0 °C. A solution of isocyanate **47e** (1.5 mL, 0.25 mmol,) in toluene was added and the reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted with methylene chloride (100 mL) and washed with aq. HCl (1 M, 50 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and

purified by chromatography (SiO_2, ethyl acetate/hexanes 1:10 1:0) and 100% ethyl acetate to yield 47 (49 mg) as a colorless solid.

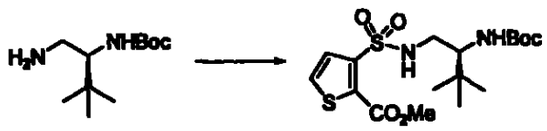
^{1}H NMR (dmso, 500 MHz) δ, 8.89 (t, 1 H, *J*=6 Hz), 8.37 (d, 1 H, *J*=9.0 Hz), 6.15 (d, 1 H, *J*=9.0 Hz) 5.83-5.76 (m, 2 H), 5.31-5.27 (m, 2 H), 4.33 (s, 1 H), 4.30-4.28 (m, 1 H), 3.91 (d, 1 H, *J*=10.5 Hz), 3.80-3.70 (m, 4 H), 3.63-3.59 (m, 1 H), 2.93 (dd, 1 H), 2.7 (s, 3 H), 2.69 (s, 6 H), 1.73-1.65 (m, 2 H), 1.51-1.02 (m, 18 H), 0.99 (s, 3 H), 0.84 (s, 3 H), 0.81 (m, 9 H) ^{13}C NMR (dmso, 125 MHz) δ, 198.3, 172.1, 171.7, 162.1, 158.2, 135.0, 116.5, 60.5, 55.8, 52.8, 51.7, 1.3, 47.6, 41.1, 38.5, 36.0, 34.9, 32.3, 31.6, 31.3, 28.5, 28.4, 27.9, 27.4, 27.4, 27.1.MS (ES) *m/z* relative intensity 746 [(M+Na)$^+$, 40]; 724 [(M+1)$^+$, 100].

Preparative Example 48: Preparation of:



48

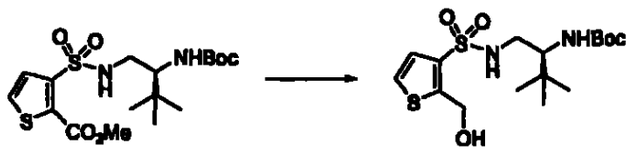
Step A:



48a 48b

Compound **48b** was prepared from **48a** and 2-carbomethoxy-3-thiophenesulfonyl chloride according to the procedures described for the preparation of compound **45b**.

Step B:

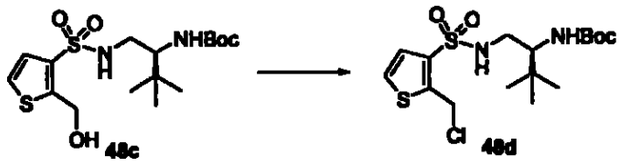


48b 48c

To the solution of ester **48b** (4.65 g, 11.1 mmol) in anhydrous toluene (40 mL) at -78 °C was added a solution of DIBAL-H in toluene (23.0 mL, 34.5

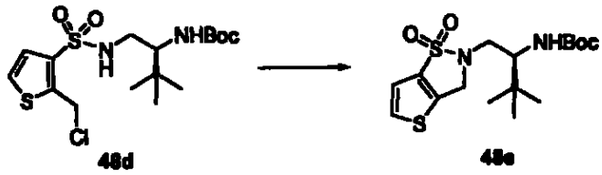
mmol). The mixture was stirred at -78 °C for 20 min and at rt. for 2 h. Methanol (20 mL) was added followed by 10% aqueous citric acid solution (100 mL). After stirred for 5 min, EtOAc (200 mL) was added and layers were separated. The aqueous solution was extracted with EtOAc (2 x100mL). The organic solutions were combined, dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography using 10-50% acetone/hexanes to give 4.6 g (quant.) of **48c**.

Step C:



To a solution of **48c** (1.04 g, 2.65 mmol) in CH_2Cl_2 I (50 mL) at 0 °C was added methanesulfonyl chloride (0.23 mL, 2.97 mmol) and triethylamine (0.80 mL, 5.74 mmol). The mixture was warmed to rt along with ice bath and stirred for 18 h. EtOAc (200 mL) and 5% H_3PO_4 solution (100 mL) was added and the layers were separated. The organic solutions were washed with 1 N sodium carbonate solution (100 mL) before it was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography using 10-50% acetone/hexanes to give 0.80 g (73%) of **48d**.

Step D:



A suspension of **48d** (1.17 g, 2.85 mmol) and cesium carbonate (1.40 g, 4.30 mmol) in anhydrous DMF (100 mL) was stirred at rt. for 18 h. Water (50 mL), brine (50 mL) and EtOAc (300 mL) were added and the layers were separated. The organic solution was washed water (3 x 150 mL) before it was dried, filtered and concentrated to give 0.99 g of the desired product **48e** (93%).

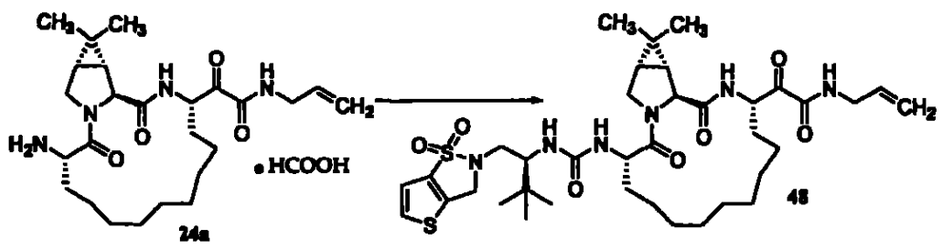
Step E:



48e 48f

Compound **48f** was prepared from **48e** according to the procedures described for the preparation of compounds **45b** and **45c**.

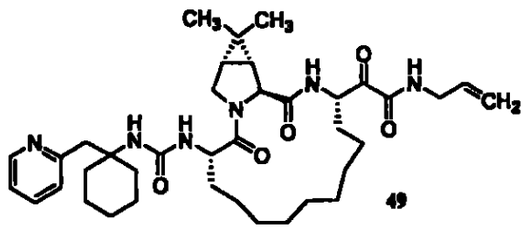
Step F:



24a 48

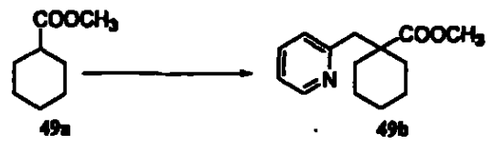
A solution of amine **24a** (100 mg, 0.197 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0 °C. A solution of isocyanate **48f** (2 mL, 0.25 mmol,) in toluene was added and the reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted with methylene chloride (100 mL) and washed with aq. HCl (1 M, 50 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, ethyl acetate/hexanes 1:1→1:0) and 100% ethyl acetate to yield **48** as a colorless solid.

Preparative Example 49: Preparation of:



49

Step A:

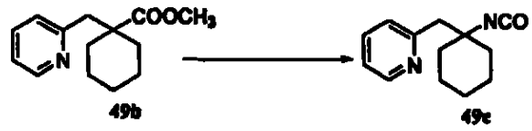


49a 49b

A solution of 2 M LDA / THF-heptane (Acros Chemical Co.) in 50 mL of THF was cooled to -70° C, methyl cyclohexanecarboxylate **49a** was added

drop wise at < -60° C. After an additional 0.5 hr stirring at –70 °C, 2-picolyl chloride in 40 mL ether was added drop wise at < -60° C. The temperature was then allowed to rise slowly to room temperature over 2 hr, and stirred an additional 2 hr. The reaction was quenched in a cold mixture of 200 mL 20% aqueous KH_2PO_4 and 5 mL of 12 N HCl, the mixture was extracted with EtOAc, the extract was washed with brine, and then dried with $MgSO_4$. The mixture was filtered, the filtrate was evaporated, the residue was evaporated twice from xylene, and the final residue was chromatographed on silica gel (1:3 Et_2O-CH_2Cl_2 to 1:1 acetone-CH_2Cl_2) to obtain **49b**.

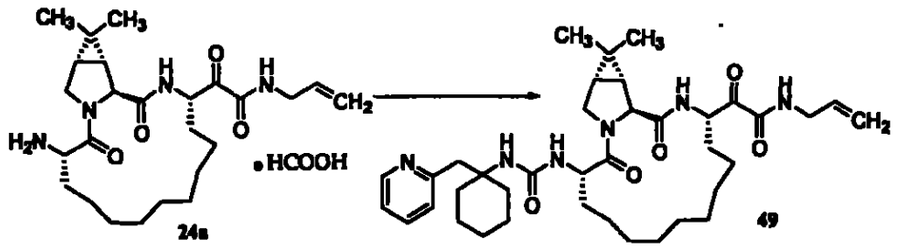
Step B:



49b 49c

A solution of ester **49b** in 20 mL of dioxane was treated with 30 mL of 1 N aqueous LiOH, and the mixture was stirred at 100° C for 6 hr. The mixture was quenched in ice-water, extracted with ether, and the cold aqueous was slowly acidified to pH ~4 with 3 N HCl. The precipitate was filtered, washed with water, and dried to leave product acid that was used in the following step without further purification. The conversion of the acid to the isocyanate **49c** was identical to the synthesis of **27b** in preparative example **27.**

Step C:

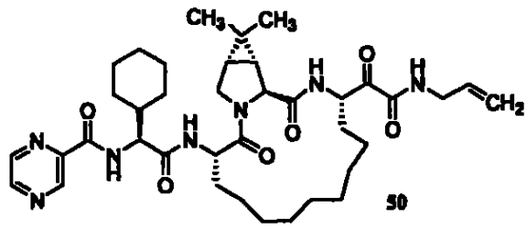


24a 49

A solution of amine **24a** (100 mg, 0.197 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0 °C. A solution of isocyanate **49c** (2.9 mL, 0.25 mmol,) in toluene was added and the reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted with methylene chloride (100 mL) and washed with aq. HCl (1 M, 50 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and

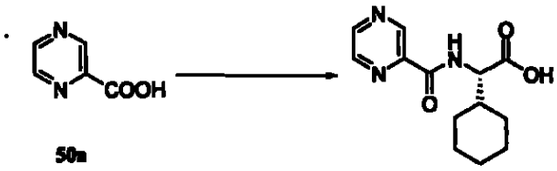
purified by chromatography (SiO_2, ethyl acetate/hexanes 1:1◊ 1:0) and 100% ethyl acetate to yield 49 as a colorless solid.

Preparative Example 50: Preparation of:



50

Step A:



50a 50b

A solution of pyrazinecarboxylic acid 50a (Aldrich, 3 g) in 150 mL of dry dichloromethane and 150 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 6.03 g). L-cyclohexylglycine-methyl ester hydrochloride (1.2 eq, 6.03 g) was added in small portions. Then, N-methylmorpholine (4 eq, 10 mL, d 0.920) was added dropwise. The reaction mixture was gradually warmed to room temperature and stirred for 20 h. All the volatiles were removed under vacuum and the residue was dissolved in 500 mL of ethyl acetate. The organic layer was washed with water (100 mL), aq. 1N HCl (100 mL), aq. saturated sodium bicarbonate solution (100 mL), and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 5:95 to 3:7) to afford the product 50b (6.5 g, 95%) as a white solid.

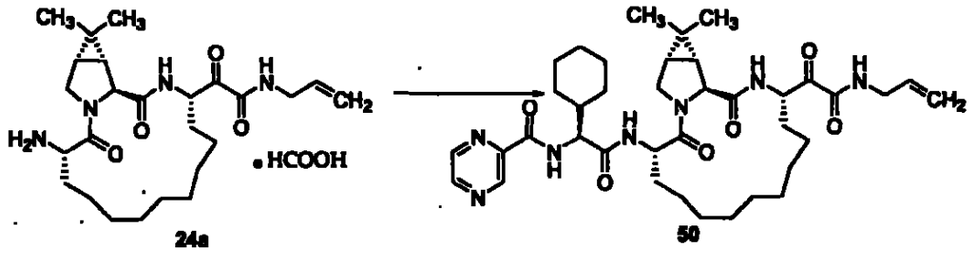
Step B:



50b 50c

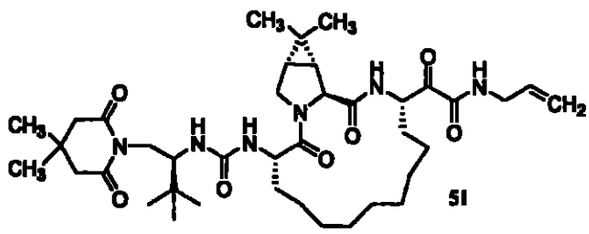
A solution of methyl ester **50b** (6.5 g) in 270 mL of a 1:1:1 mixture of THF/MeOH/H_2O was cooled to 0 °C and treated with lithium hydroxide monohydrate (2.5 eq, 2.45 g). The mixture was stirred and monitored by TLC (acetone/hexanes; 2:8). When all the starting material had been consumed, the reaction mixture was treated with 100 mL of aq 1N HCl and the mixture was concentrated in *vacuo*. Dichloromethane (250 mL) was added and layers separated. The aqueous layer was extracted with dichloromethane (3 x 80 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford acid **50c**.

Step C:



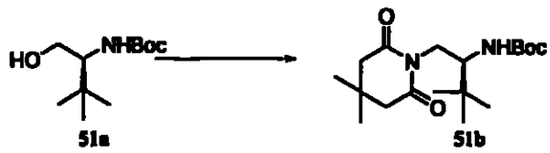
A solution of acid **24a** (100 mg, 0.197 mmol) in dry CH_2Cl_2 (2 mL) and DMF (2 mL) was cooled to 0° C and treated with acid **50c** (51.8 mg, 0.197 mmol), HATU (94 mg, 0.25 mmol) and NMM (45 mg, 0.45 mmol). The reaction was stirred at 0° C for 12 h and concentrated in *vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL) and washed with aq. HCl (1 M, 2x 30 mL), aq. saturated $NaHCO_3$ (2x30mL), brine (30 mL), dried ($MgSO_4$), filtered, concentrated in *vacuo*. The crude dipeptide was purified by chromatography (SiO_2, acetone/Hexanes 0:1→1:1) to yield **50**. ^{1}H NMR (dmso, 400 MHz) δ, 9.16 (δ, 1 H, *J*=12 Hz), 8.89 (d, 1 H, *J*=2.4 Hz), 8.74 (s, 1 H), 8.59 (d, 1 H, *J*=7.4 Hz), 8.43-8.38 (m, 2 H), 5.81-5.75 (m, 1 H), 5.28 (t, 1 H, *J*=10.8 Hz), 5.11-5.03 (m, 2 H), 4.45-4.31 (m, 3 H), 3.88-3.70 (m, 5 H), 1.65-1.22 (m, 31 H), 0.97 (s, 3 H), 0.83 (s, 3 H).MS (ES) *m/z* relative Intensity 728 [$(M+Na)^+$, 4]; 706 [$(M+1)^+$, 80].

Preparative Example 51: Preparation of:



51

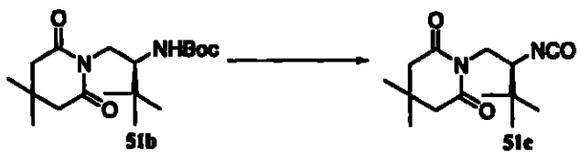
Step A:



51a 51b

A solution of the alcohol **51a** (1.00 g, 4.6 mmol) in anhydrous CH_2Cl_2 (30 mL) in an inert atmosphere was treated with triphenylphosphine (1.52 g, 5.75 mmol) and dimethylglutarimide (780 mg, 5.52 mmol). The reaction mixture was cooled to 0 °C and treated with DIAD (930 mg, 4.60 mmol, in 4 mL CH_2Cl_2) dropwise and warmed to rt. It was stirred at rt. for 5 h and concentrated in *vacuo*. The residue was purified by chromatography (SiO_2, Hexanes/acetone 1:0→1:1) to obtained **51b** (600 mg) as a colorless solid.

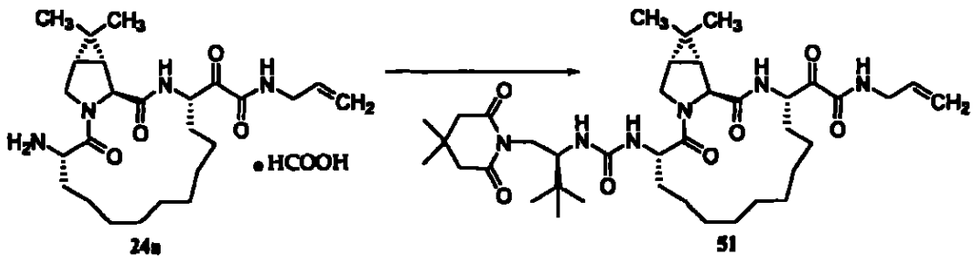
Step B:



51b 51c

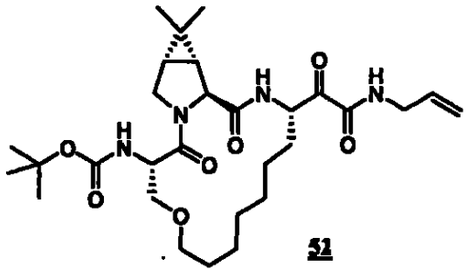
A solution of **51b** (500 mg, 1.5 mmol) in HCl (15 mL, 4M soln. in dioxane) was stirred at rt. for 1 h and concentrated in *vacuo*. The residue was used in further reaction without purification. A solution of the deprotected amine in CH_2Cl_2 (10 mL) aq. saturated $NaHCO_3$ (10 mL) at 0° C was treated with phosgene (5 mL, 15% soln. in toluene) and stirred at 0° C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with cold aq. $NaHCO_3$. The organic layer was dried ($MgSO_4$) filtered and further diluted with 3 mL toluene, concentrated the methylene chloride layer and used as a solution.

Step C:



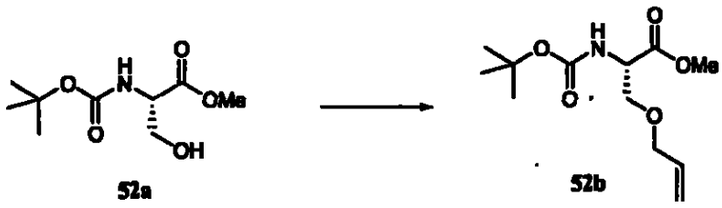
A solution of amine **24a** (100 mg, 0.196 mmol) in methylene chloride (3.0 mL) was treated with NMM (60 mg, 0.6 mmol) and cooled to 0° C. A solution of isocyanate **51c** (2 mL, 0.5 mmol,) in toluene was added and the reaction mixture was stirred at rt. for 2 h. The reaction mixture was diluted with methylene chloride (100 mL) and washed with aq. HCl (1 M, 50 mL). The organic layers were dried with ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2 Acetone/hexanes 0:1→1:1) yield **51** as a colorless solid. ^{1}H NMR (dmso, 500 MHz) δ, 8.91 (d, 1H), 6.19 (d, 1 H, *J*=8.5 Hz), 5.84-5.57 (m, 1 H), 5.58 (d, 1 H, *J*=10.5 Hz), 5.28 (t, 1 H, *J*=7.0 Hz), 5.05 (m, 2 H), 4.31 (s, 1 H), 4.18 (t, 1 H, *J*=8.5 Hz), 3.83-3.57 (m, 7 H), 2.44-2.38 (AB, 4 H), 1.66-1.62 (m, 2 H), 1.44-1.03 (m, 18 H), 0.98 & 0.96 (2s, 9 H), 0.84 & 0.81 (2s, 12 H). ^{13}C NMR (dmso, 125 MHz) δ,198.2, 172.7, 172.1, 171.3, 162.1, 158.1, 135.0, 116.4, 60.5, 55.5, 52.9, 51.3, 47.5, 46.4, 41.7, 39.6, 35.0, 32.4, 31.5, 31.3, 29.3, 28.3, 27.9, 27.0, 26.9, 26.6, 26.1, 24.5, 22.4, 19.5, 13.7.MS (ES) *m/z* relative Intensity 749 [(M+Na)$^+$, 20]; 727 [(M+1)$^+$, 100].

Preparative Example 52: Preparation of:



51

Step A:



52a 52b

A solution of N-Boc-L-Ser-OMe (3.6 g, Aldrich) in 150 mL of dry THF was degassed (vacuum/N2-flush) and treated with allylmethyl carbonate (1.4 eq, 2.6 mL, d 1.022). A catalytic amount of tetrakis(triphenylphosphine)palladium (0.02 mol%, 379 mg) was added. The slightly yellow mixture was degassed again and heated at 60 °C for about 3 h until TLC analysis (acetone/hexanes; 2:8) showed no more starting material left (reaction mixture became brown). The THF was removed under reduced pressure and the residue was diluted with 300 mL of ethyl acetate and washed with 80 mL of aqueous saturated sodium bicarbonate solution and 80 mL of brine. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 5:95 to 2:8) to afford the product **52b** as a clear oil (2.7 g, 64%).

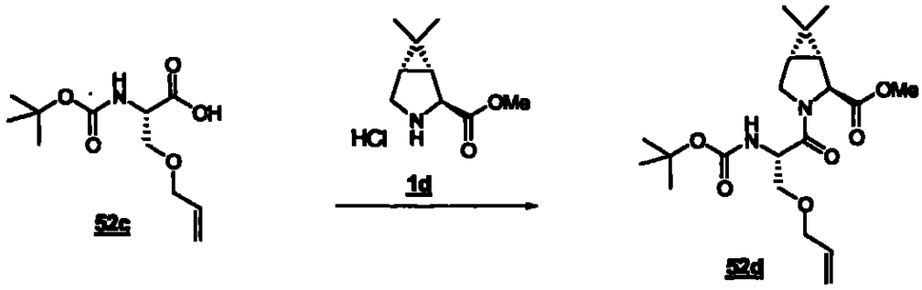
Step B



52b 52c

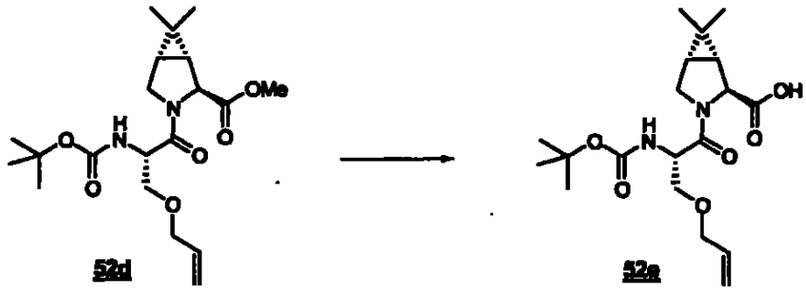
A solution of methyl ester **52b** (1.5 g) in 90 mL of a mixture of THF/MeOH/H_2O (1:1:1) was treated with lithium hydroxide monohydrate (2.5 eq, 630 mg). Reaction was stirred at room temperature and monitored by TLC (acetone/hexanes; 1:9). After 45 min, all the volatiles were removed under reduced pressure. The residue was partitioned between 80 mL of aqueous 1N HCl and 200 mL of dichloromethane. The aqueous layer was back extracted with dichloromethane (2 x 80 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the product **52c** as a clear oil (1.4 g, 95%).

Step C



A solution of acid **52c** (6 mmol) in 40 mL of dry dichloromethane and 40 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 3.2 g). The amine hydrochloride **1d** (1.3 eq, 1.6 g) and N-methylmorpholine (4 eq, 2.6 mL, d 0.920) were successively added. The reaction mixture was gradually warmed to room temperature and stirred overnight. All the volatiles were removed under vacuum and the residue was taken into 300 mL of ethyl acetate. The organic layer was washed with aqueous 1N HCl (50 mL), aqueous saturated sodium bicarbonate (50 mL), and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 5:95 to 2:8) to afford the desired product **52d** (2.23 g, 93%) as a clear oil.

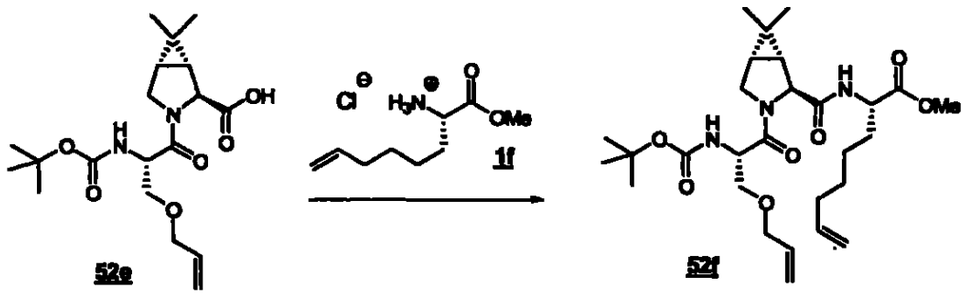
Step D



A solution of methyl ester **52d** (2.23 g) in 45 mL of a mixture of THF/MeOH/H_2O (1:1:1) was treated with lithium hydroxide monohydrate (2.5 eq, 300 mg) at 0 °C. The cooling bath was removed and the reaction mixture was stirred at room temperature and monitored by TLC (acetone/hexanes; 2:8). After 1 h, 10 mL of aq 1N HCl were added and all the volatiles were removed under reduced pressure. The residue was partitioned between 30

mL of aqueous 1N HCl and 100 mL of dichloromethane. The aqueous layer was back extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the product **52e** (1.88 g, 88%) as a clear oil.

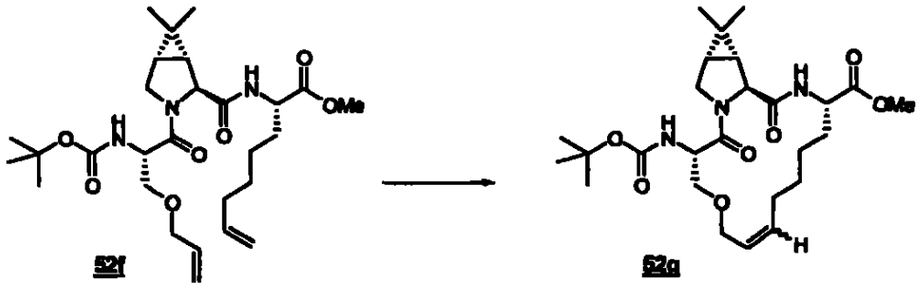
Step E



52e 52f

A solution of acid **52e** (830 mg) in 20 mL of dry dichloromethane and 20 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 1.15 g). The amine hydrochloride **1f** (1.1 eq, 227 mg) was added in 10 mL of dichloromethane followed by N-methylmorpholine (4 eq, 0.95 mL, d 0.920). The reaction mixture was kept in the freezer (-20 °C) for 48 h. All the volatiles were removed under vacuum and the residue was dissolved in 200 mL of ethyl acetate. The organic layer was washed with water (50 mL), aqueous 1N HCl (50 mL), aqueous saturated sodium bicarbonate solution (50 mL), and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 5:95 to 3:7) to afford the product **52f** (680 mg) as a white solid along with a minor diastereomeric product (130 mg) for a combined yield of 70%.

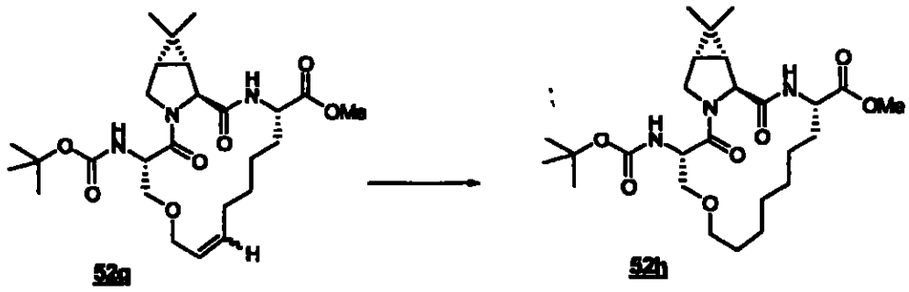
Step F



52f 52g

A 0.01M solution of diene **52f** (670 mg) in toluene was degassed for 30 min (argon bubbling) and treated with Grubb's catalyst (0.2 eq, 205 mg). The pink solution was heated to 60 °C for 16 h (the solution became dark after heating 10 min). The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (gradient: ethyl acetate/hexanes; 2:8 to 1:1) to afford the alkene product **52g** (570 mg, 90%) as a mixture of E- and Z-isomers (approx 4:1).

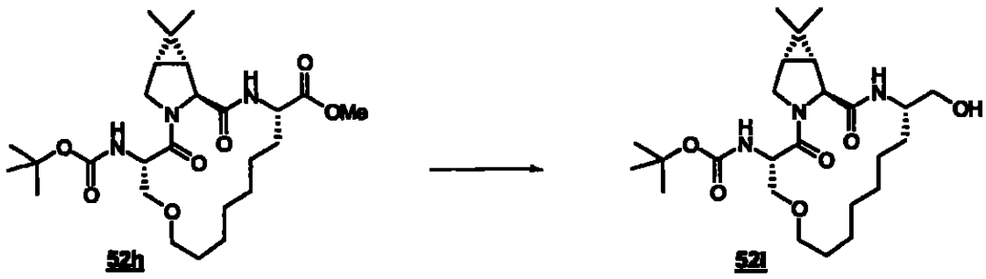
Step G



52g **52h**

A solution of alkene **52g** (570 mg) in 20 mL of methanol was treated with palladium dihydroxide on carbon (0.1 mol%, 78 mg of 20% Pd(OH)2/C). The mixture was hydrogenated at 50 psi until all the starting material had been consumed. The reaction mixture was diluted with 100 mL of dichloromethane and filtered thru a short path of celite. The filtrate was concentrated and the residue was chromatographed on silica gel to afford the product **52h** (590 mg, 70%) as a clear oil.

Step H

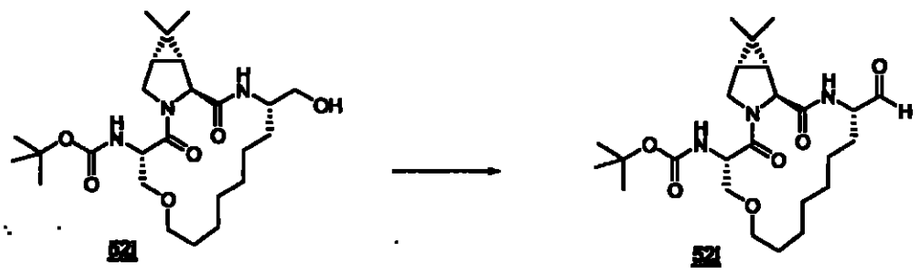


52h **52i**

A solution of methyl ester **52h** (580 mg) in 20 mL of dry THF was treated with lithium borohydride (2.1 eq, 1.2 mL of a 2M soln in THF). The reaction mixture was stirred at room temperature and monitored by TLC

(acetone/hexanes; 3:7) for disappearance of the starting material. After 5 h, the excess lithium borohydride was quenched by addition of aqueous saturated ammonium chloride solution (3 mL). The mixture was partitioned between ethyl acetate (100 mL) and aqueous saturated sodium bicarbonate solution (50 mL). The aqueous layer was back extracted with ethyl acetate (2 x 30 mL) and dichloromethane (2 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 5:5) to afford the product **52I** (360 mg, 68%) as a white solid.

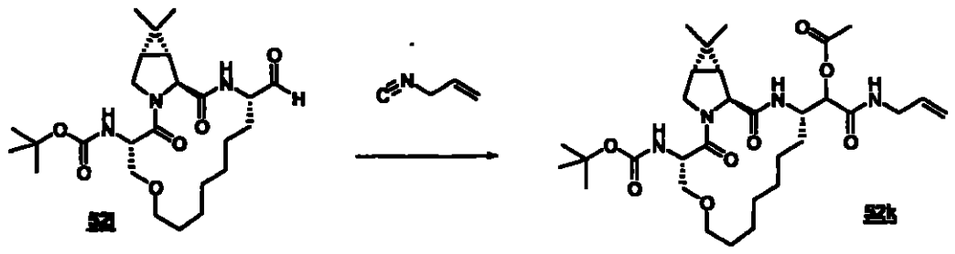
Step I



52I **52I**

A solution of alcohol **52I** (350 mg) in 20 mL of dry dichloromethane was treated with Dess-Martin periodinane (3 eq, 925 mg). The reaction mixture was stirred at room temperature for 45 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (15 mL) and aqueous saturated sodium bicarbonate solution (15 mL) and stirred for 15 min. The mixture was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 4:6) to afford the product **52J** (285 mg, 83%) as a colorless solid.

Step J

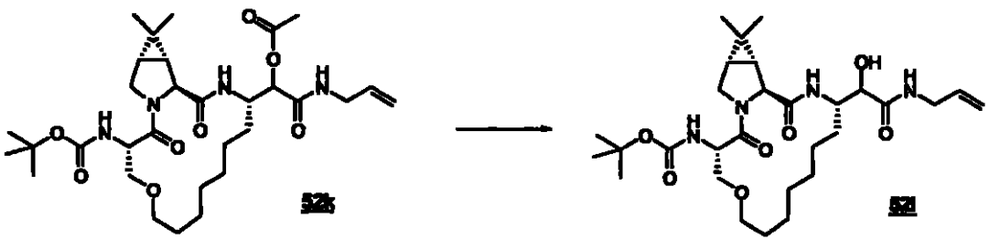


52I **52k**

215
218

A solution of aldehyde 52j (270 mg) in 10 mL of dry dichloromethane was treated with allylisocyanide (2 eq, 77 mg) and acetic acid (2 eq, 0.064 mL, d 1.049). The mixture was stirred for about 5 h. All the volatiles were removed under vacuum and the residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 1:1) to afford the product 52k (303 mg, 90%) as a white solid.

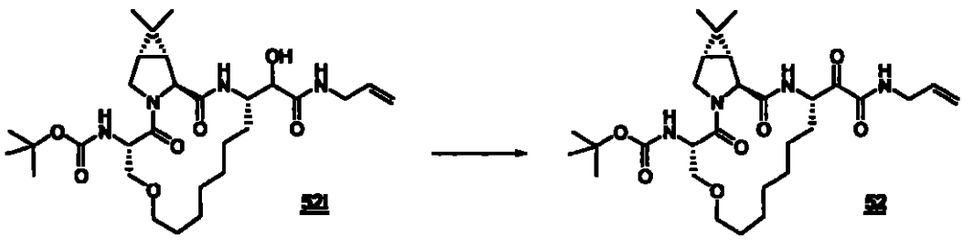
Step K



52k 52l

The acetate 52k (300 mg) was dissolved in 15 mL of a 1:1:1 mixture of THF/MeOH/H_2O and treated with lithium hydroxide monohydrate (2.5 eq, 51 mg). The flow of the reaction was followed by TLC (acetone/hexanes; 4:6). After 15 min the reaction mixture was concentrated in the rotavap and the residue was partitioned between dichloromethane (80 mL) and aqueous saturated sodium bicarbonate solution (20 mL). The aqueous layer was back extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude product 52l (276 mg, 98%) was used without further purification.

Step L

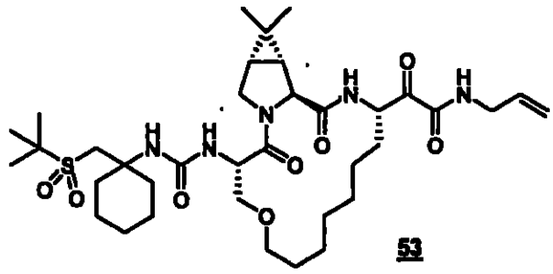


52l 52

A solution of hydroxyamide 52l (276 mg) in 20 mL of dry dichloromethane was treated with Dess-Martin periodinane (3 eq, 424 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (20 mL) and

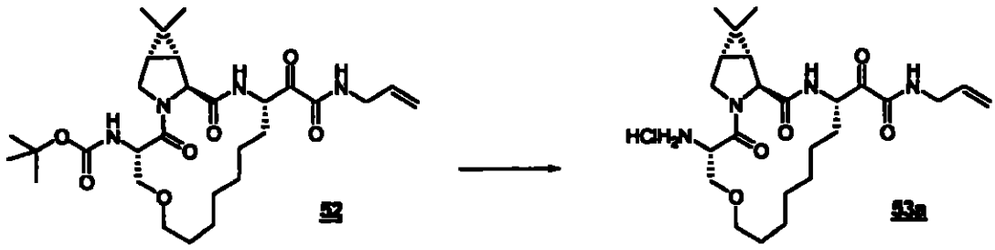
aqueous saturated sodium bicarbonate solution (10 mL) and stirred for 10 min. The mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 4:6) to afford the product 52 (236 mg, 86%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 7.47 (d, 1H, J = 7.56 Hz), 7.03 (dd, 1H, J = 5.68, 5.99 Hz), 5.88 (ddt, 1H, J = 5.6, 10.0, 17.0 Hz), 5.50 (d, 1H, J = 8.83 Hz), 5.46 (m, 1H), 5.28 (dd, 1H, J = 0.9, 17.0 Hz), 5.25 (dd, 1H, J = 0.9, 10.0 Hz), 4.61 (m, 1H), 4.51 (s, 1H), 3.99 (dt, 2H, J = 1.2, 5.6 Hz), 3.88 (dd, 1H, J = 5.0, 10.8 Hz), 3.83 (d, 1H, J = 11.0 Hz), 3.66 (m, 2H), 3.48 (dd, 2H, J = 4.7, 5.6 Hz), 1.95 (m, 1H), 1.81 (d, 1H, J = 7.56 Hz), 1.47 (s, 9H), 1.27-1.63 (m, 12H), 1.09 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 196.7, 170.9, 170.7, 159.3, 155.6, 133.2, 117.9, 80.4, 71.0, 70.8, 61.2, 54.5, 52.9, 48.2, 42.1, 31.4, 29.3, 28.7, 27.8, 26.8, 26.6, 26.4, 23.6, 23.4, 19.2, 13.2 ppm; HRMS calcd for $C_{29}H_{47}N_4O_7$ $[M+H]^+$: 563.3445, found 563.3457.

Preparative Example 53: Preparation of:



53

Step A

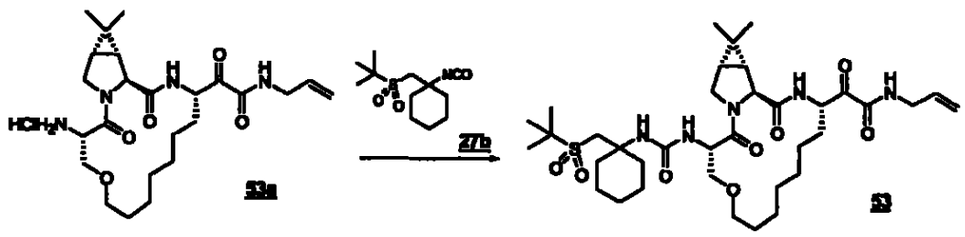


52 53a

The N-Boc protected amine 52 (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes and stirred at room temperature for 1 h. All the volatiles were removed under reduced pressure and the product was placed

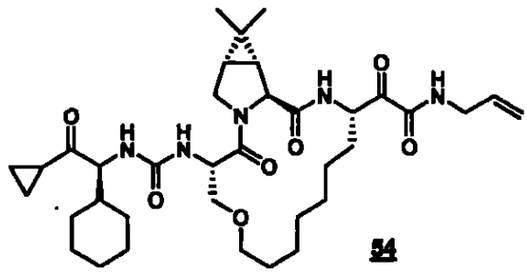
under high vacuum for 3 h. No further purification was done for the product **53a** (99%).

Step B



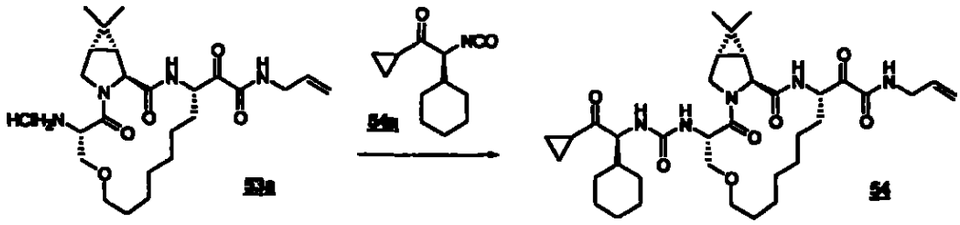
The amine salt **53a** (31 mg) was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 10 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min, a solution of the isocyanate **27b** (2.5 eq, 0.8 mL of a 0.2M solution in toluene) was added and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 3 h. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 4:6) to yield the product **53** (25 mg, 58%) as a white solid. ^{1}H NMR (500 MHz, CDCl3): δ, 7.90 (d, 1H, J = 8.5 Hz), 7.38 (br s, 1H), 5.9 (ddt, 1H, J = 5.6, 10.4, 17.0 Hz), 5.61 (ddd, 1H, J = 1.6, 8.8, 10.4 Hz), 5.27 (dd, 1H, J = 1.26, 17.3 Hz), 5.24 (dd, 1H, J = 1.26, 10.0 Hz), 4.9 (dd, 1H, J = 3.4, 8.8 Hz), 4.53 (s, 1H), 3.94-4.08 (m, 4H), 3.62 (dd, 1H, J = 8.5, 8.8 Hz), 3.56 (m, 1H), 3.47 (dd, 1H, J = 4.0, 7.9 Hz), 3.37 (ddd, 1H, J = 2.2, 7.2, 9.4), 3.15 (d, 1H, J = 13.5 Hz), 2.4 (m, 1H), 2.24 (m, 1H), 1.95 (m, 1H), 1.85 (m, 1H), 1.27-1.70 (m, 20H), 1.4 (s, 9H), 1.2 (m, 1H), 1.07 (s, 3H), 0.94 (s, 3H), 0.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 198.0, 172.1, 171.0, 159.5, 157.0, 133.3, 117.7, 70.8, 70.5, 61.0, 60.8, 54.9, 53.8, 51.0, 48.4, 42.2, 36.2, 32.0, 30.5, 28.7, 27.9, 27.2, 27.0, 26.8, 25.9, 24.1, 23.9,23.5, 21.9, 21.8, 19.3, 13.4 ppm; HRMS calcd for $C_{38}H_{60}N_5O_8S$ $[M+H]^+$: 722.4163, found 722.4193.

Preparative Example 54: Preparation of:



54

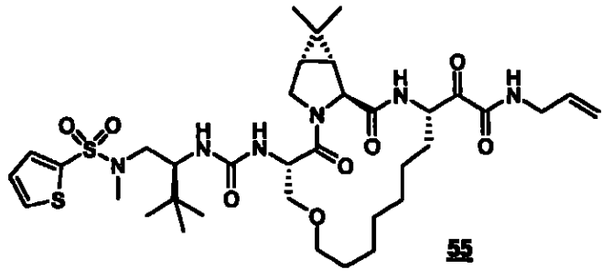
Step A



53a 54a 54

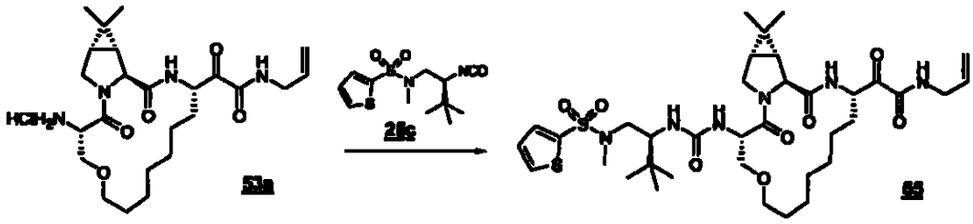
A solution of amine salt 53a (17 mg) in 2 mL of dry dichloromethane was treated with solid sodium bicarbonate (3 eq, 8 mg) followed by the addition of isocyanate 54a (2.5 eq, 0.26 mL of a 0.307M solution in toluene). The resulting heterogeneous mixture was stirred at room temperature for approximately 3 h. The mixture was diluted with 50 mL of ethyl acetate and washed with aqueous 1M HCl (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 1:1) to yield the product 54 (8 mg, 34%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ, 7.91 (br s, 1H), 7.40 (m, 1H), 6.37 (br s, 1H), 5.91 (ddt, 1H, J = 5.6, 10.4, 17.3 Hz), 5.88 (br s, 1H), 5.62 (dt, 1H, J = 1.26, 9.45 Hz), 5.28 (dd, 1H, J = 1.26, 17.3 Hz), 5.23 (dd, 1H, J = 1.26, 10.4 Hz), 4.92 (ddd, 1H, J = 3.46, 8.5, 8.5 Hz), 4.77 (dd, 1H, J = 4.7, 8.8 Hz), 4.55 (s, 1H), 3.94-4.06 (m, 4H), 3.63 (t, 1H, J = 8.2 Hz), 3.54 (ddd, 1H, J = 3.4, 6.6, 9.7 Hz), 3.47 (m, 1H), 3.38 (m, 1H), 2.09 (ddd, 1H, J = 4.4, 7.8, 12.3 Hz), 1.91 (m, 2H), 0.91-1.83 (m, 27H), 1.07 (s, 3H), 0.94 (s, 3H); HRMS calcd for $C_{36}H_{56}N_5O_7$ $[M+H]^+$: 670.4180, found 670.4177.

Preparative Example 55: Preparation of:



55

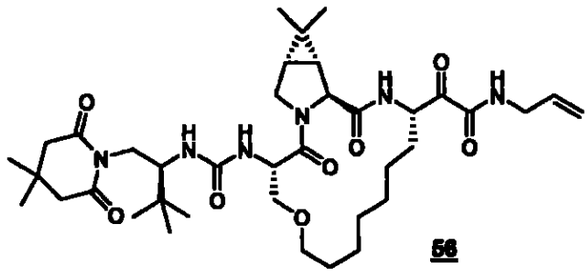
Step A



53a 25c 55

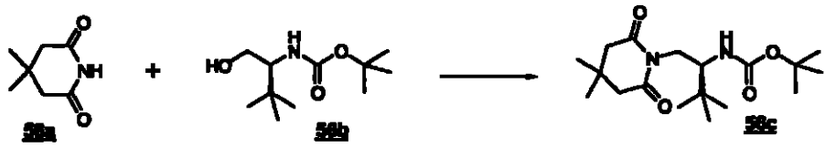
A solution of amine salt **53a** (17 mg) in 2 mL of dry dichloromethane was treated with solid sodium bicarbonate (3 eq, 8 mg) followed by the addition of isocyanate **25c** (2.5 eq, 0.45 mL of a 0.18M solution in toluene). The resulting heterogeneous mixture was stirred at room temperature for approximately 3 h. The mixture was diluted with 50 mL of ethyl acetate and washed with aq 1M HCl (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 1:1) to yield the product **55** (8 mg, 30%) as a white solid. HRMS calcd for $C_{36}H_{57}N_6O_8S_2$ $[M+H]^+$: 765.3679, found 765.3687.

Preparative Example 56: Preparation of:



56

Step A



A solution of 4,4-dimethylglutarimide **56a** (Aldrich, 1.5 eq, 4.86 g) in 200 mL of dry THF was cooled to 0 °C and treated with triphenylphosphine (3 eq, 18.07 g) and S-Boc-tert-butylglycinol **56b** (Aldrich, 5 g).

Diisopropylazodicarboxylate (2.5 eq, 11.3 mL, d 1.027) was added dropwise and the resulting solution was stirred at 0 °C. After 10 min, the mixture became a slurry and stirring was continued overnight (0 to 25 °C). The mixture was concentrated under reduced pressure and the residue was dissolved in 80 mL of ether. Hexanes (100 mL) was added and the precipitated solids were filtered off. The filtrate was concentrated to half its volume and hexanes (100 mL) was added again. The solids were filtered off. The filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate/hexanes; 2:8) to afford the product **56c** (4.0 g, 51%) as a white solid.

Step B



The N-Boc protected amine **56c** (4.0 g) was dissolved in 200 mL of 4M HCl solution in dioxanes. The mixture was stirred at room temperature and a white solid precipitated after 10 min. The mixture was further stirred for 2 h. All the volatiles were removed under reduced pressure to afford the product **56d** (3.24 g, 98%) as a white solid.

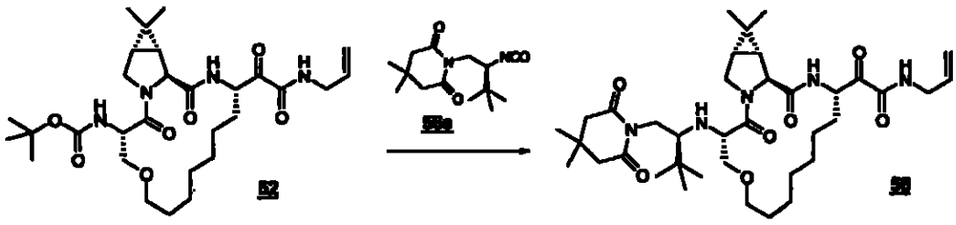
Step C



A solution of amine hydrochloride **56d** (1.5 g) in 60 mL of dichloromethane was treated with 50 mL of aqueous saturated sodium bicarbonate solution and stirred vigorously for 10 min at 0 °C. Stirring was

stopped and layers were allowed to separate. Phosgene (15 mL of 20% soln in toluene) was added through a needle to the organic layer (lower layer) in one portion. The mixture was vigorously stirred immediately after addition for 10 min at 0 °C and further stirred at room temp for 2.5 h. The mixture was diluted with 100 mL of dichloromethane and layers were separated. The organic layer was washed with 40 mL of cold aqueous saturated sodium bicarbonate solution and dried over magnesium sulfate. The organic layer was filtered and diluted with 50 mL of toluene. The product **56e** (1.44 g, 98%) was kept as a 0.216M solution in toluene.

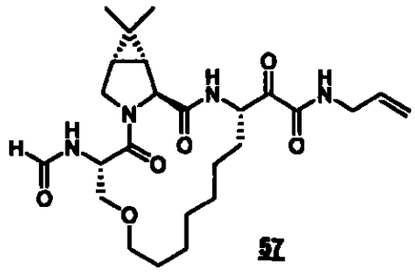
Step C



The N-Boc amine **52** (200 mg) was dissolved in 20 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 10 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min, a solution of the isocyanate **56e** was added dropwise (1.2 eq, 1.97 mL of a 0.216M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (70 mL) and washed with aqueous saturated sodium bicarbonate solution (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 15:85 to 55:45) to afford the product **56** (172 mg, 66%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ, 7.95 (d, 1H, J = 8.8 Hz), 7.59 (br s, 1H), 5.91 (br s, 1H), 5.84 (ddt, 1H, J = 5.8, 10.2, 16.8 Hz), 5.61 (ddd, 1H, J = 1.5, 8.7, 10.2 Hz), 5.21 (dd, 1H, J = 1.4, 17.5 Hz), 5.17 (dd, 1H, J = 1.4, 10.2

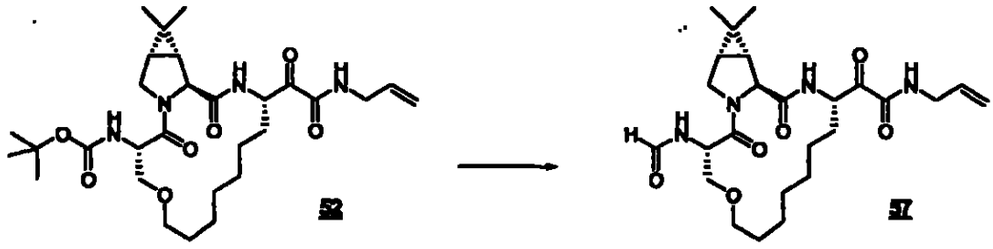
Hz), 5.13 (br s, 1H), 4.86 (br s, 1H), 4.52 (s, 1H), 4.05 (d, 1H, *J* = 10.2 Hz), 3.80-3.99 (m, 6H), 3.50 (m, 2H), 3.27 (m, 2H), 2.51 (d, 2H, *J* = 16.8 Hz), 2.43 (d, 2H, *J* = 16.8 Hz), 1.88 (m, 1H), 1.77 (m, 1H), 0.84-1.58 (m, 12H), 1.05 (s, 6H), 0.97 (s, 3H), 0.92 (s, 9H), 0.81 (s, 3H); ^{13}C NMR (CDCl3, 125 MHz): δ 198.6, 172.8, 172.0, 171.2, 159.3, 157.8, 133.4, 117.7, 71.4, 70.8, 60.7, 57.0, 53.5, 48.5, 46.8, 42.2, 40.0, 34.9, 32.1, 30.9, 29.4, 28.7, 28.1, 27.7, 27.4, 26.9, 24.3, 19.3, 13.5 ppm; HRMS calcd for $C_{38}H_{61}N_6O_8$ $[M+H]^+$: 729.4551, found 729.4529.

Preparative Example 57: Preparation of:



57

Step A

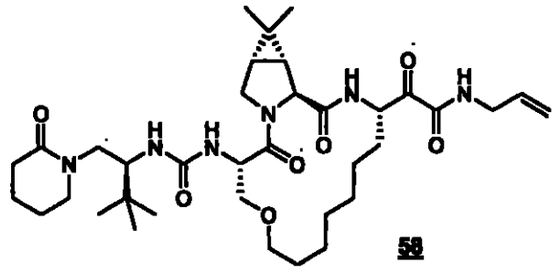


52 57

The N-Boc protected amine 52 (101 mg) was dissolved in 10 mL of formic acid and stirred at room temperature for 1 h. All the volatiles were removed in rotovap and the residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to give the formylated product 57 (35 mg, 40%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ, 8.24 (s, 1H), 7.35 (d, 1H, *J* = 7.8 Hz), 7.07 (br s, 1H), 6.83 (d, 1H, *J* = 6.9 Hz), 5.89 (ddt, 1H, *J* = 5.6, 10.0, 17.0 Hz), 5.47 (m, 1H), 5.28 (dd, 1H, *J* = 1.2, 17.3 Hz), 5.25 (dd, 1H, *J* = 1.2, 10.4 Hz), 4.95 (ddd, 1H, *J* = 3.1, 5.9, 8.5 Hz), 4.51 (s, 1H), 3.99 (m, 2H), 3.92 (dd, 1H, *J* = 5.3, 11.0 Hz), 3.75 (d, 1H, *J* = 11.0 Hz), 3.74 (m, 1H), 3.70 (dd, 1H, *J* = 5.6, 9.1 Hz), 3.48 (m, 2H), 1.96 (m, 1H), 1.77 (d, 1H, *J*

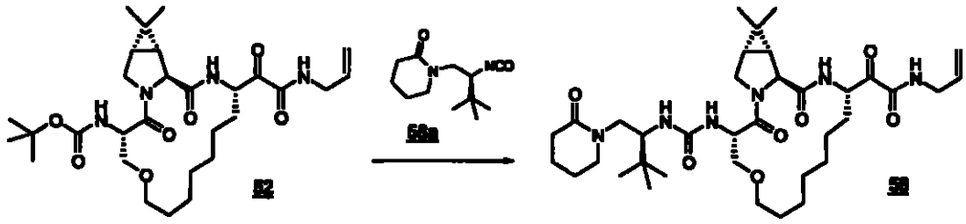
= 7.8 Hz), 1.76 (m, 1H), 1.27-1.63 (m, 11H), 1.10 (s, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.8, 170.5, 169.4, 160.8, 159.3, 133.1, 117.9, 71.3, 70.0, 61.5, 54.4, 50.8, 48.2, 42.1, 32.0, 31.5, 29.4, 28.6, 27.8, 26.7, 26.6, 23.6, 23.5, 19.3, 14.5, 13.2 ppm; HRMS calcd for $C_{25}H_{39}N_4O_6$ $[M+H]^+$: 491.2870, found 491.2882.

Preparative Example 58: Preparation of:



58

Step A

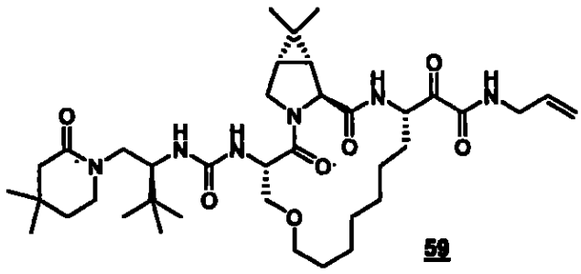


52 58a 58

The N-Boc protected amine 52 (80 mg) was dissolved in 5 mL of 4M HCl soln in dioxanes and stirred at room temperature for 45 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 3 mL of dry dichloromethane and treated with N-methylmorpholine (3 eq, 0.05 mL, d 0.920). The isocyanate 58a was added in solution (2 eq, 3.8 mL of a 0.075M solution in toluene). The reaction mixture was stirred at room temperature for about 3 h. The mixture was diluted with ethyl acetate (50 mL) and washed with aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 3:7 to 7:3) to afford the product 58 (16 mg, 16%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ, 8.19-8.39 (br s, 1H), 8.05 (d, 1H, J = 8.5 Hz), 6.22 (br s, 1H), 5.91

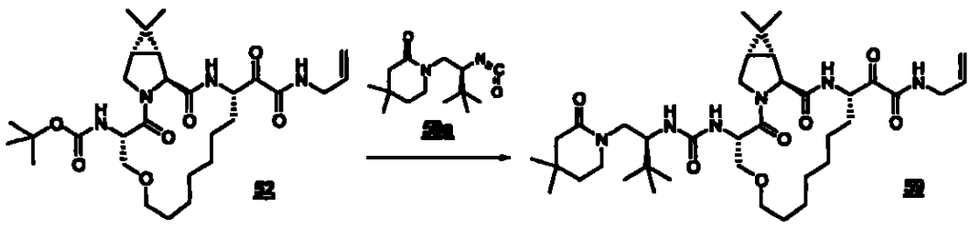
(ddt, 1H, J = 5.6, 10.0, 17.0 Hz), 5.71 (dd, 1H, J = 9.4, 10.0 Hz), 5.33 (d, 1H, J = 9.4 Hz), 5.28 (m, 1H), 5.26 (dd, 1H, J = 1.2, 17.0 Hz), 5.20 (dd, 1H, J = 1.2, 10.4 Hz), 4.96 (ddd, 1H, J = 4.0, 9.4, 9.4 Hz), 4.60 (s, 1H), 4.32 (t, 1H, J = 12.6 Hz), 4.12 (d, 1H, J = 10.7 Hz), 3.86-4.07 (m, 4H), 3.49-3.63 (m, 3H), 3.38 (dd, 1H, J = 4.1, 7.9 Hz), 3.31 (m, 1H), 3.16 (m, 1H), 2.66 (dd, 1H, J = 2.8, 13.8 Hz), 2.39 (dt, 1H, J = 5.6, 17.3 Hz), 2.27 (dt, 1H, J = 6.6, 17.3 Hz), 1.89-2.04 (m, 2H), 1.71-1.87 (m, 4H), 0.88-1.64 (m, 11H), 1.03 (s, 3H), 0.93 (s, 9H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.2, 171.8, 171.3, 159.5, 158.2, 133.7, 117.3, 71.4, 70.8, 60.6, 55.7, 53.5, 51.0, 48.3, 48.1, 46.5, 42.2, 34.3, 32.7, 31.8, 31.0, 28.7, 27.8, 27.6, 27.0, 26.9, 24.6, 24.4, 23.5, 21.7, 19.2, 13.5 ppm; HRMS calcd for $C_{36}H_{59}N_6O_7$ $[M+H]^+$: 687.4445, found 687.4434.

Preparative Example 59: Preparation of:



59

Step A

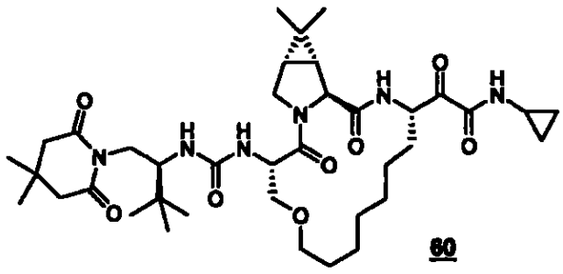


52 59a 59

The N-Boc amine 52 (56 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 15 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min, a soln of the isocyanate 59a was added dropwise (1.0 eq) and stirring was

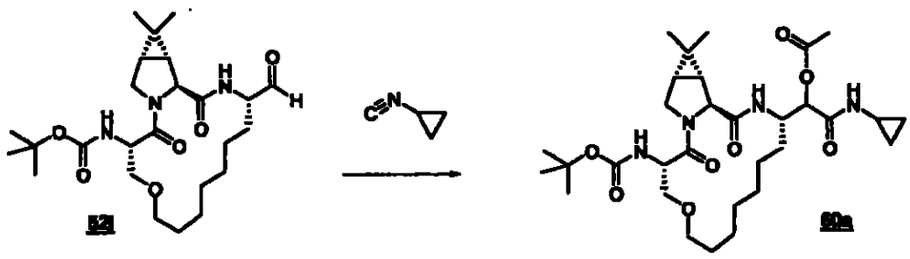
continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with aqueous 1M HCl (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product **59** (35 mg, 50%) as a white solid. HRMS calcd for $C_{38}H_{63}N_6O_7$ $[M+H]^+$: 715.4758, found 715.4739.

Preparative Example 60: Preparation of:



60

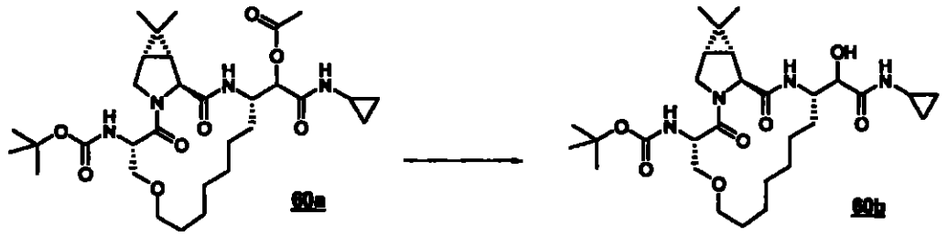
Step A



52j **60a**

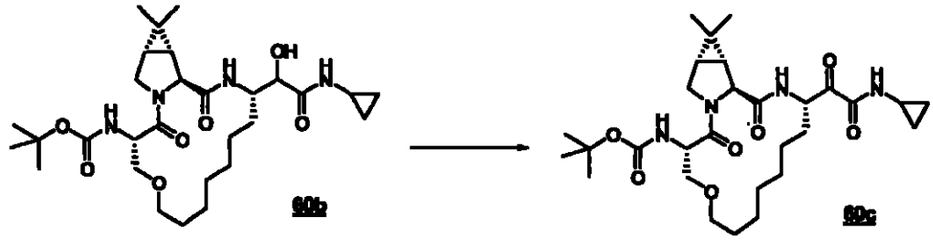
A solution of aldehyde **52j** (405 mg) in 15 mL of dry dichloromethane was treated with cyclopropylisocyanide (Oakwood Prod., 2 eq, 117 mg) and acetic acid (2 eq, 0.1 mL, d 1.049). The mixture was stirred at room temperature overnight. All the volatiles were removed under reduced pressure and the residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 1:1) to afford the product **60a** (500 mg, 98%) as a white solid.

Step B



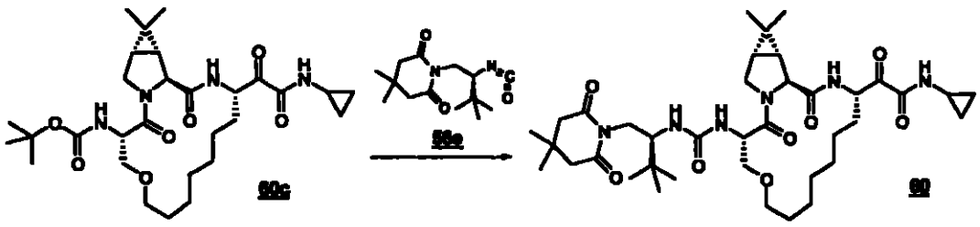
A solution of acetate **60a** (500 mg) in 15 mL of a 1:1:1 mixture of THF/MeOH/water was treated with lithium hydroxide monohydrate (2.5 eq, 86 mg) and stirred for approx. 30 min until all the starting material had been consumed as determined by TLC analysis (ethyl acetate/hexanes; 6:4). The reaction mixture was diluted with 30 mL of aqueous saturated sodium bicarbonate solution and extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford the crude product **60b** (464 mg, 98%) as a colorless semi-solid which was used without further purification.

Step C



A solution of hydroxyamide **60b** (0.824 mmol) in 20 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 698 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (15 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (20 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 5:95 to 35:65) to afford the product **60c** (333 mg, 72%) as white solid.

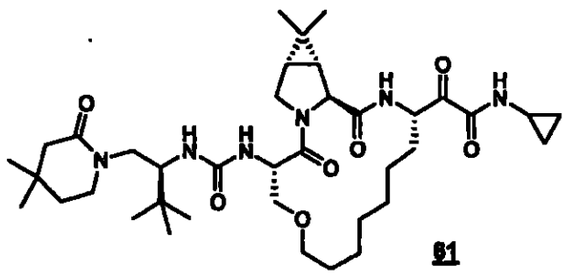
Step D



The N-Boc amine 60c (70 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum overnight. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a solution of the isocyanate 56a (1.3 eq, 0.7 mL of a 0.241M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (50 mL) and washed with aqueous saturated sodium bicarbonate solution (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 55:45) to afford the product 60 (70 mg, 77%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (br s, 1H), 7.56 (br s, 1H), 5.86 (br s, 1H), 5.65 (t, 1H, J = 8.8 Hz), 5.09 (br s, 1H), 4.91 (br s, 1H), 4.56 (s, 1H), 4.07 (d, 1H, J = 10.4 Hz), 3.98 (dd, 1H, J = 5.0, 10.7 Hz), 3.91 (m, 3H), 3.54 (m, 2H), 3.34 (m, 2H), 2.88 (ddd, 1H, J = 3.7, 7.5, 15.1 Hz), 2.56 (d, 2H, J = 16.7 Hz), 2.50 (d, 2H, J = 16.7 Hz), 1.94 (m, 1H), 0.87-1.76 (m, 15H), 1.11 (s, 6H), 1.03 (s, 3H), 0.97 (s, 9H), 0.86 (s, 3H), 0.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.0, 172.9, 172.0, 171.2, 160.8, 157.7, 71.5, 70.8, 60.7, 56.9, 53.4, 51.1, 48.4, 46.8, 39.9, 34.9, 32.1, 30.8, 29.4, 28.7, 28.1, 27.7, 27.5, 26.9, 26.8, 24.4, 23.0, 19.2, 13.5, 6.8, 6.7 ppm. HRMS calcd for $C_{38}H_{61}N_6O_8$ $[M+H]^+$: 729.4551, found 729.4558.

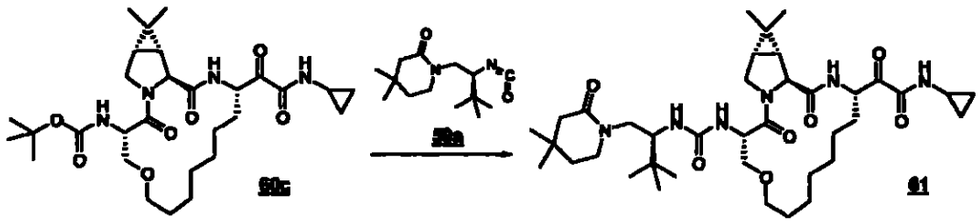
Preparative Example 61: Preparation of:

231



61

Step A

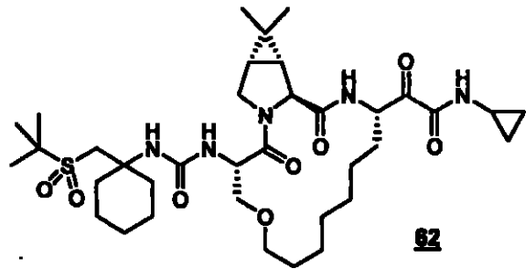


60c 59a 61

The N-Boc amine 60c (56 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a soln of the isocyanate 59a in toluene (1.3 eq) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (60 mL) and washed with aqueous saturated sodium bicarbonate solution (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product 61 (52 mg, 73%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30-8.53 (br s, 1H), 8.15 (d, 1H, J = 8.8 Hz), 6.13 (br s, 1H), 5.74 (dd, 1H, J = 8.8, 9.7 Hz), 5.38 (d, 1H, J = 9.1 Hz), 4.96 (br s, 1H), 4.59 (s, 1H), 4.35 (dd, 1H, J = 12.9, 12.9 Hz), 4.10 (d, 1H, J = 10.4 Hz), 4.01 (dd, 1H, J = 5.0, 10.4 Hz), 3.94 (m, 1H), 3.56 (m, 2H), 3.50 (dd, 1H, J = 8.5, 8.8 Hz), 3.31 (m, 2H), 3.17 (ddd, 1H, J = 5.6, 6.0, 12.3 Hz), 2.91 (ddd, 1H, J = 4.0, 7.8, 15.4 Hz), 2.67 (dd, 1H, J = 3.4, 13.5 Hz), 2.17 (d, 1H, J = 17.0 Hz), 2.10 (d, 1H, J = 17.0 Hz), 1.94 (m, 3H),

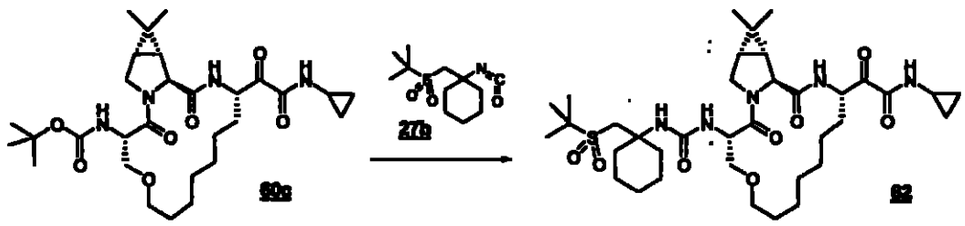
1.24-1.70 (m, 12H), 1.14 (m, 1H), 1.04 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.91 (s, 9H), 0.89 (s, 3H), 0.84 (m, 2H), 0.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.9, 171.9, 171.3, 171.0, 160.9, 158.0, 71.4, 70.9, 60.4, 55.4, 53.2, 48.2, 46.3, 45.0, 35.8, 34.6, 31.7, 30.3, 28.8, 28.7, 27.8, 27.7, 27.6, 27.1, 26.9, 26.8, 24.8, 24.7, 23.2, 19.1, 13.4, 6.4 ppm. HRMS calcd for $C_{38}H_{63}N_6O_7$ $[M+H]^+$: 715.4758, found 715.4768.

Preparative Example 62: Preparation of:



62

Step A

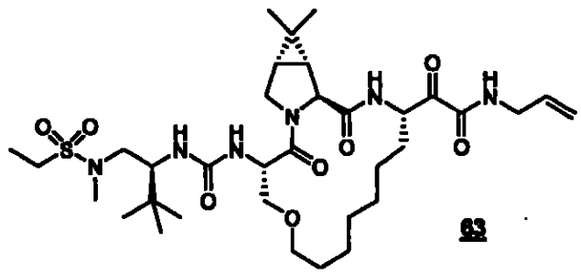


60c 27b 62

The N-Boc amine 60c (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a soln of the isocyanate 27b in toluene (1.2 eq) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (60 mL) and washed with aqueous saturated sodium bicarbonate solution (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product 62 (65

mg, 85%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, 1H, *J* = 8.2 Hz), 7.28 (br s, 1H), 5.73-6.02 (br s, 1H), 5.57 (ddd, 1H, *J* = 1.9, 8.2, 8.5 Hz), 5.22 (br s, 1H), 4.88 (dd, 1H, *J* = 3.4, 8.5 Hz), 4.51 (s, 1H), 4.01 (m, 3H), 3.62 (dd, 1H, *J* = 8.5, 8.5 Hz), 3.55 (ddd, 1H, *J* = 3.7, 6.3, 9.7 Hz), 3.48 (dd, 1H, *J* = 4.0, 8.1 Hz), 3.38 (m, 1H), 3.18 (d, 1H, *J* = 13.5 Hz), 2.86 (ddd, 1H, *J* = 3.8, 7.2, 14.8 Hz), 2.41 (d, 1H, *J* = 11.6 Hz), 2.24 (d, 1H, *J* = 11.6 Hz), 1.93 (m, 1H), 1.72-1.89 (m, 4H), 1.40 (s, 9H), 1.28-1.70 (m, 16H), 1.21 (m, 1H), 1.06 (s, 3H), 0.93 (s, 3H), 0.91 (m, 2H), 0.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.9, 172.0, 171.0, 160.9, 157.0, 70.8, 70.6, 61.0, 60.8, 54.9, 53.7, 51.1, 48.4, 36.2, 32.0, 30.5, 28.7, 27.9, 27.2, 26.9, 26.8, 25.9, 24.1, 23.8, 23.5, 23.0, 21.9, 21.8, 19.3, 13.4, 6.9, 6.8 ppm.

Preparative Example 63: Preparation of:



63

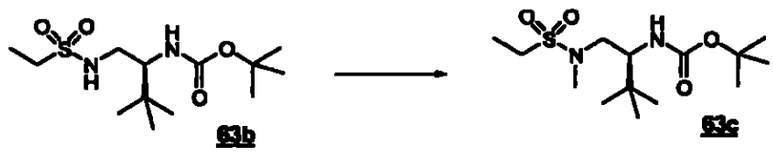
Step A



63a 63b

A solution of amine 63a (2.0 g) in 100 mL of dry dichloromethane was cooled to 0 °C and treated with pyridine (3.0 eq, 2.24 mL, d 0.978) and ethanesulfonyl chloride (1.2 eq, 1.05 mL, d 1.357). The resulting yellow homogeneous solution was stirred overnight (temp 0 to 25 °C). The mixture was diluted with 200 mL of ether and washed with aqueous 1M HCl (100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel (gradient: dichloromethane to ethyl acetate/dichloromethane 3:7) to afford the product 63b (850 mg, 30%) as a white solid.

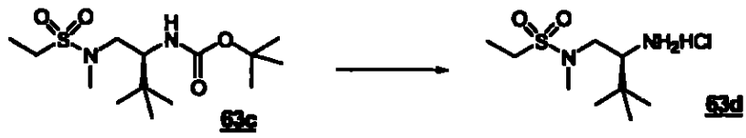
Step B



63b 63c

A solution of ethylsulfonamide **63b** (850 mg) in dry DMF (30 mL) was treated with cesium carbonate (3.0 eq, 2.74 g) and iodomethane (3.0 eq, 0.51 mL, d 2.280). The reaction mixture was stirred for approximately 4 h. TLC analysis (acetone/hexanes; 2:8) showed that all the starting material had been consumed. The mixture was diluted with ethyl acetate (300 mL) and washed with water (3 x 50 mL) and brine (1 x 50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the product **63c** (860 mg, 97%) as a white solid. No further purification was carried out for the product.

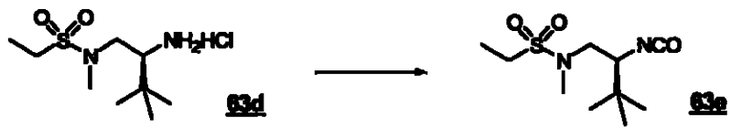
Step C



63c 63d

The N-Boc protected amine **63c** (850 mg) was dissolved in 100 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature until all the starting material had been consumed as determined by TLC (acetone/hexanes; 2:8). All the volatiles were removed under reduced pressure and the residue was placed under high vacuum to afford the product **63d** (680 mg, 98%).

Step D

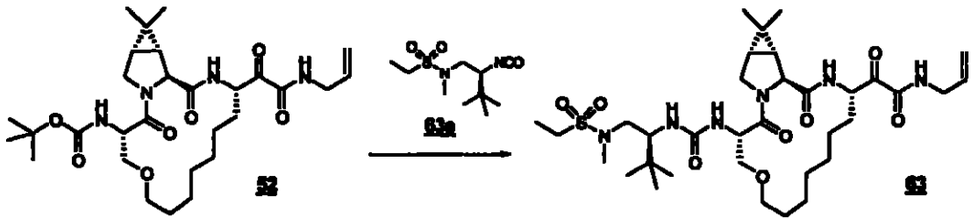


63d 63e

A solution of amine hydrochloride **63d** (2.636 mmol) in 40 mL of dichloromethane was treated with 40 mL of aqueous saturated sodium bicarbonate solution and stirred vigorously for 10 min at 0 °C. Stirring was stopped and layers were allowed to separate. Phosgene (10 mL of 20% soln in toluene) was added through a needle to the organic layer (lower layer) in one portion. The mixture was vigorously stirred immediately after addition for

10 min at 0 °C and further stirred at room temp for 2.5 h. The mixture was diluted with 100 mL of dichloromethane and layers were separated. The organic layer was washed with 30 mL of cold aqueous saturated sodium bicarbonate solution and dried over magnesium sulfate. The organic layer was filtered and the filtrate was diluted with 50 mL of toluene. The product **63e** (654 mg, 98%) was concentrated and kept as a 0.131M solution in toluene (the solution contains about 2 mL of dichloromethane).

Step E

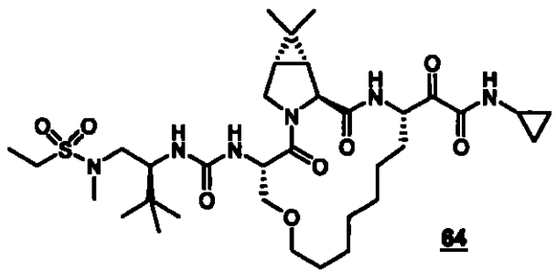


The N-Boc amine **52** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 10 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min, a soln of the isocyanate **63e** was added dropwise (1.2 eq, 0.97 mL of a 0.131M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (70 mL) and washed with aqueous saturated sodium bicarbonate solution (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product **63** (49 mg, 65%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, 1H, J = 8.5 Hz), 7.52 (br s, 1H), 6.04 (br s, 1H), 5.89 (ddt, 1H, J = 5.6, 10.4, 17.0 Hz), 5.65 (dd, 1H, J = 8.8, 10.4 Hz), 5.26 (dd, 1H, J = 1.2, 17.0 Hz), 5.22 (dd, 1H, J = 1.2, 10.0 Hz), 5.17 (d, 1H, J = 10.0 Hz), 4.99 (br s, 1H), 4.61 (s, 1H), 4.19 (d, 1H, J = 10.7 Hz), 4.02 (m, 2H), 3.95 (m, 2H), 3.60 (dd, 1H, J = 8.1, 9.1 Hz), 3.54 (m, 1H), 3.49

235
236

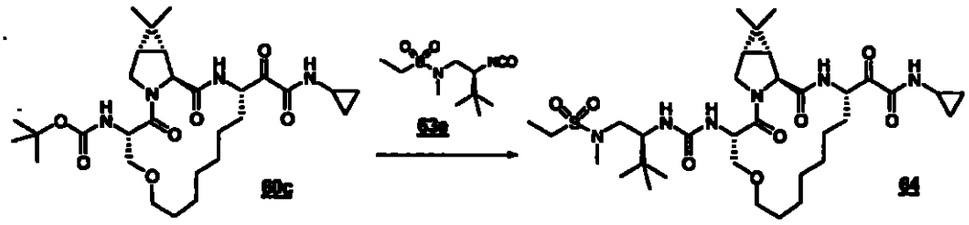
(d, 1H, 1.9 Hz), 3.44 (m, 1H), 3.32 (m, 1H), 3.07 (m, 3H), 2.94 (s, 3H), 1.93 (m, 1H), 1.35 (t, 3H, J = 7.5 Hz), 1.27-1.62 (m, 15H), 1.16 (m, 1H), 1.03 (s, 3H), 0.92 (s, 9H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ, 198.6, 172.3, 171.3, 159.4, 158.0, 133.4, 117.6, 71.1, 70.6, 60.7, 54.7, 53.5, 51.0, 50.6, 48.4, 45.8, 42.2, 34.8, 34.5, 32.0, 30.9, 28.7, 27.8, 27.3, 27.0, 26.9, 24.3, 24.2, 19.2, 13.5, 8.6 ppm; HRMS calcd for $C_{34}H_{59}N_6O_8S$ $[M+H]^+$: 711.4115, found 711.4133.

Preparative Example 64: Preparation of:



64

Step A

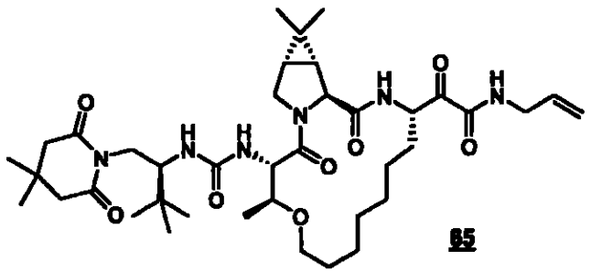


60c 63e 64

The N-Boc amine 60c (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 10 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min, a soln of the isocyanate 63e was added dropwise (1.2 eq, 0.97 mL of a 0.131M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (70 mL) and washed with aqueous saturated sodium bicarbonate solution (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced

pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product 64 (62 mg, 82%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (br s, 1H), 7.47 (br s, 1H), 5.94-6.19 (br s, 1H), 5.65 (dd, 1H, J = 8.8, 10.7 Hz), 5.21 (d, 1H, J = 7.8 Hz), 5.00 (dd, 1H, J = 3.7, 9.4 Hz), 4.59 (s, 1H), 4.21 (d, 1H, J = 10.7 Hz), 4.02 (dd, 1H, J = 5.0, 10.7 Hz), 3.93 (dd, 1H, J = 9.1, 9.7 Hz), 3.55 (m, 2H), 3.48 (d, 1H, J = 12.6 Hz), 3.40 (m, 1H), 3.29 (m, 1H), 3.07 (q, 2H, J = 7.2 Hz), 3.06 (m, 1H), 2.93 (s, 3H), 2.85 (dddd, 1H, J = 1.8, 4.0, 7.5, 15.1 Hz), 1.91 (m, 1H), 1.34 (t, 3H, J = 7.2 Hz), 1.25-1.61 (m, 12H), 1.13 (m, 1H), 1.01 (s, 3H), 0.90 (s, 9H), 0.89 (s, 3H), 0.87 (m, 2H), 0.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.9, 172.3, 171.4, 160.9, 158.0, 71.0, 70.6, 60.6, 53.2, 50.9, 50.6, 48.4, 45.9, 34.8, 34.5, 32.1, 31.1, 28.7, 27.8, 27.5, 27.0, 26.9, 24.4, 23.0, 19.2, 13.6, 8.6, 6.7 ppm; HRMS calcd for $C_{34}H_{59}N_6O_8S$ $[M+1]^+$: 711.4115, found 711.4133.

Preparative Example 65: Preparation of:



65

Step A



65a 65b

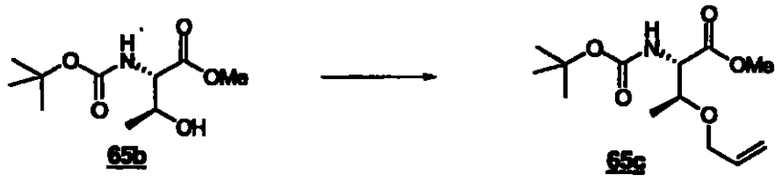
A solution of (S)-allo-threonine-OMe hydrochloride 65a (Chem-Impex, 5 g) in dry dichloromethane (150 mL) was cooled to 0 °C and treated with di-tert-butyldicarbonate (1.1 eq, 7.0 g) in 50 mL of dry dichloromethane. N-methylmorpholine (2.5 eq, 8.1 mL, d 0.920) was added dropwise and the mixture was stirred for 30 min. The cooling bath was removed and the mixture was stirred for further 3 h. The mixture was concentrated to one third of its volume and then diluted with ethyl acetate (300 mL) and washed with aqueous 1M HCl (100 mL), aqueous saturated sodium bicarbonate (80 mL)

239

238

and brine (80 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the product **65b** (6.78 g, 98%) as a colorless oil.

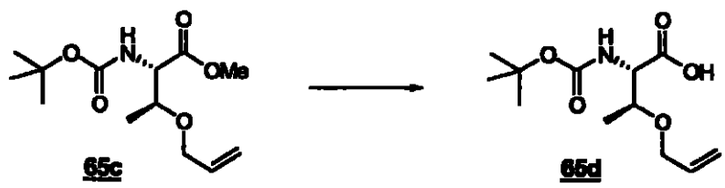
Step B



65b **65c**

A solution of Boc-L-allo-Thr-OMe **65b** (6.8 g) in 250 mL of dry THF was degassed (vacuum/N2-flush) and treated with allylmethyl carbonate (1.3 eq, 4.3 mL, d 1.022). A catalytic amount of tetrakis(triphenylphosphine)palladium (0.02 mol%, 673 mg) was added. The slightly yellow mixture was degassed again and heated at 60 °C for about 3 h until TLC analysis (acetone/hexanes; 2:8) showed no more starting material left (reaction mixture became brown). The mixture was concentrated under reduced pressure and the residue was chromatographed on silica gel (ethyl acetate/hexanes; 1:9) to afford the product **65c** (5.72 g, 72%) as a colorless oil.

Step C

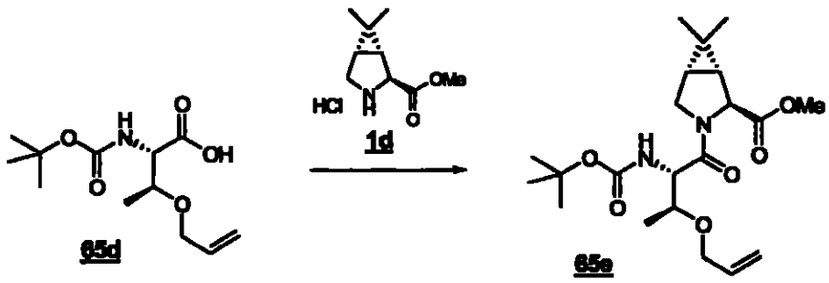


65c **65d**

A solution of methyl ester **65c** (1.45 g) in 250 mL of a 4:2:1 mixture of THF/water/MeOH was cooled to 0 °C and treated with lithium hydroxide monohydrate (2.5 eq, 2.19 mg). The cooling bath was removed after 30 min and the mixture was stirred at room temp for further 4 h until all the starting material had been consumed as determined by TLC analysis . (acetone/hexanes; 15:85). The reaction mixture was treated with 200 mL of aqueous 1M HCl (pH of mixture = 1) and the product was taken into dichloromethane (4 x 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure to

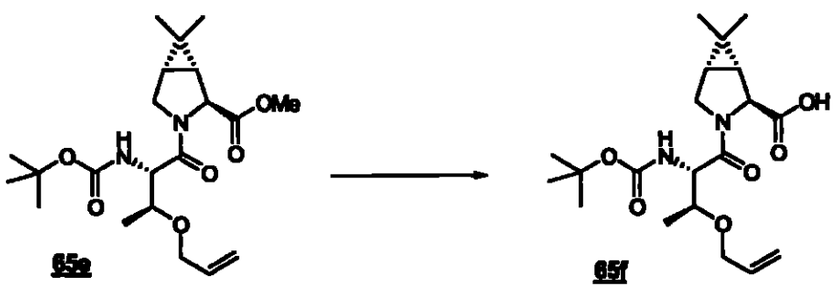
afford the product. No further purification was carried out for the product **65d** (5.42 g, 98%).

Step D



A solution of acid **65d** (20.92 mmol) in 200 mL of dry dichloromethane and 100 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 11.16 g). The amine salt **1d** (1.2 eq, 5.16 g) was added followed by N-methylmorpholine (4 eq, 9.19 mL, d 0.920). The reaction mixture was stirred overnight. All the volatiles were removed under vacuum and the residue was dissolved in 500 mL of ethyl acetate. The organic layer was washed with water (200 mL), aqueous 1M HCl (100 mL), aqueous saturated sodium bicarbonate solution (100 mL), and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate/hexanes; 2:8) to give the product **65e** (7.6 g, 88%) as a colorless oil along with a small amount of its corresponding diastereomeric product.

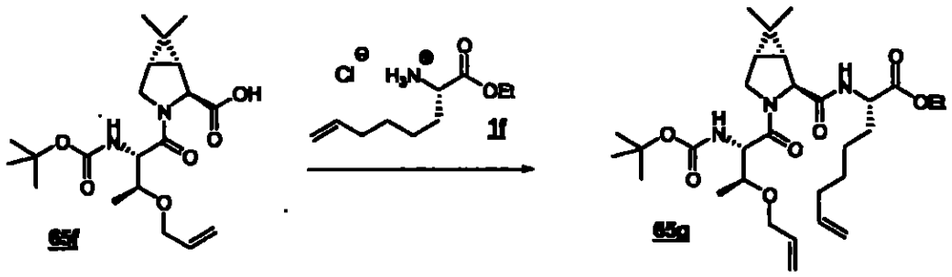
Step E



A solution of methylester **65e** (7.6 g) in 300 mL of a 2:1 mixture of THF/water was cooled to 0 °C and treated with lithium hydroxide monohydrate (2.5 eq, 1.93 mg). The cooling bath was removed after 30 min and the mixture was stirred at room temp for further 4 h until all the starting material had been

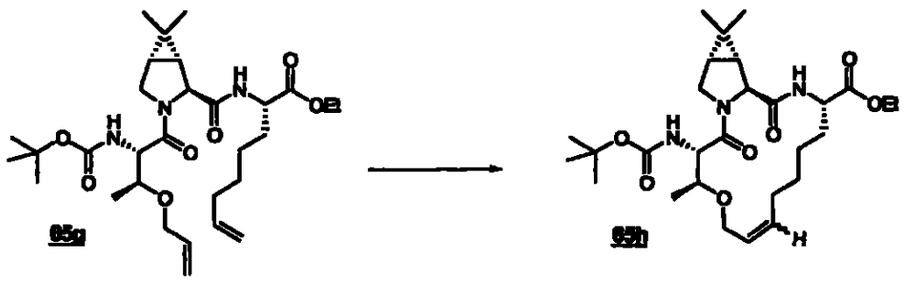
consumed as determined by TLC analysis (ethyl acetate/hexanes; 25:75). The reaction mixture was treated with 200 mL of aqueous 1M HCl (pH of mixture = 1) and the product was taken into dichloromethane (4 x 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the product **65f** (6.86 g, 93%) as a colorless solid.

Step F



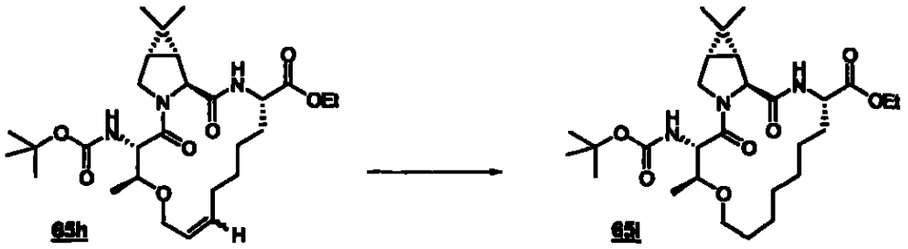
A solution of acid **65f** (6.86 g) in 100 mL of dry dichloromethane and 100 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 9.23 g). The amine salt **1f** (1.1 eq, 4.21 g) was added in 100 mL of dichloromethane followed by addition of N-methylmorpholine (4 eq, 7.6 mL, d 0.920). The reaction mixture was stirred at 0 °C overnight. All the volatiles were removed under vacuum and the residue was dissolved in 500 mL of ethyl acetate. The organic layer was washed with water (2 x 100 mL), aqueous 1M HCl (100 mL), aqueous saturated sodium bicarbonate solution (100 mL), and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate/hexanes; 3:7) to afford the product **65g** (8.17 g, 84%) as a colorless oil.

Step G



A solution of diene **65g** (8.17 g) in 1.5 L of toluene was degassed for 30 min (argon bubbling) and treated with Grubb's catalyst (0.2 eq, 2.38 g). The pink solution was heated to 60 °C for 18 h (the solution became dark after 10 min of heating). The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (ethyl acetate/hexanes; 3:7) to give the alkene product **65h** (7.0 g, 90%) as a mixture of E- and Z-isomers (approx 4:1).

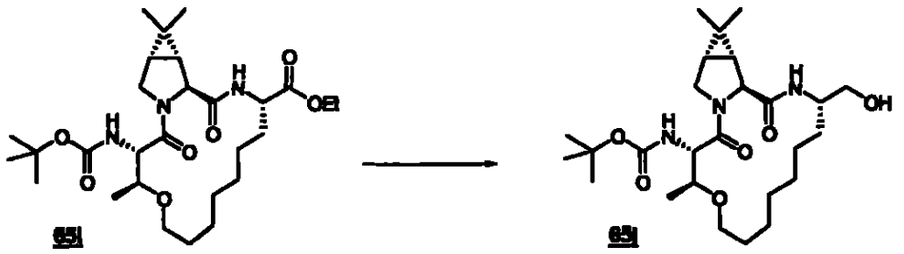
Step H



65h **65i**

A solution of alkene **65h** (7.0 g) in 300 mL of methanol was treated with palladium on carbon (0.1 mol%, 1.37 g of 10% Pd/C). The mixture was hydrogenated at 35 psi until all the starting material had been consumed (approx 3 h). The reaction mixture was diluted with 300 mL of dichloromethane and filtered thru a short path of celite. The filtrate was concentrated and the residue was chromatographed on silica gel (ethyl acetate/hexanes; 3:7) to afford the product **65i** (5.33 g, 76%) as a white solid.

Step I

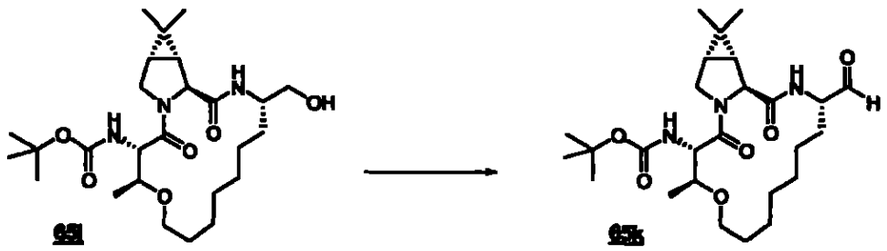


65i **65j**

A solution of ethyl ester **65i** (5.33 g) in 100 mL of dry THF was treated with lithium borohydride (2.1 eq, 10.4 mL of a 2M soln in THF). The reaction mixture was stirred at room temperature and monitored by TLC (acetone/hexanes; 3:7) for disappearance of the starting material. After 2 h, more lithium borohydride solution was added (1 eq) and stirring was continued for 1h. The excess lithium borohydride was quenched by addition of

aqueous saturated ammonium chloride solution. The mixture was partitioned between ethyl acetate (300 mL) and aqueous saturated sodium bicarbonate solution (100 mL). The aqueous layer was back extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (acetone/hexanes; 3:7) to afford the product **65j** (3.93 g, 80%) as a white solid.

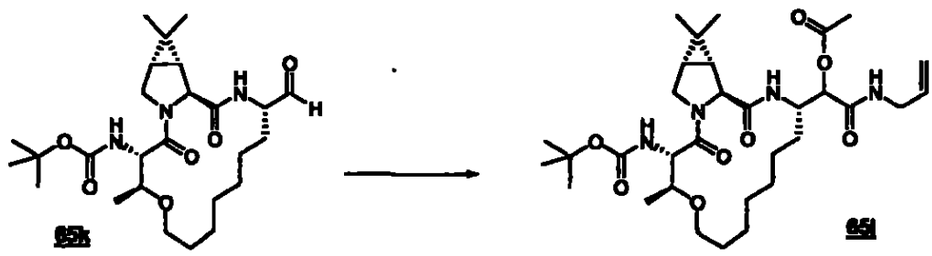
Step J



65j **65k**

A solution of alcohol **65j** (1.0 g) in 40 mL of dry dichloromethane was treated with Dess-Martin periodinane (1.5 eq, 1.28 g). The reaction mixture was stirred at room temperature for 3 h. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (30 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 80 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: ethyl acetate/hexanes; 4:6 to 8:2) to afford the product **65k** (750 mg, 75%) as a colorless solid.

Step K

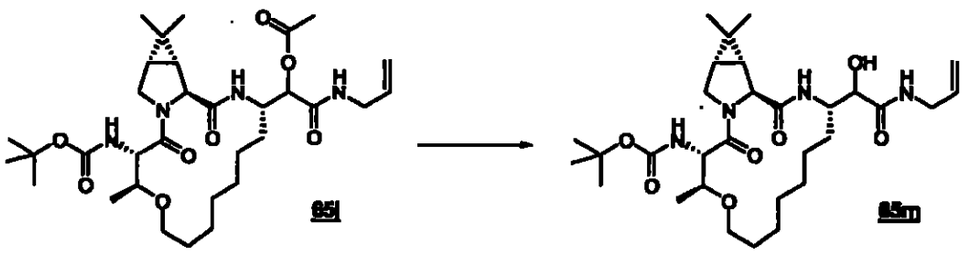


65k **65l**

A solution of aldehyde **65k** (750 mg) in 20 mL of dry dichloromethane was treated with allylisocyanide (2 eq, 0.26 mL, d 0.8) and acetic acid (2 eq,

0.17 mL, d 1.049). The mixture was stirred at room temperature for about 5 h. All the volatiles were removed under vacuum and the residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 45:55) to afford the product **65l** (700 mg, 74%) as a white solid.

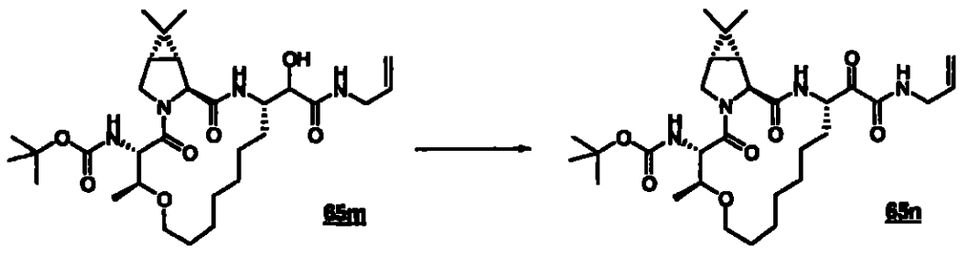
Step L



65l **65m**

A solution of acetate **65l** (700 mg) in 20 mL of a 2:1 mixture of THF/water was treated with lithium hydroxide monohydrate (2.5 eq, 118 mg) and stirred for approx 30 min until all the starting material had been consumed as determined by TLC analysis (ethyl acetate/hexanes; 8:2). The reaction mixture was diluted with 50 mL of aqueous saturated sodium bicarbonate solution and extracted with dichloromethane (3 x 80 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford the product **65m** (651 mg, 98%) as a colorless semi-solid which was used without further purification.

Step M

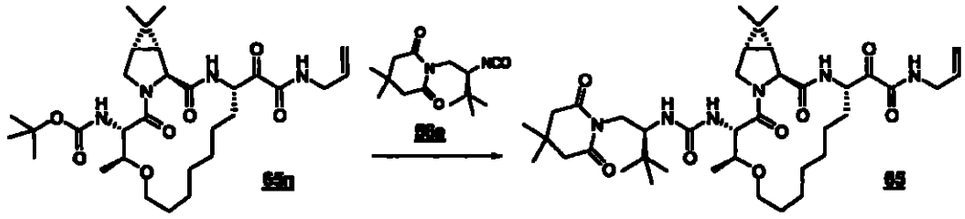


65m **65n**

A solution of hydroxyamide **65m** (1.127 mmol) in 25 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 956 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (20 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (30 mL) was also

added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 80 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 45:55) to afford the product **65n** (585 mg, 90%) as white solid.

Step N

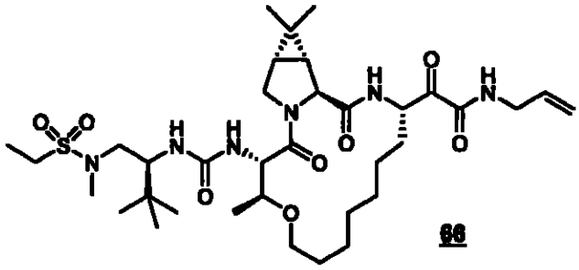


The N-Boc amine **65n** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 10 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min, a soln of the isocyanate **56e** was added dropwise (1.2 eq, 0.57 mL of a 0.216M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (70 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 15:85 to 5:5) to afford the product **65** (50 mg, 65%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (br s, 1H), 7.42-7.82 (br s, 1H), 6.30 (br s, 1H), 5.90 (ddt, 1H, J = 5.6, 10.4, 17.0 Hz), 5.71 (br s, 1H), 5.38 (br s, 1H), 5.27 (dd, 1H, J = 1.2, 17.0 Hz), 5.23 (dd, 1H, J = 1.2, 10.4 Hz), 4.63 (dd, 1H, J = 7.8, 8.1 Hz), 4.50 (br s, 1H), 4.23 (d, 1H, J = 10.4 Hz), 4.05 (m, 2H), 3.98 (dd, 1H, J = 5.6, 5.9 Hz), 3.95 (d, 1H, J = 11.0 Hz), 3.88 (dd, 1H, J = 10.7, 10.8 Hz), 3.82 (q, 1H, J = 11.6 Hz), 3.71 (m, 1H), 3.62 (ddd, 1H, J = 5.0, 5.3, 9.4 Hz), 3.20 (m, 1H), 2.55 (d, 2H, J = 16.7 Hz), 2.47 (d, 2H, J = 16.7 Hz), 1.73-1.97 (m, 4H), 1.14 (d, 3H, J = 6.0 Hz), 1.10 (s, 6H), 1.00 (s, 3H), 0.99 (s, 9H), 0.83 (s, 3H);

245

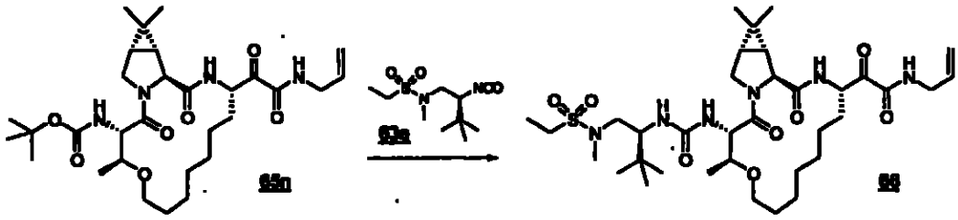
^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.0, 172.8, 171.5, 159.4, 157.8, 117.7, 75.5, 68.1, 60.8, 57.2, 55.9, 48.7, 46.8, 42.3, 35.2, 29.3, 28.7, 28.3, 27.8, 27.6, 26.9, 26.8, 24.7, 24.4, 19.4, 16.3, 13.6 ppm; HRMS calcd for $C_{39}H_{63}N_6O_8$ $[M+H]^+$: 743.4707, found 743.4717.

Preparative Example 66: Preparation of:



66

Step A

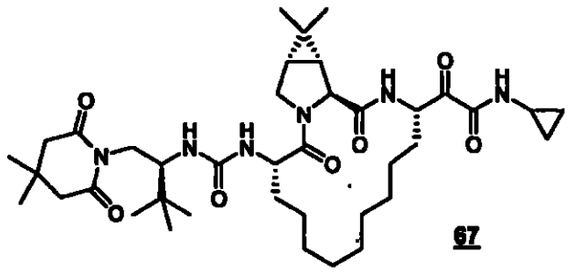


65n 63e 66

The N-Boc amine 65n (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum overnight. The resulting amine salt was dissolved in 5 mL of dichloromethane and cooled to 0 °C. Then, 10 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min, a soln of the isocyanate 63e was added dropwise (1.2 eq, 0.95 mL of a 0.131M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 3 h. The reaction mixture was diluted with dichloromethane (70 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product 66 (55 mg, 73%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, 1H, J = 6.6 Hz), 7.58-7.77 (br s, 1H), 6.13 (br s, 1H), 5.90 (ddt, 1H, J = 5.6, 10.0, 17.0 Hz), 5.76 (br s, 1H), 5.27 (dd, 1H, J = 1.2,

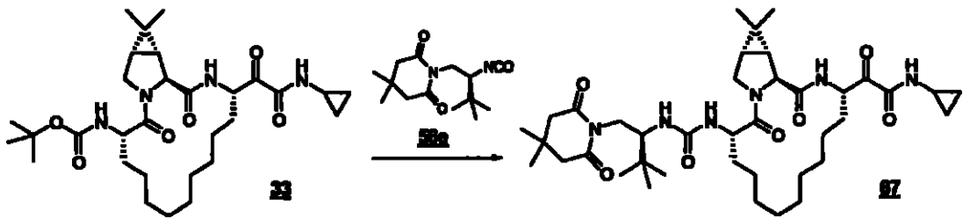
17.0 Hz), 5.22 (dd, 1H, *J* = 1.2, 10.0 Hz), 5.15 (d, 1H, *J* = 9.1 Hz), 4.69 (dd, 1H, *J* = 8.8, 8.8 Hz), 4.57 (s, 1H), 4.29 (d, 1H, *J* = 10.7 Hz), 3.91-4.09 (m, 4H), 3.61 (m, 2H), 3.47 (dd, 1H, *J* = 11.9, 13.5 Hz), 3.19 (m, 1H), 3.07 (m, 3H), 2.94 (s, 3H), 1.95 (m, 1H), 1.35 (t, 3H, *J* = 7.5 Hz), 1.27-1.69 (m, 12H), 1.22 (d, 3H, *J* = 6.3 Hz), 1.14 (m, 1H), 1.02 (s, 3H), 0.93 (s, 9H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.0, 172.8, 171.5, 159.3, 158.1, 133.5, 117.5, 75.8, 68.4, 60.7, 56.2, 50.4, 48.6, 45.6, 42.2, 34.7, 34.5, 32.0, 31.6, 28.6, 27.7, 27.0, 26.9, 26.7, 24.8, 24.6, 19.3, 16.2, 14.5, 13.5, 8.5 ppm; HRMS calcd for $C_{35}H_{61}N_5O_8S$ $[M+H]^+$: 725.4272, found 725.4285.

Preparative Example 67: Preparation of:



67

Step A

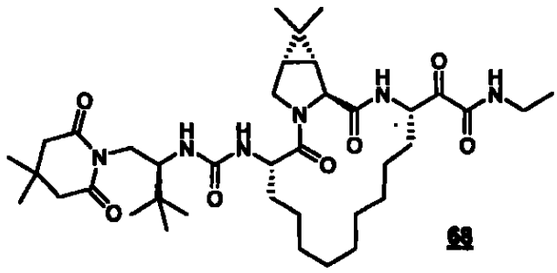


The N-Boc amine 33 (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum overnight. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, N-methylmorpholine (2 eq, 0.03 mL, d 0.920) was added. After 10 min, a soln of the isocyanate 56e was added dropwise (1.5 eq, 0.8 mL of a 0.2M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with aq 1M HCl (10 mL) and

247

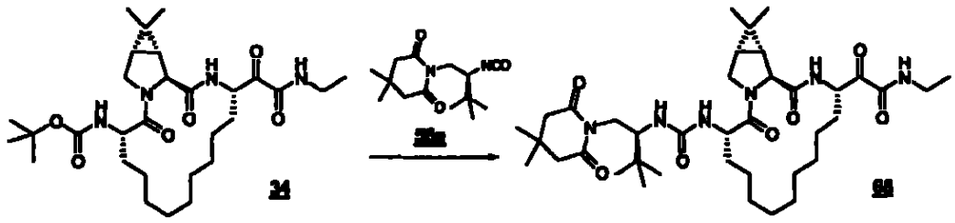
brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 1:1) to afford the product **67** (50 mg, 64%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, 1H, J = 6.9 Hz), 7.66-7.82 (br s, 1H), 6.11 (br s, 1H), 5.70 (br s, 1H), 5.32 (br s, 1H), 4.63 (br s, 1H), 4.60 (s, 1H), 4.19 (d, 1H, J = 10.0 Hz), 3.96 (dd, 1H, J 5.0, 10.0 Hz), 3.91 (m, 3H), 2.91 (ddd, 1H, J = 3.7, 7.8, 15.1 Hz), 2.57 (d, 2H, J = 16.7 Hz), 2.50 (d, 2H, J = 16.7 Hz), 1.86 (m, 3H), 1.69 (m, 1H), 1.18-1.61 (m, 16H), 1.10 (s, 6H), 1.01 (s, 3H), 0.95 (s, 9H), 0.89 (m, 2H), 0.87 (s, 3H), 0.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.2, 173.5, 172.9, 171.9, 160.7, 158.0, 60.5, 56.6, 51.5, 48.5, 46.8, 39.9, 35.0, 34.2, 31.4, 29.4, 28.1, 27.8, 27.6, 27.4, 27.3, 27.0, 26.9, 26.5, 26.1, 23.4, 23.1, 19.4, 13.6, 6.8, 6.7 ppm.

Preparative Example 68: Preparation of:



68

Step A



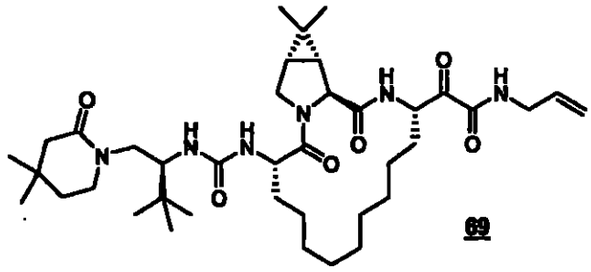
34 **68**

The N-Boc amine **34** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, N-methylmorpholine (2 eq, 0.02 mL, d 0.920) was added. After 10 min, a soln of

248

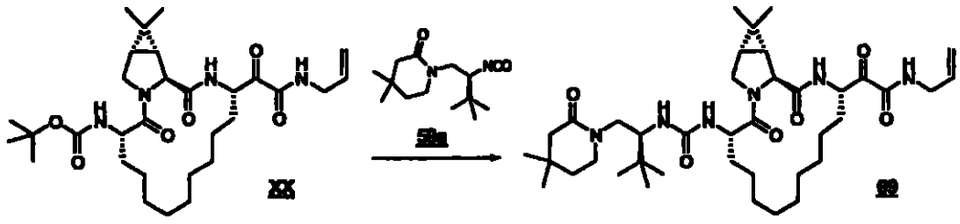
the isocyanate **56e** was added dropwise (1.4 eq, 0.6 mL of a 0.241M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with aq 1M HCl (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 45:55) to afford the product **68** (44 mg, 56%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (br s, 1H), 7.52-7.77 (br s, 1H), 6.06 (br s, 1H), 5.70 (br s, 1H), 5.26 (br s, 1H), 4.63 (m, 2H), 4.20 (d, 1H, J = 10.0 Hz), 3.97 (dd, 1H, J = 5.0, 10.0 Hz), 3.92 (m, 3H), 3.43 (m, 2H), 2.57 (d, 2H, J = 16.7 Hz), 2.50 (d, 2H, J = 16.7 Hz), 1.90 (m, 1H), 1.74 (m, 2H), 1.27 (t, 3H, J = 7.2 Hz), 1.20-1.62 (m, 17H), 1.11 (s, 6H), 1.02 (s, 3H), 0.96 (s, 9H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.1, 173.5, 172.9, 171.8, 159.3, 157.9, 60.6, 56.6, 51.5, 48.5, 46.8, 40.0, 34.9, 34.8, 34.1, 32.8, 29.4, 28.1, 27.8, 27.5, 27.4, 27.3, 27.0, 26.9, 26.5, 26.0, 25.1, 23.4, 19.4, 14.8, 13.6 ppm; HRMS calcd for $C_{38}H_{63}N_6O_7$ $[M+H]^+$: 715.4758, found 715.4751.

Preparative Example 69: Preparation of:



69

Step A

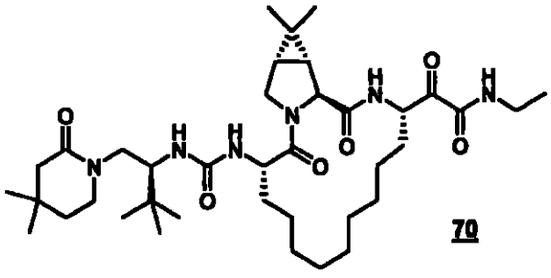


XX **56a** **69**

The N-Boc amine **XX** (93 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature

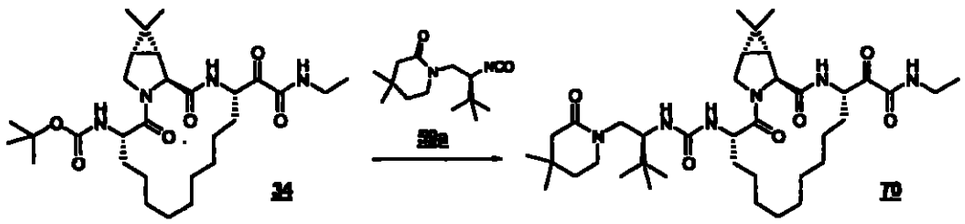
for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, N-methylmorpholine (2 eq, 0.04 mL, d 0.920) was added. After 10 min, a soln of the isocyanate **59a** in toluene was added dropwise (1.2 eq) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with aq 1M HCl (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 45:55) to afford the product **69** (45 mg, 38%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26-8.67 (br s, 1H), 8.17 (br s, 1H), 6.19 (br s, 1H), 5.92 (ddt, 1H, J = 5.6, 10.4, 17.3 Hz), 5.74 (dd, 1H, J = 8.8, 9.1 Hz), 5.41 (br s, 1H), 5.26 (dd, 1H, J = 1.2, 17.3 Hz), 5.20 (d, 1H, J = 10.0 Hz), 4.67 (br s, 1H), 4.62 (s, 1H), 4.35 (dd, 1H, J = 1.9, 12.9 Hz), 4.20 (d, 1H, J = 9.8 Hz), 3.99 (m, 4H), 3.58 (ddd, 1H, J = 5.9, 6.9, 12.6 Hz), 3.18 (ddd, 1H, J = 5.9, 5.9, 11.9 Hz), 2.69 (d, 1H, J = 10.7 Hz), 2.18 (d, 1H, J = 17.0 Hz), 2.12 (d, 1H, J = 17.0 Hz), 1.96 (m, 1H), 1.18-1.89 (m, 20H), 1.12 (m, 1H), 1.04 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.92 (s, 9H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.3, 173.3, 171.8, 171.1, 159.4, 158.2, 133.7, 117.3, 60.4, 55.3, 51.5, 48.3, 46.3, 45.0, 42.3, 35.8, 34.6, 34.0, 31.2, 30.3, 28.6, 27.8, 27.7, 27.6, 27.3, 27.2, 27.0, 26.3, 25.9, 25.4, 23.2, 19.3, 13.5 ppm.

Preparative Example 70: Preparation of:



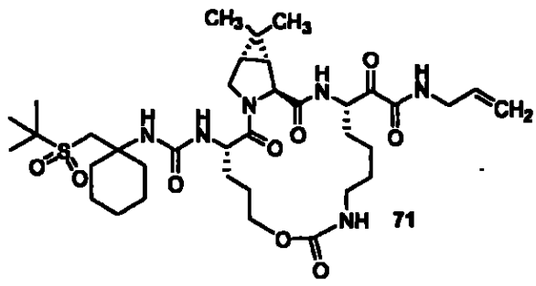
70

Step A

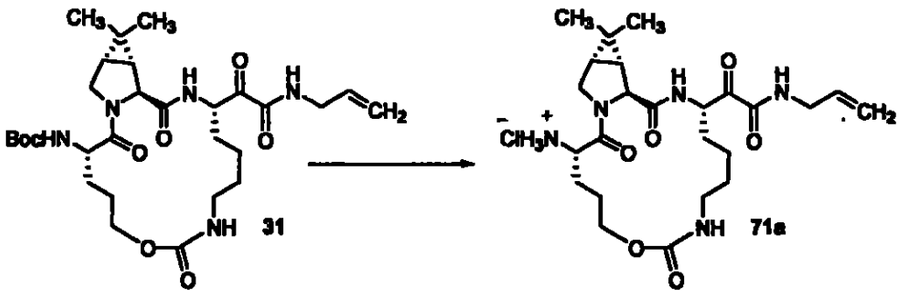


The N-Boc amine 34 (73 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, N-methylmorpholine (2 eq, 0.03 mL, d 0.920) was added. After 10 min, a soln of the isocyanate 59a in toluene was added dropwise (1.2 eq) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with aqueous 1M HCl (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 45:55) to afford the product 70 (63 mg, 69%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20-8.43 (br s, 1H), 8.17 (br s, 1H), 6.20 (br s, 1H), 5.75 (dd, 1H, J = 8.2, 9.4 Hz), 5.41 (br s, 1H), 4.66 (d, 1H, J = 9.1 Hz), 4.63 (s, 1H), 4.36 (dd, 1H, J = 12.6, 13.2 Hz), 4.18 (d, 1H, J = 10.4 Hz), 3.96 (m, 2H), 3.57 (m, 1H), 3.41 (m, 2H), 3.18 (ddd, 1H, J = 5.9, 11.9 Hz), 2.69 (d, 1H, J = 13.2 Hz), 2.19 (d, 1H, J = 17.0 Hz), 2.14 (d, 1H, 17.0 HZ), 1.76-1.99 (m, 4H), 1.25 (t, 3H, J = 7.2 Hz), 1.18-1.75 (m, 17H), 1.12 (m, 1H), 1.04 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H), 0.92 (s, 9H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.9, 173.3, 171.8, 171.1, 159.4, 158.2, 60.4, 55.2, 53.5, 51.5, 48.3, 46.3, 35.8, 34.8, 34.6, 31.3, 30.3, 28.7, 27.8, 27.7, 27.6, 27.3, 27.0, 26.4, 26.0, 23.2, 19.3, 14.8, 13.5 ppm; HRMS calcd for $C_{38}H_{65}N_6O_6$ $[M+H]^+$: 701.4966, found 701.4960.

Preparative Example 71: Preparation of:

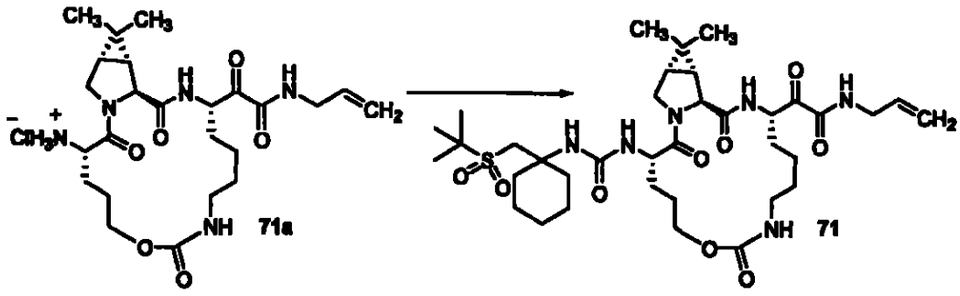


Step A:



A solution of 31 (100 mg, 0.169 mmol) in 4 N. HCl in dioxane (5 ml) was stirred at room temperature for 1 hour. Solvent was removed to dryness to give 71a (120 mg) which was used without further purification

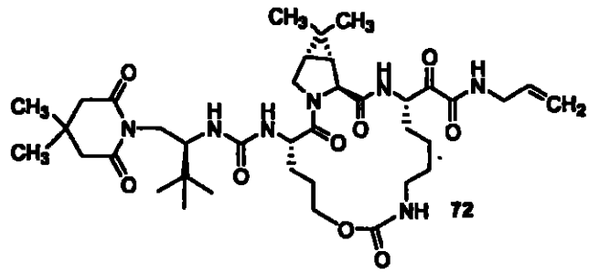
Step B:



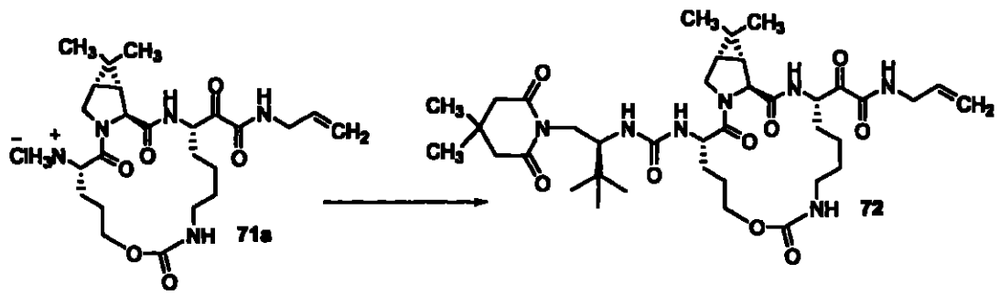
A solution of 71a (89 mg, 0.169 mmol) in CH_2Cl_2 (10 ml) was treated with isocyanate 27b (3 equiv), sat. $NaHCO_3$ (3 ml) and stirred vigorously for 2 hours. The solution was allowed to stand at 5 °C for 12 hours. The CH_2Cl_2 layer was separated, washed with water, brine and filtered through Na_2SO_4. Solvent was removed to dryness and the residue was purified on silica gel column (40% to 60% acetone/hexanes) to give 71 (73 mg). MS (ES) *m/z* relative intensity 773 [(M+Na)$^+$, 20]; 751 [(M+1)$^+$, 100]. Calcd. for $C_{38}H_{58}N_6O_9S$ [M+1]$^+$: 751.4064; Found 751.4075.

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Preparative Example 72: Preparation of:

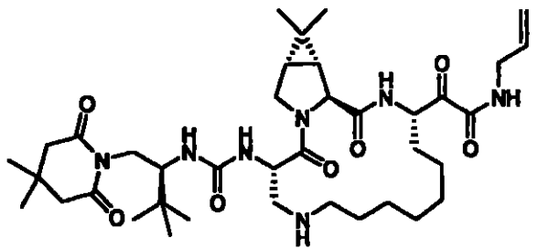


Step A:



A solution of **71a** (89 mg, 0.169 mmol) in CH_2Cl_2 (10 ml) was treated with isocyanate **51c** (1.5 equiv), sat. $NaHCO_3$ (4 ml) and stirred vigorously for 30 minutes. The solution was allowed to stand at 5 °C for 12 hours. The CH_2Cl_2 layer was separated, washed with water, brine and filtered through Na_2SO_4. Solvent was removed to dryness and the residue was purified on silica gel column (40% to 50% acetone/hexanes) to give **72** (95 mg). MS (ES) *m/z* relative intensity 790 [$(M+CH_3OH+1)^+$, 40]; 758 [$(M+1)^+$, 100]. Calcd. for $C_{38}H_{59}N_7O_9$ [M+1]$^+$: 758.4453; Found 758.4449.

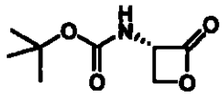
Preparative Example 73: Preparation of:



73

Step A

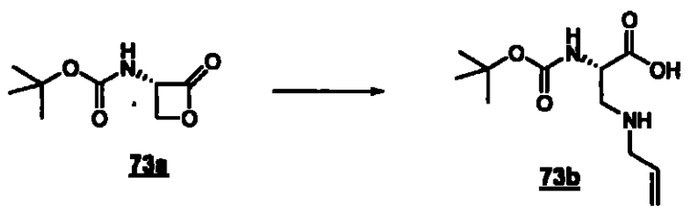
253



73a

The N-(tert-Butoxycarbonyl)-L-serine-beta-lactone 73a will be prepared according to the procedure described by Vederas and co-workers (Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105-7109) starting from commercially available N-Boc-L-Ser-OH.

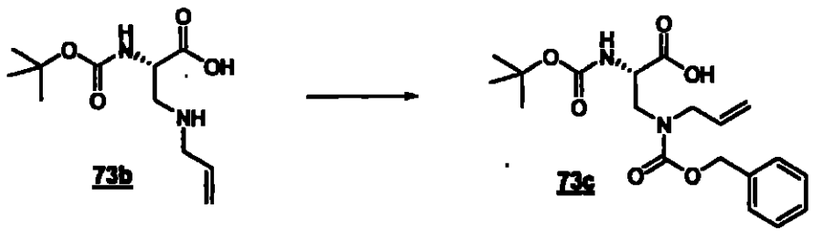
Step B



73a 73b

A solution of N-(tert-Butoxylcarbonyl)-L-serine-beta-lactone 73a (1 mmol) in 20 mL of dry acetonitrile will be added dropwise at ambient temperature over 1 h to a stirred solution of allylamine (25 mmol) in 30 mL dry acetonitrile. After 2 h, the solution will be concentrated under reduced pressure. The residue will be slurried with acetonitrile and the acid product 73b will be recovered by filtration.

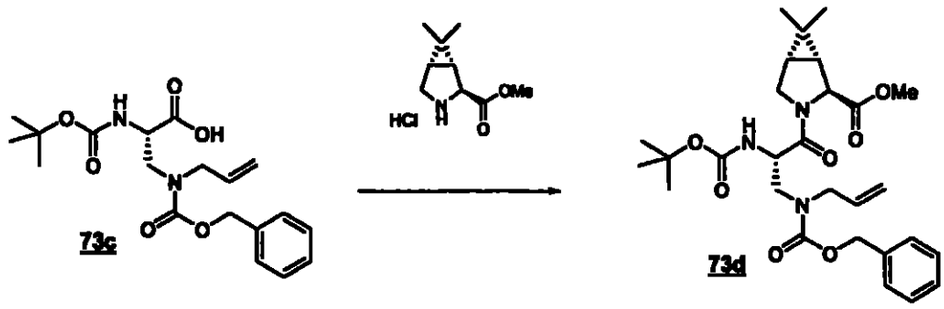
Step C



73b 73c

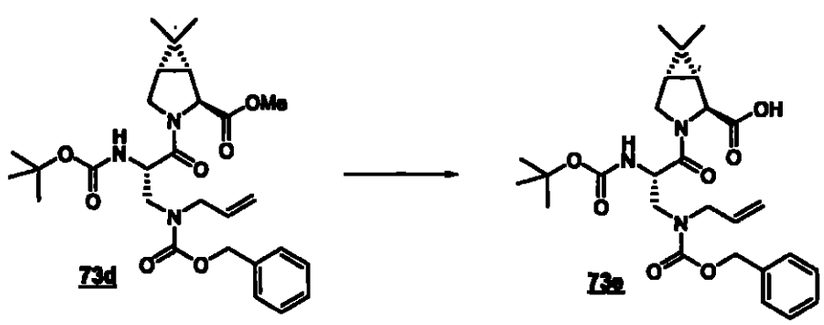
A solution of acid 2 (1 mmol) in aqueous saturated sodium bicarbonate solution (4 mL) and water (1 mL) at room temperature will be treated with benzyl chloroformate (1.12 mmol) in acetone (1 mL). The reaction mixture will be stirred for 2 h. The mixture will be partitioned between ether (20 mL) and water (20 mL). The aqueous layer will be cooled in an ice-water bath, brought to pH 2 using 5% aqueous HCl and extracted with dichloromethane (3 x 30 mL). The combined organic layers will be dried over magnesium sulfate, filtered and concentrated to afford the acid product 73c.

Step D



A solution of acid 73c (1 mmol) in 10 mL of dry dichloromethane and 10 mL of dry DMF will be stirred at 0 °C and treated with HATU (1.4 mmol). The amine hydrochloride (1.3 mmol) and N-methylmorpholine (4 mmol) will be successively added. The reaction mixture will be gradually warmed to room temperature and stirred overnight. All the volatiles will be removed under vacuum and the residue will be taken into 100 mL of ethyl acetate. The organic layer will be washed with water (20 mL), aqueous 1N HCl (20 mL), aqueous saturated sodium bicarbonate solution (20 mL), and brine (20 mL). The organic layer will be dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The product 73d will be purified by column chromatography on silica gel.

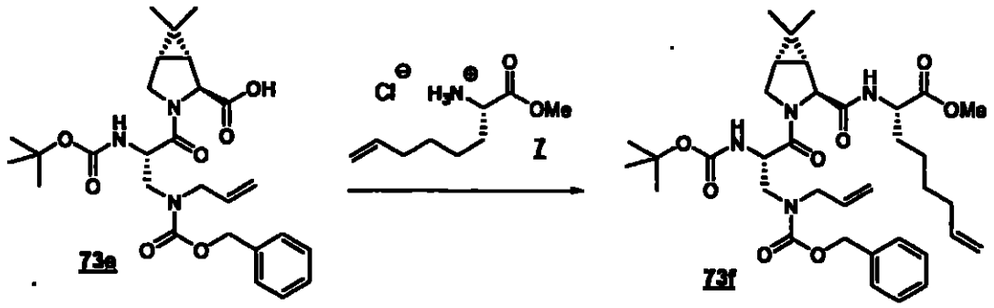
Step E



A solution of methyl ester 73d (1 mmol) in 15 mL of a mixture of THF/MeOH/H2O (1:1:1) will be treated with lithium hydroxide monohydrate (2.5 mmol) at 0 °C. The cooling bath will be removed and the reaction mixture stirred at room temperature and monitored by TLC (acetone/hexanes; 2:8). After 1 h, 10 mL of aqueous 1N HCl will be added and all the volatiles will be removed under reduced pressure. The residue will be partitioned between 30

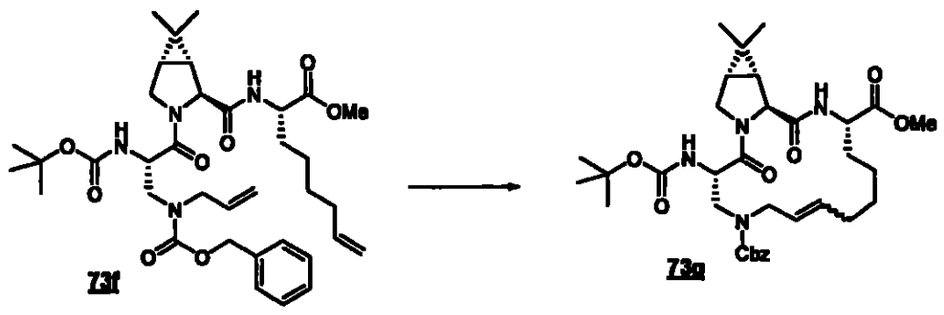
mL of aqueous 1N HCl and 100 mL of dichloromethane. The aqueous layer will be back extracted with dichloromethane (2 x 50 mL). The combined organic layers will be dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give the acid product **73e**.

Step F



A solution of acid **73e** (1 mmol) in 10 mL of dry dichloromethane and 10 mL of dry DMF will be stirred at 0 °C and treated with HATU (1.4 eq, 1.15 g). The amine hydrochloride **7** (1.2 mmol) will be added in 10 mL of dichloromethane followed by N-methylmorpholine (4 mmol). The reaction mixture will be stirred overnight (temp from 0 to 25 °C). All the volatiles will be removed under vacuum and the residue will be dissolved in 100 mL of ethyl acetate. The organic layer will be washed with water (20 mL), aqueous 1N HCl (20 mL), aqueous saturated sodium bicarbonate solution (20 mL), and brine (20 mL). The organic layer will be dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **73f** will be purified by column chromatography on silica gel.

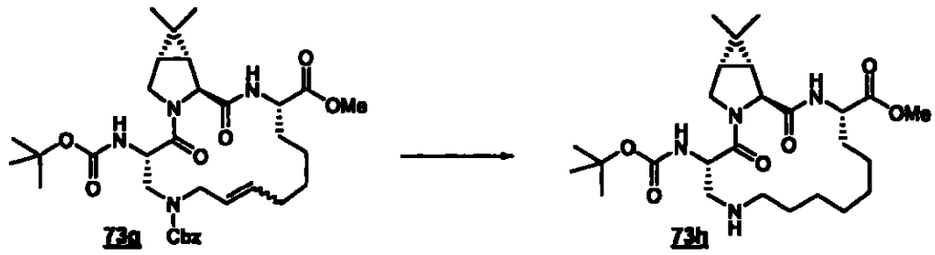
Step G



256

A 0.01M solution of diene 73f (1 mmol) in toluene will be degassed for 30 min (argon bubbling) and treated with Grubb's catalyst (0.2 mmol). The pink solution will be heated to 60 °C for 16 h. The solvent will be removed under reduced pressure and the residue will chromatographed on silica gel to afford the alkene product 73g as a mixture of E- and Z-isomers.

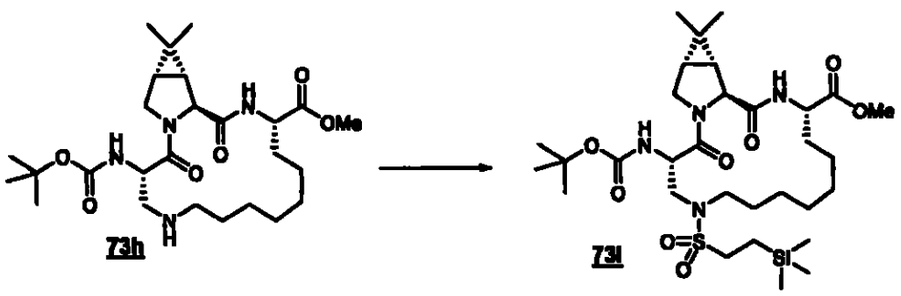
Step H



73g 73h

A solution of alkene 73g (1 mmol) in 20 mL of methanol will be treated with 5% palladium on carbon (0.1 mol%). The mixture will be hydrogenated at 50 psi until all the starting material is consumed. The reaction mixture will be diluted with 100 mL of dichloromethane and filtered thru a short path of celite. The filtrate will be concentrated and the product 73h will be purified by column chromatography on silica gel.

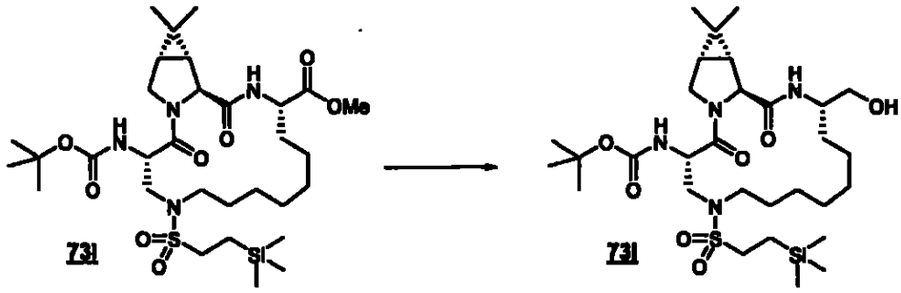
Step I



73h 73i

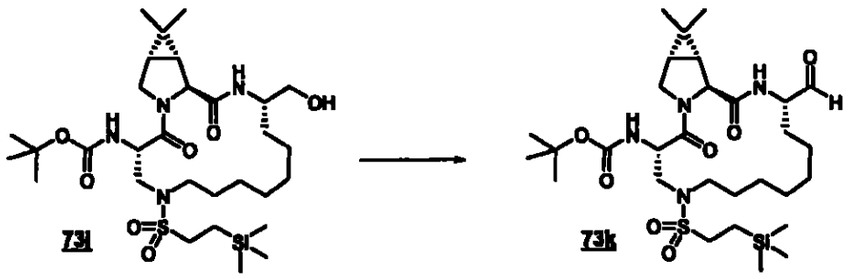
A solution of macrocyclic amine 73h (1 mmol) in 10 mL of dichloromethane will be treated with potassium carbonate (2 mmol) and (trimethylsilyl)ethanesulfonyl chloride (1 mmol). The mixture is stirred for 1 day and solvent will be evaporated. The product 73i will be purified by column chromatography on silica gel.

Step J



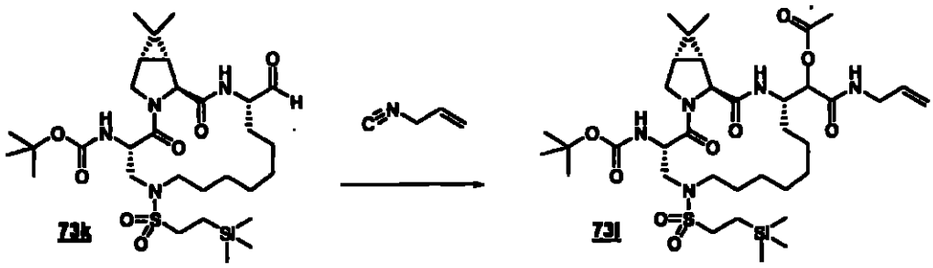
A solution of methyl ester 73i (1 mmol) in 10 mL of dry THF will be treated with lithium borohydride (2.1 mmol). The reaction mixture will be stirred at room temperature. After 5 h, the excess lithium borohydride will be quenched by addition of aqueous saturated ammonium chloride solution (3 mL). The mixture will be partitioned between ethyl acetate (50 mL) and aqueous saturated sodium bicarbonate solution (30 mL). The aqueous layer will be back extracted with ethyl acetate (2 x 30 mL) and dichloromethane (2 x 30 mL). The combined organic layers will be dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue will be chromatographed on silica gel to afford the product 73j.

Step K



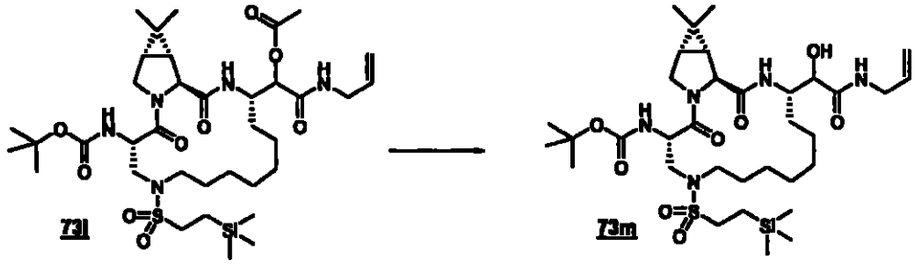
A solution of alcohol 73j (1 mmol) in 20 mL of dry dichloromethane will be treated with Dess-Martin periodinane (1.5 mmol). The reaction mixture will be stirred at room temperature for 45 min. The mixture will be treated with aqueous 1M sodium thiosulfate solution (10 mL) and aqueous saturated sodium bicarbonate solution (20 mL) and stirred for 15 min. The mixture will be extracted with dichloromethane (3 x 40 mL). The combined organic layers will be dried over magnesium sulfate, filtered, and concentrated. The residue will be chromatographed on silica gel to afford the aldehyde product 73k.

Step L



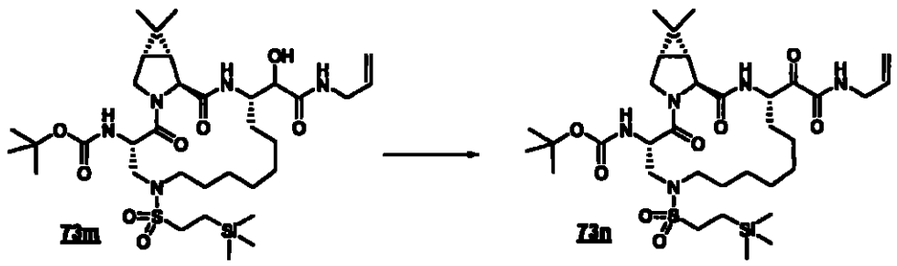
A solution of aldehyde 73k (1 mmol) in 10 mL of dry dichloromethane will be treated with allylisocyanide (2 mmol) and acetic acid (2 mmol). The mixture will be stirred for about 5 h. All the volatiles will be removed under vacuum and the residue will be chromatographed on silica gel to afford the acetate product 73l.

Step M



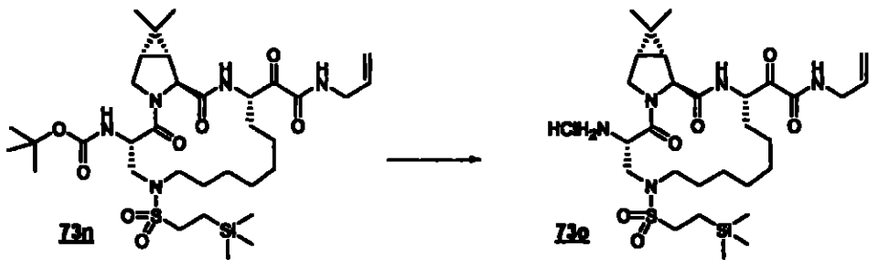
The acetate 73l (1 mmol) will be dissolved in 16 mL of a 1:1 mixture of THF/water and treated with lithium hydroxide monohydrate (2.5 mmol). After 30 min the mixture will be partitioned between dichloromethane (50 mL) and aqueous saturated sodium bicarbonate solution (20 mL). The aqueous layer will be back extracted with dichloromethane (3 x 30 mL). The combined organic layers will be dried over magnesium sulfate, filtered, and concentrated. The hydroxyamide product 73m will be used without further purification.

Step N



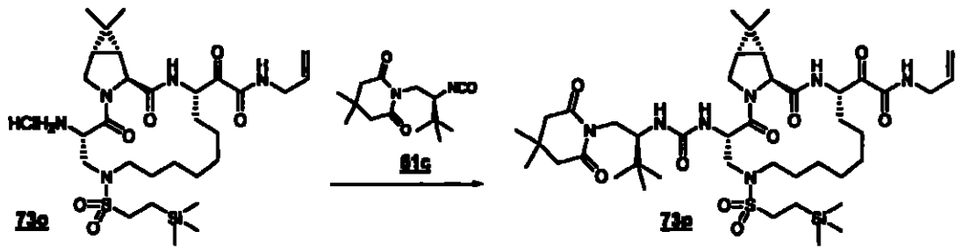
A solution of hydroxyamide **73m** (1 mmol) in 20 mL of dry dichloromethane will be treated with Dess-Martin periodinane (2.5 mmol). The reaction mixture will be stirred at room temperature for 30 min. The mixture will be treated with aqueous 1M sodium thiosulfate solution (20 mL) and aqueous saturated sodium bicarbonate solution (10 mL) and stirred for 15 min. The mixture will be extracted with dichloromethane (3 x 30 mL). The combined organic layers will be dried over magnesium sulfate, filtered, and concentrated. The ketoamide product **73n** will be purified by column chromatography.

Step O



The N-Boc protected amine **73n** (0.1 mmol) will be dissolved in 5 mL of 4M HCl solution in dioxanes. The resulting solution will be stirred for 30 min and then evaporated under reduced pressure to give the amine hydrochloride product **73o**.

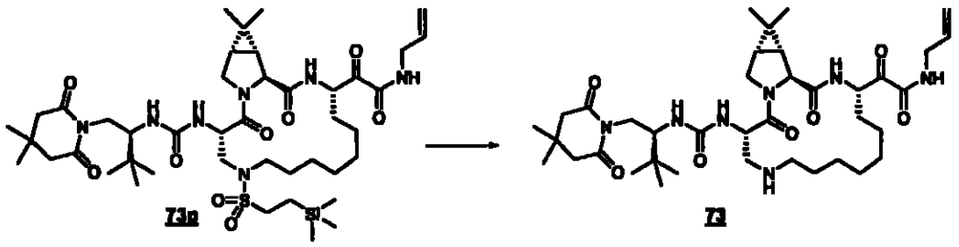
Step P



The amine hydrochloride **73o** (0.1 mmol) will be dissolved in 5 mL of dichloromethane and treated with 20 drops of aqueous saturated sodium bicarbonate solution followed by a solution of isocyanate **51c** (0.12 mmol) in toluene. The mixture will be stirred for 5 h and then diluted with 50 mL of dichloromethane and dried over magnesium sulfate. The mixture will be

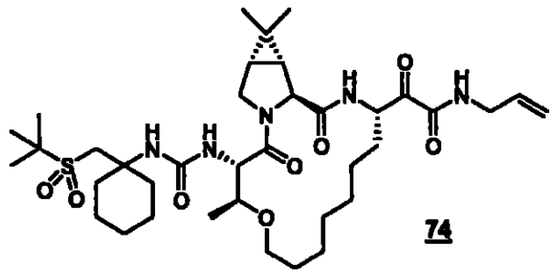
filtered, and concentrated under reduced pressure. The product **73p** will be purified by column chromatography on silica gel.

Step Q

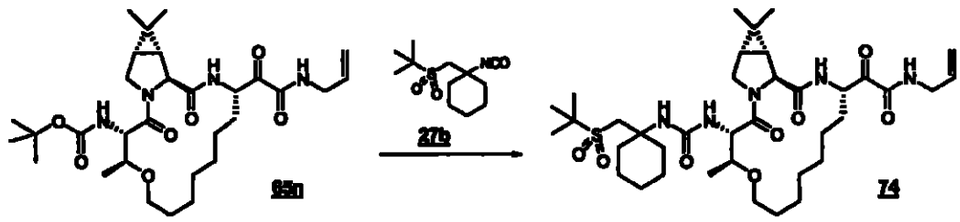


The SES-protected amine **73p** (0.1 mmol) will be dissolved in 2 mL of DMF and treated with cesium fluoride (0.4 mmol). The reaction mixture will be stirred at room temperature for 4 h and poured onto water (10 mL). The mixture will be extracted with ethyl acetate (3 x 20 mL). The combined organic layers will be dried over magnesium sulfate, filtered and concentrated under reduced pressure. The macrocyclic amine **73** will be purified by column chromatography on silica gel.

Preparative Example 74: Preparation of:



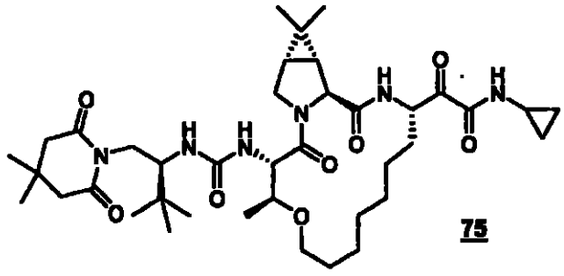
Step A



The N-Boc amine **65n** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was

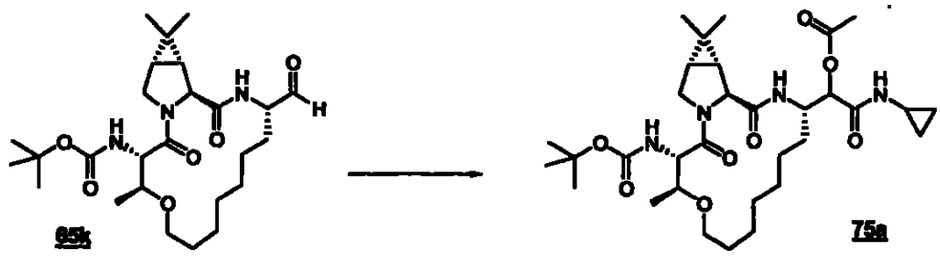
dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a soln. of the isocyanate **27b** in toluene (1.2 eq, 0.6 mL of a 0.2M soln. in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (60 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 1:1) to afford the product **74** (45 mg, 59%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (br s, 1H), 7.40-7.69 (br s, 1H), 6.08-6.43 (br s, 1H), 5.91 (ddt, 1H, J = 5.6, 10.4, 17.3 Hz), 5.70 (br s, 1H), 5.29 (dd, 1H, J = 1.2, 17.3 Hz), 5.24 (dd, 1H, J = 1.2, 10.4 Hz), 4.66 (d, 1H, J = 9.4 Hz), 4.46 (br s, 1H), 4.38 (m, 1H), 4.25 (d, 1H, J = 10.7 Hz), 4.06 (m, 2H), 3.98 (m, 1H), 3.71 (dq, 5.6, 11.6 Hz), 3.64 (ddd, 1H, J = 5.0, 5.3, 9.7 Hz), 3.25 (m, 1H), 2.88 (d, 1H, J = 13.5 Hz), 2.47 (br s, 1H), 2.19 (d, 1H, J = 11.6 Hz), 1.39 (s, 9H), 1.28-1.99 (m, 22H), 1.21 (d, 3H, J = 5.6 Hz), 1.13 (m, 1H), 1.04 (s, 3H), 0.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.7, 173.0, 171.3, 159.4, 157.0, 133.4, 117.7, 75.2, 67.7, 61.2, 60.8, 55.6, 54.6, 48.7, 42.2, 36.3, 31.6, 28.9, 27.9, 27.8, 27.1, 26.8, 25.9, 24.8, 24.0, 23.6, 21.9, 21.5, 19.4, 15.8, 13.4 ppm; HRMS calcd for $C_{37}H_{62}N_5O_8S$ $[M+H]^+$: 736.4319, found 736.4325.

Preparative Example 75: Preparation of:



75

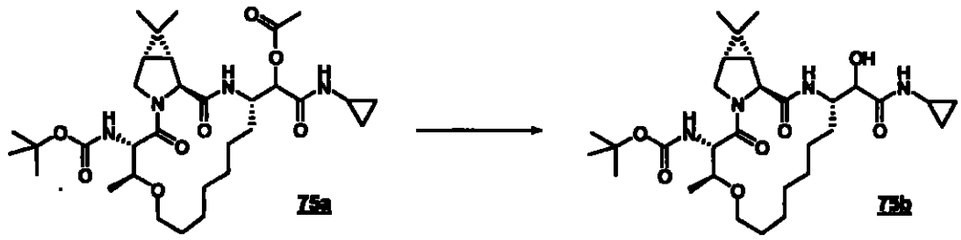
Step A



65k 75a

A solution of aldehyde **65k** (710 mg) in 30 mL of dry dichloromethane was treated with cyclopropylisocyanide (Oakwood Prod., 2.0 eq, 0.25 mL, d 0.8) and acetic acid (2 eq, 0.16 mL, d 1.049). The mixture was stirred at room temp for 5 h. All the volatiles were removed under reduced pressure and the residue was chromatographed on silica gel (gradient: acetone/hexanes; 15:85 to 55:45) to afford the product **75a** (740 mg, 83%) as a white solid.

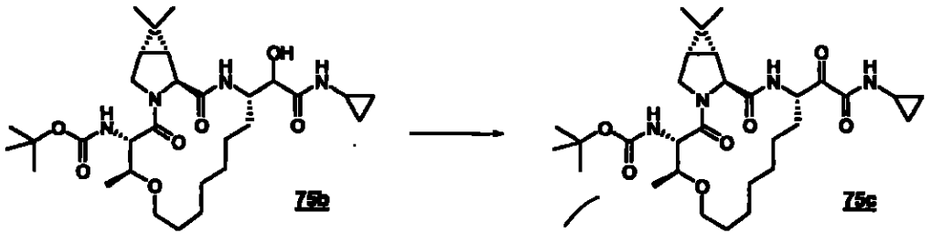
Step B



75a 75b

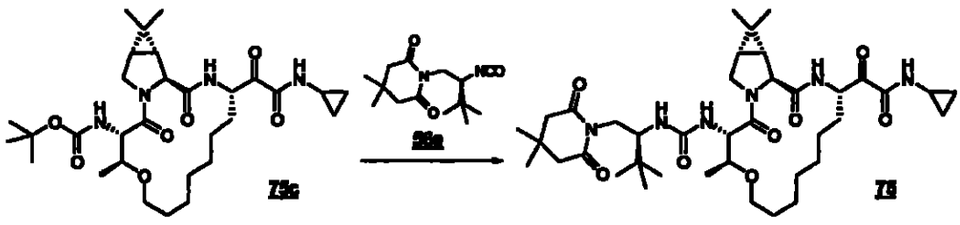
A solution of acetate **75a** (740 mg) in 20 mL of a 2:1 mixture of THF/water was treated with lithium hydroxide monohydrate (2.5 eq, 125 mg) and stirred for approx 30 min until all the starting material had been consumed as determined by TLC analysis (ethyl acetate/hexanes; 8:2). The reaction mixture was diluted with 50 mL of aqueous saturated sodium bicarbonate solution and extracted with dichloromethane (3 x 80 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford the product **75b** (688 mg, 98%) as a colorless semi-solid which was used without further purification.

Step C



A solution of hydroxyamide **75b** (1.192 mmol) in 25 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 1.01 g). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (30 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (30 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 80 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 5:95 to 4:6) to afford the product **75c** (476 mg, 69%) as white solid.

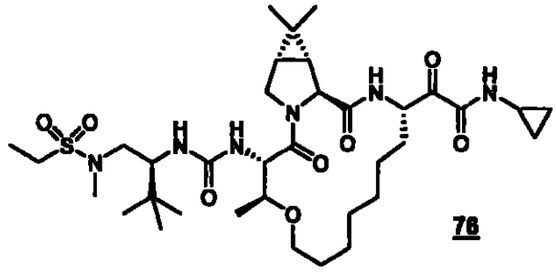
Step D



The N-Boc amine **75c** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 10 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min, a soln of the isocyanate **56e** was added dropwise (1.2 eq, 0.59 mL of a 0.216M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (70 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The

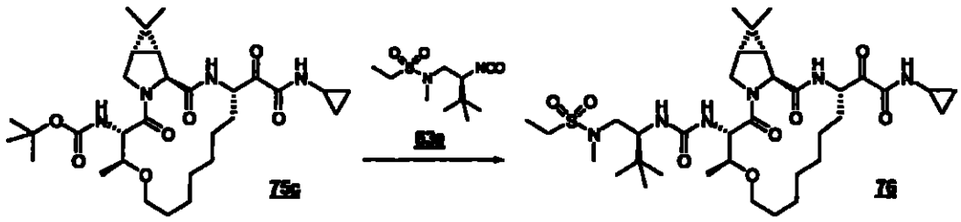
residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 1:1) to afford the product 75 (41 mg, 53%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (br s, 1H), 7.40-7.70 (br s, 1H), 6.28 (br s, 1H), 5.68 (br s, 1H), 5.37 (br s, 1H), 4.62 (s, 1H), 4.49 (br s, 1H), 4.22 (d, 1H, J = 10.7 Hz), 4.05 (dd, 1H, J = 5.0, 10.4 Hz), 3.94 (d, 1H, J = 1.6 Hz), 3.88 (dd, 1H, J = 10.4, 10.7 Hz), 3.82 (q, 1H, J = 11.0 Hz), 3.69 (m, 1H), 3.62 (ddd, 1H, J = 5.0, 5.6, 9.4 Hz), 3.20 (m, 1H), 2.89 (ddd, 1H, J = 3.4, 7.2, 14.8 Hz), 2.55 (d, 2H, J = 17.0 Hz), 2.48 (d, 2H, J = 17.0 Hz), 1.79-1.99 (m, 4H), 1.28-1.69 (m, 10H), 1.14 (d, 3H, J = 6.0 Hz), 1.10 (s, 6H), 1.00 (s, 3H), 0.99 (s, 9H), 0.90 (m, 2H), 0.83 (s, 3H), 0.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.8, 172.8, 171.5, 160.9, 157.8, 75.5, 68.1, 60.8, 57.2, 55.9, 48.7, 46.8, 35.2, 29.3, 28.6, 28.3, 27.7, 26.9, 26.8, 24.8, 24.4, 23.1, 19.3, 16.3, 13.6, 6.8 ppm; HRMS calcd for $C_{39}H_{63}N_6O_8$ $[M+H]^+$: 743.4707, found 743.4686.

Preparative Example 76: Preparation of:



76

Step A

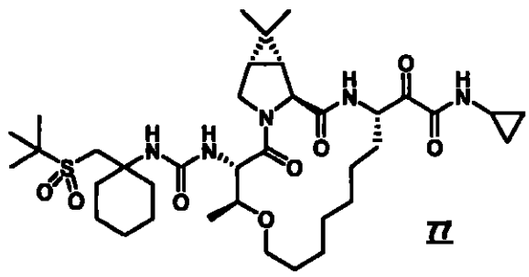


75c 83a 76

The N-Boc amine 75c (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum overnight. The resulting amine salt was dissolved in 5 mL of dichloromethane and cooled to 0 °C. Then, 10 drops of aqueous saturated sodium bicarbonate solution were added. After 10 min,

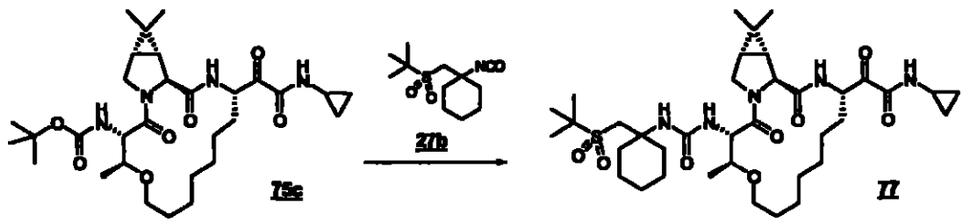
a soln. of the isocyanate **63e** was added dropwise (1.2 eq, 0.95 mL of a 0.131M solution in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 3 h. The reaction mixture was diluted with dichloromethane (70 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product **76** (54 mg, 72%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (br s, 1H), 7.58 (br s, 1H), 6.13 (br s, 1H), 5.75 (br s, 1H), 5.15 (d, 1H, J = 8.5 Hz), 4.68 (br s, 1H), 4.56 (s, 1H), 4.28 (d, 1H, J = 10.7 Hz), 4.06 (dd, 1H, J = 4.7, 10.4 Hz), 3.99 (dd, 1H, J = 9.1, 9.7 Hz), 3.60 (m, 2H), 3.47 (dd, 1H, J 12.2, 13.2 Hz), 3.19 (m, 1H), 3.07 (m, 3H), 2.94 (s, 3H), 2.87 (ddd, 1H, J = 4.0, 7.8, 15.1 Hz), 1.72-1.99 (m, 4H), 1.37 (t, 3H, J = 7.5 Hz), 1.27-1.68 (m, 9H), 1.21 (d, 3H, J = 6.0 Hz), 1.13 (m, 1H), 1.01 (s, 3H), 0.92 (s, 9H), 0.89 (s, 3H), 0.87 (m, 2H), 0.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.5, 172.8, 171.6, 160.8, 158.1, 75.8, 68.4, 60.6, 56.2, 54.4, 50.4, 48.5, 45.7, 34.7, 34.5, 32.1, 31.6, 28.6, 27.8, 27.7, 27.0, 26.9, 26.7, 24.9, 24.6, 23.0, 19.2, 16.2, 13.5, 8.5, 6.7 ppm; HRMS calcd for $C_{35}H_{61}N_6O_6S$ $[M+H]^+$: 725.4272, found 725.4292.

Preparative Example 77: Preparation of:



77

Step A

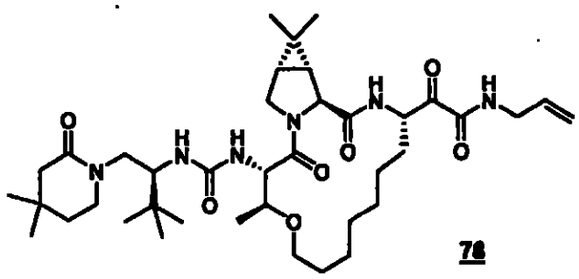


265

266

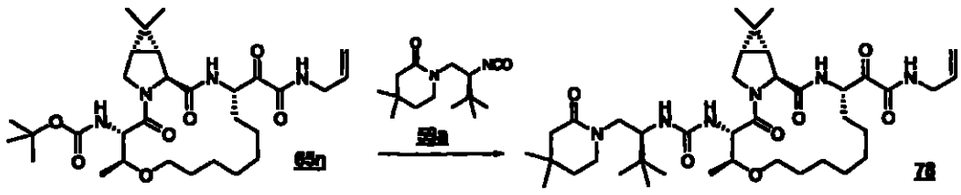
The N-Boc amine **75c** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a soln of the isocyanate **27b** in toluene (1.2 eq, 0.6 mL of a 0.2M soln in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 2 h. The reaction mixture was diluted with dichloromethane (60 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product **77** (50 mg, 65%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (br s, 1H), 7.33-7.63 (br s, 1H), 6.07-6.47 (br s, 1H), 5.67 (br s, 1H), 4.65 (d, 1H, J = 9.7 Hz), 4.45 (br s, 1H), 4.37 (m, 1H), 4.24 (d, 1H, J = 10.7 Hz), 4.07 (dd, 1H, J =5.0, 10.7 Hz), 3.70 (dq, 1H, 5.9, 9.7 Hz), 3.64 (ddd, 1H, J = 5.0, 5.6, 9.7 Hz), 3.24 (m, 1H), 2.89 (ddd, 1H, J = 3.7, 7.5, 14.5 Hz), 2.88 (m, 1H), 2.47 (br s, 1H), 2.18 (d, 1H, J = 12.6 Hz), 1.74-1.97 (m, 5H), 1.39 (s, 9H), 1.27-1.73 (m, 17H), 1.20 (d, 3H, J = 6.3 Hz), 1.11 (m, 1H), 1.04 (s, 3H), 0.91 (s, 3H), 0.90 (m, 2H), 0.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.7, 173.0, 171.3, 161.0, 157.0, 75.2, 67.8, 61.1, 60.8, 55.5, 54.6, 50.1, 48.6, 36.3, 31.6, 28.8, 27.9, 27.0, 26.9, 25.9, 24.8, 24.0, 23.6, 23.1, 21.9, 21.5, 19.4, 15.8, 13.4, 6.9, 6.8 ppm. HRMS calcd for $C_{37}H_{62}N_5O_8S$ $[M+1]^+$: 736.4319, found 736.4329.

Preparative Example 78



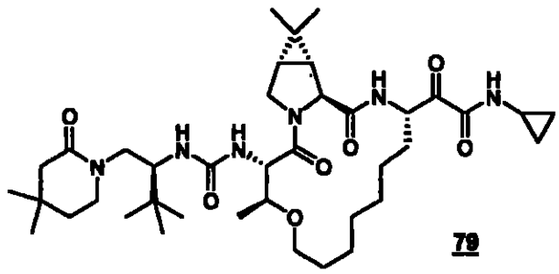
78

Step A



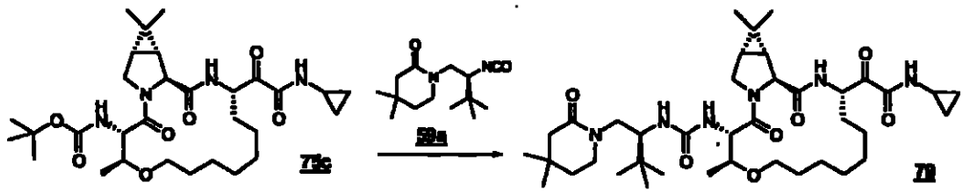
The N-Boc amine **65n** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a solution of the isocyanate **59a** in toluene (1.2 eq, 0.6 mL of a 0.2M soln in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 3 h. The reaction mixture was diluted with dichloromethane (60 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/(hexanes-dichloromethane; 1:1); 1:9 to 1:1) to afford the product **78** (51 mg, 67%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (br s, 1H), 6.42-6.79 (br s, 1H), 5.90 (ddt, 1H, J = 5.6, 10.7, 17.0 Hz), 5.73 (br s, 1H), 5.57 (br s, 1H), 5.27 (d, 1H, J = 17.0 Hz), 5.22 (d, 1H, J = 10.0 Hz), 4.62 (dd, 1H, J = 9.1, 9.7 Hz), 4.52 (br s, 1H), 4.29 (m, 2H), 3.86-4.11 (m, 4H), 3.64 (m, 3H), 3.17 (m, 2H), 2.74 (d, 1H, J = 11.9 Hz), 2.24 (d, 1H, J = 17.3 Hz), 2.10 (d, 1H, J = 17.0 Hz), 1.95 (m, 4H), 1.24-1.68 (m, 11H), 1.16 (d, 3H, J = 5.9 Hz), 1.11 (m, 1H), 1.02 (s, 3H), 1.01 (s, 6H), 0.95 (s, 9H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.8, 172.9, 171.6, 170.7, 159.4, 158.2, 133.6, 117.5, 75.7, 68.2, 60.8, 56.0, 55.3, 48.5, 46.8, 46.2, 44.9, 42.3, 35.7, 34.8, 32.3, 31.6, 30.2, 28.6, 28.4, 27.8, 27.7, 27.1, 27.0, 26.8, 24.8, 24.5, 19.3, 16.5, 13.6 ppm. HRMS calcd for $C_{39}H_{65}N_6O_7$ $[M+1]^+$: 729.4915, found 729.4917.

Preparative Example 79



79

Step A

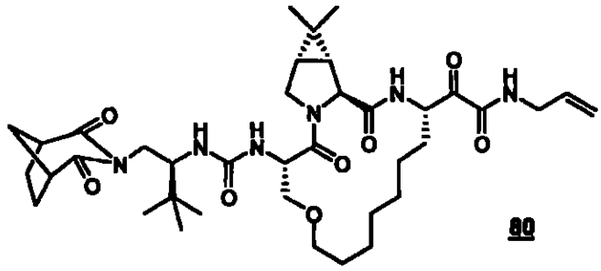


75c 59a 79

The N-Boc amine **75c** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a solution of the isocyanate **59a** in toluene (1.2 eq, 0.6 mL of a 0.2M soln in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 3 h. The reaction mixture was diluted with dichloromethane (60 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/(hexanes-dichloromethane, 1:1); 1:9 to 1:1) to afford the product **79** (36 mg, 48%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 (br s, 1H), 6.38-6.70 (br s, 1H), 5.73 (br s, 1H), 5.55 (d, 1H, J = 7.8 Hz), 4.61 (t, 1H, J = 9.7 Hz), 4.51 (br s, 1H), 4.27 (m, 2H), 4.05 (dd, 1H, J = 5.0, 10.4 Hz), 3.95 (dd, 1H, J = 9.4, 9.7 Hz); 3.62 (m, 3H), 3.18 (m, 2H), 2.90 (ddd, 1H, J = 3.7, 7.2, 14.8 Hz), 2.73 (d, 1H, J = 12.6 Hz), 2.21 (d, 1H, J = 17.0 Hz), 2.09 (d, 1H, J = 17.3 Hz), 1.93 (br s, 4H), 1.27-1.68 (m, 11H), 1.15 (d, 3H, J = 5.9 Hz), 1.11 (m, 1H), 1.02 (s, 3H), 1.00 (s, 6H), 0.94 (s, 9H), 0.87 (m, 2H), 0.86 (s, 3H), 0.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.1, 172.9, 171.6, 170.6, 160.9, 158.2, 75.6, 68.3, 60.7, 56.0, 55.3, 48.5, 46.7,

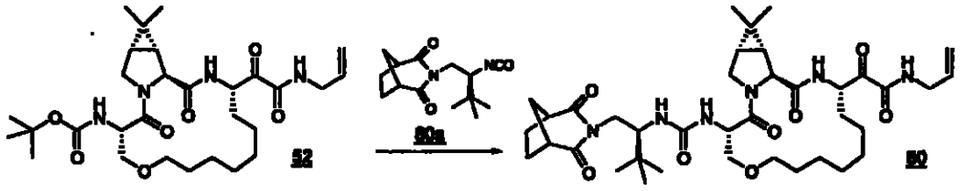
46.3, 44.9, 35.7, 34.8, 32.4, 31.6, 30.2, 29.7, 28.6, 28.5, 27.8, 27.7, 27.0, 26.7, 24.8, 24.7, 23.1, 19.3, 16.5, 13.6, 6.7, 6.6 ppm. HRMS calcd for $C_{39}H_{65}N_6O_7$ $[M+1]^+$: 729.4915, found 729.4926.

Preparative Example 80



80

Step A

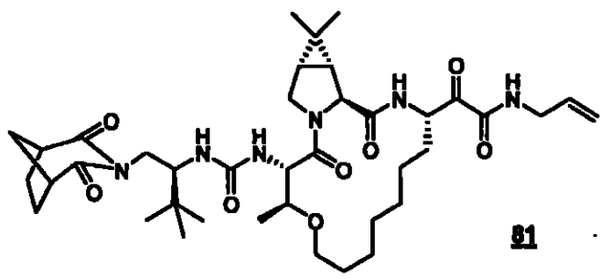


52 80a 80

The N-Boc amine **52** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a solution of the isocyanate **80a** in toluene (1.2 eq, 0.8 mL of a 0.155M soln in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 3 h. The reaction mixture was diluted with dichloromethane (60 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product **80** (41 mg, 61%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ, 8.01 (d, 1H, J = 8.2 Hz), 7.85 (br s, 1H), 6.01 (br s, 1H), 5.91 (ddt, 1H, J = 5.6, 10.0, 17.0 Hz), 5.68 (dd, 1H, J = 9.1, 9.4 Hz), 5.27 (dd, 1H, J = 1.2, 17.0 Hz), 5.23 (dd, 1H, J = 1.2, 10.0 Hz), 5.20 (m, 1H), 4.98 (br s, 1H); 4.59 (s, 1H), 4.13 (d, 1H, J = 10.7 Hz), 4.01 (m, 3H), 3.89 (ddd, 1H, J = 2.2, 10.4, 10.7 Hz), 3.79 (dd, 1H, J

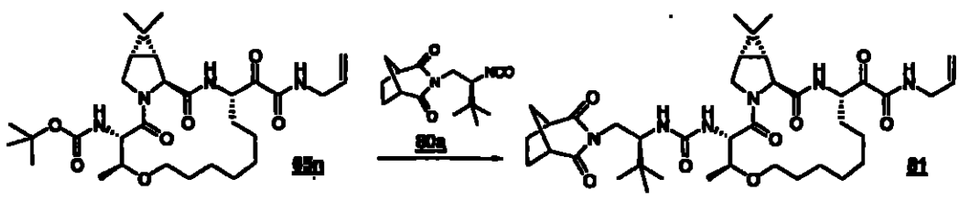
= 3.4, 12.9 Hz), 3.76 (m, 1H), 3.56 (m, 2H), 3.36 (dd, 1H, *J* = 4.1, 7.5 Hz), 3.31 (m, 1H), 3.18 (brs, 1H), 3.14 (br s, 1H), 2.22 (d, 1H, *J* = 10.7 Hz), 2.07 (br s, 2H), 1.73-2.00 (m, 5H), 1.25-1.70 (m, 11H), 1.16 (m, 1H), 1.02 (s, 3H), 0.96 (s, 9H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.8, 177.4, 172.1, 171.3, 159.3, 157.9, 133.4, 117.7, 71.4, 70.7, 60.7, 56.7, 53.4, 50.8, 48.6, 45.4, 45.2, 42.2, 39.4, 34.7, 33.1, 32.2, 31.0, 28.7, 27.7, 27.5, 27.3, 26.9, 24.3, 19.3, 13.5 ppm. HRMS calcd for $C_{38}H_{59}N_6O_8$ $[M+1]^+$: 727.4394, found 727.4387.

Preparative Example 81



81

Step A

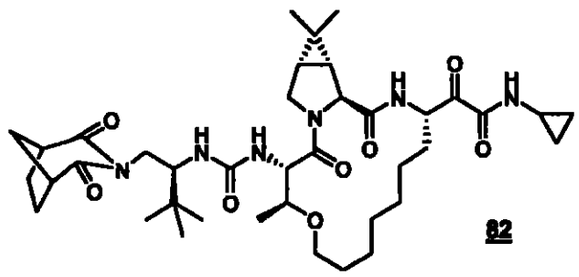


65n 80a 81

The N-Boc amine 65n (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a solution of the isocyanate 80a in toluene (1.2 eq, 0.8 mL of a 0.155M soln in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 3 h. The reaction mixture was diluted with dichloromethane (60 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product 81 (54

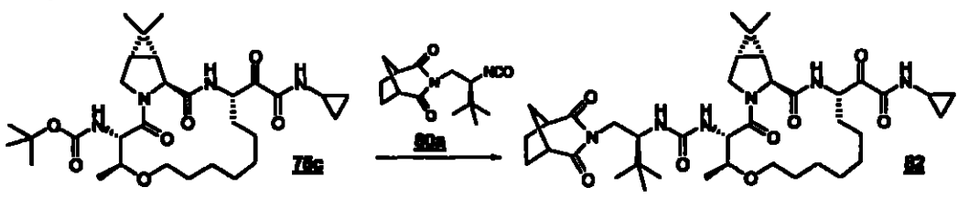
mg, 70%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ, 8.12 (br s, 1H), 7.39-7.79 (br s, 1H), 6.29 (br s, 1H), 5.91 (ddt, 1H, J = 5.9, 10.4, 17.0 Hz), 5.71 (br s, 1H), 5.40 (br s, 1H), 5.27 (dd, 1H, J = 1.2, 17.0 Hz), 5.23 (dd, 1H, J = 1.2, 10.4 Hz), 4.67 (dd, 1H, J = 7.8, 8.1 Hz); 4.50 (br s, 1H), 4.24 (d, 1H, J = 10.7 Hz), 4.07 (dd, 1H, J = 5.3, 10.4 Hz), 4.03 (m, 1H), 3.97 (ddd, 1H, J = 5.6, 5.9, 15.7 Hz), 3.81 (m, 2H), 3.73 (m, 1H), 3.67 (d, 1H, J = 12.2 Hz), 3.62 (m, 1H), 3.20 (s, 2H), 3.07 (s, 1H), 2.29 (d, 1H, J = 11.0 Hz), 2.07 (br s, 3H), 1:93 (br s, 2H), 1.83 (br s, 3H), 1.28-1.68 (m, 10H), 1.17 (d, 3H, J = 5.9 Hz), 1.11 (m, 1H), 1.01 (s, 3H), 0.99 (s, 9H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.5, 177.1, 172.8, 171.5, 159.4, 158.0, 133.4, 117.7, 75.5, 68.1, 60.8, 57.4, 55.9, 48.7, 45.4, 42.3, 40.4, 34.8, 32.8, 31.7, 28.6, 27.8, 27.6, 27.4, 26.9, 26.8, 24.7, 24.4, 19.4, 16.2, 13.5 ppm. HRMS calcd for $C_{39}H_{61}N_6O_8$ $[M+1]^+$: 741.4551, found 741.4543.

Preparative Example 82



82

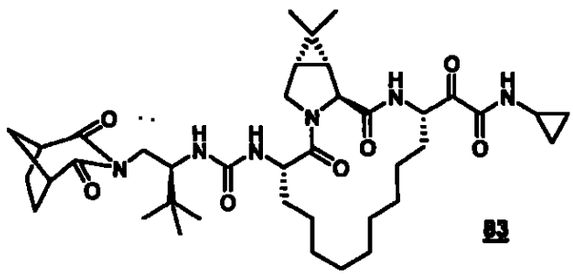
Step A



The N-Boc amine 75c (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a solution of the isocyanate 80a in toluene (1.2 eq, 0.8 mL of a 0:155M soln in toluene) and

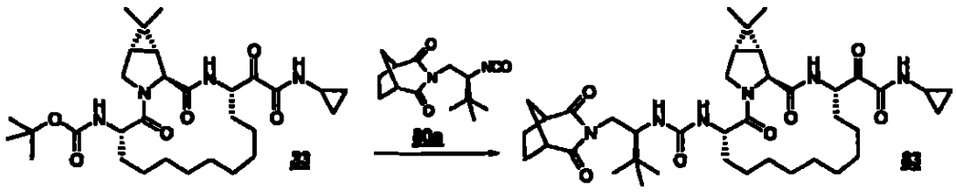
stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 3 h. The reaction mixture was diluted with dichloromethane (60 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 6:4) to afford the product **82** (50 mg, 65%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 (br s, 1H), 7.38-7.68 (br s, 1H), 6.28 (br s, 1H), 5.68 (br s, 1H), 5.39 (br s, 1H), 4.66 (dd, 1H, J = 7.5, 7.5 Hz), 4.49 (br s, 1H), 4.23 (d, 1H, J = 10.4 Hz), 4.06 (dd, 1H, J = 5.0, 10.4 Hz); 3.81 (m, 2H), 3.71 (m, 1H), 3.67 (d, 1H, J = 12.2 Hz), 3.61 (m, 1H), 3.19 (br s, 2H), 3.07 (s, 1H), 2.89 (ddd, 1H, J = 3.7, 7.5, 14.8 Hz), 2.29 (d, 1H, J = 11.0 Hz), 1.98-2.13 (m, 3H), 1.75-1.96 (m, 6H), 1.26-1.67 (m, 9H), 1.17 (d, 3H, J = 5.9 Hz), 1.10 (m, 1H), 1.00 (s, 3H), 0.98 (s, 9H), 0.90 (m, 2H), 0.83 (s, 3H), 0.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.9, 178.8, 172.8, 171.5, 160.9, 158.0, 75.5, 68.1, 60.8, 57.4, 55.9, 48.7, 45.4, 40.2, 34.8, 32.8, 31.7, 28.6, 27.8, 27.7, 27.4, 26.9, 26.8, 24.8, 24.4, 23.1, 19.3, 16.2, 13.5, 6.9, 6.8 ppm.

Preparative Example 83



83

Step A

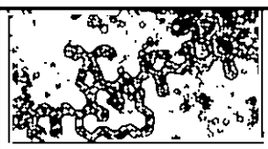


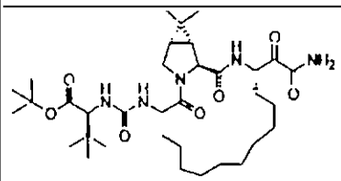
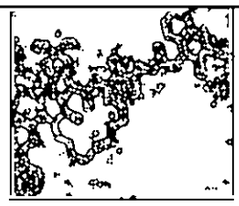
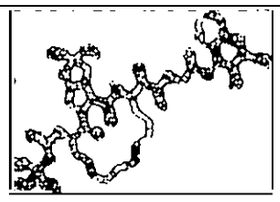
The N-Boc amine **33** (60 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min. All the volatiles were removed under reduced pressure and the residue was

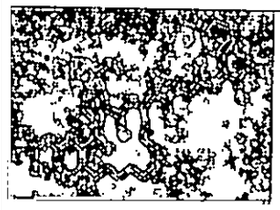
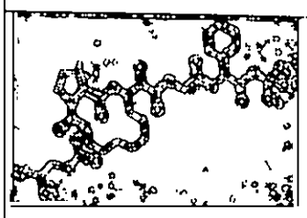
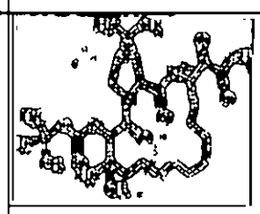
placed under high vacuum for 3 h. The resulting amine salt was dissolved in 5 mL of dry dichloromethane and cooled to 0 °C. Then, 20 drops of aqueous saturated sodium bicarbonate solution were added followed by a solution of the isocyanate **80a** in toluene (1.2 eq, 0.8 mL of a 0.155M soln in toluene) and stirring was continued for 10 min. The cooling bath was removed and the mixture was stirred at room temp for 3 h. The reaction mixture was diluted with dichloromethane (60 mL) and dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 1:1) to afford the product **83** (63 mg, 81%) as a white solid.

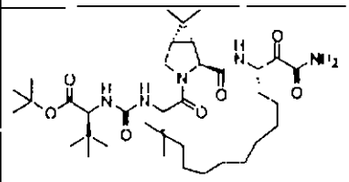
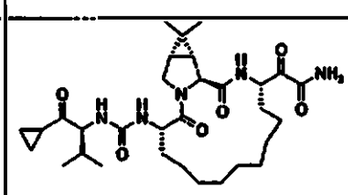
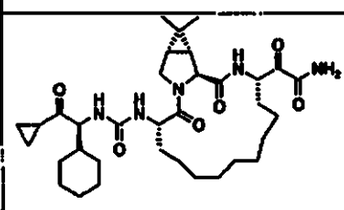
Example compounds are shown in **Tables 1** and **2** below. The Ki values for the compounds are rated as follows:
"A" for Ki values less than 100nM, "B" for Ki values greater than or equal to 100nM but less than 1μM and "C" for Ki values greater than or equal to 1μM.

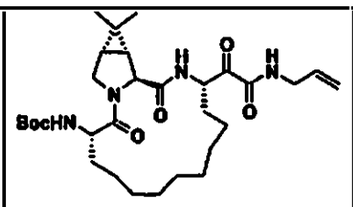
Table 1

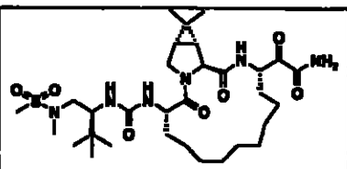
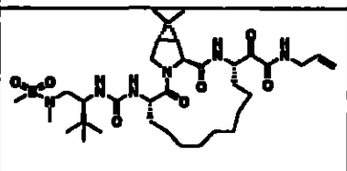
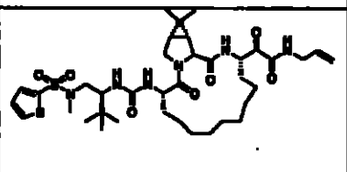
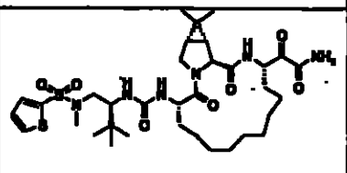
Example	Structure	Binding Activity
1		A
2		A
3		A

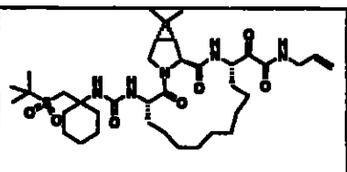
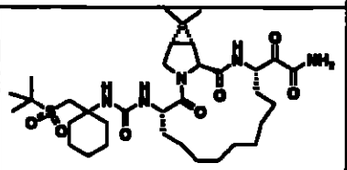
4		A
5		A
6		A
7		A
8		A
9		A
10		A

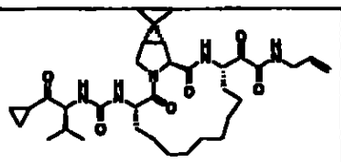
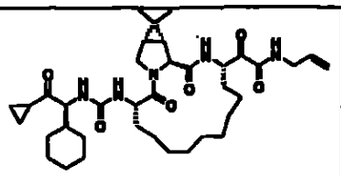
11		C
12		B
13		A
14		A
15		C
16		C

17		A
18		A
19		A
20		A
21		A

22		A

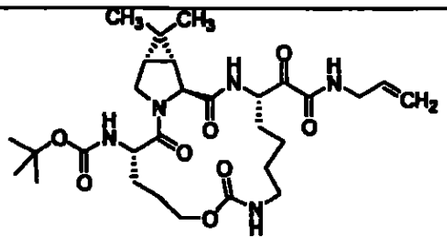
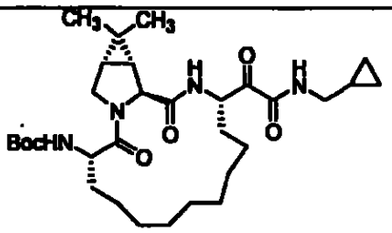
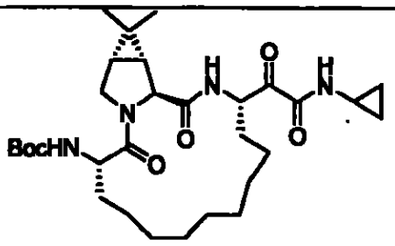
23		A
24		A
25		A
26		A

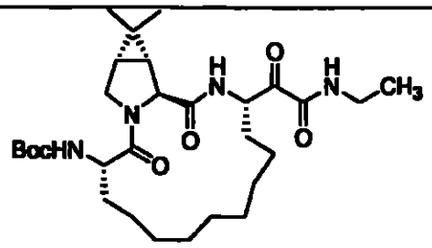
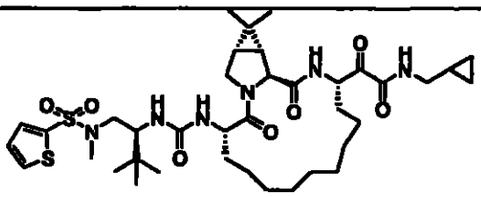
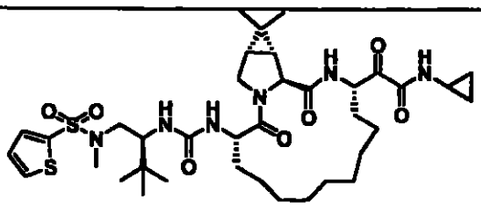
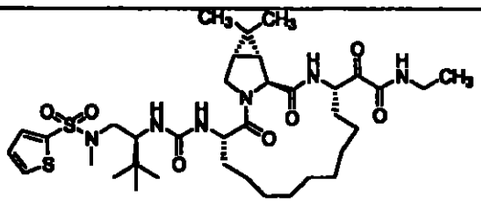
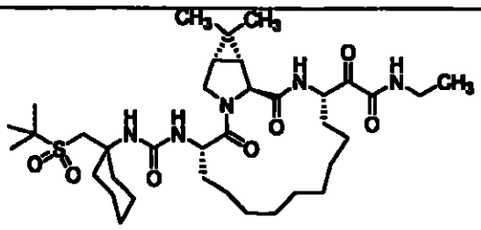
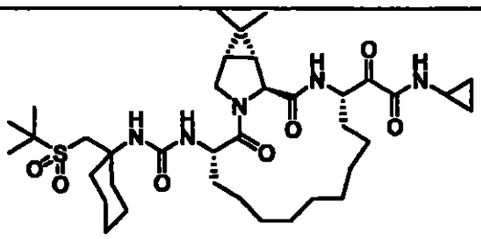
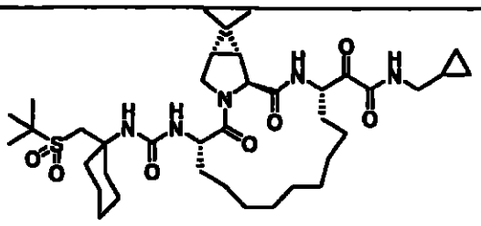
27		A
28		A

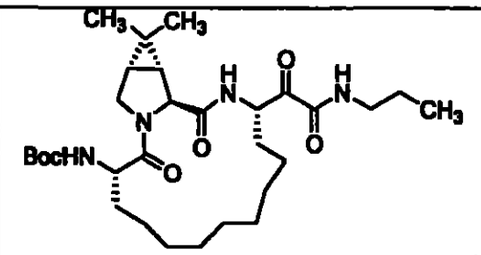
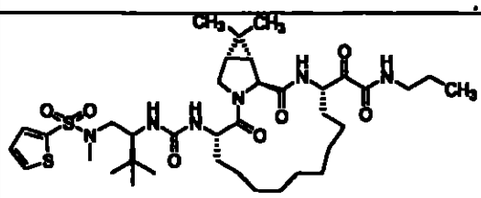
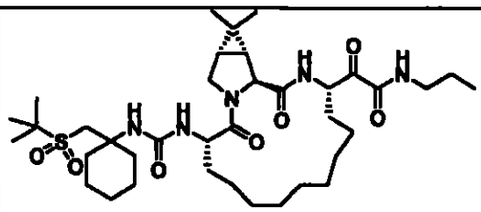
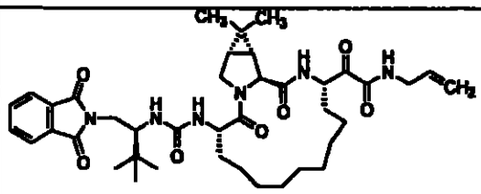
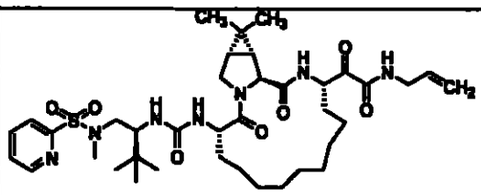
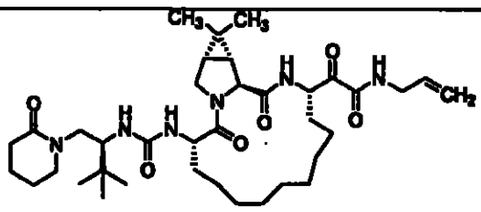
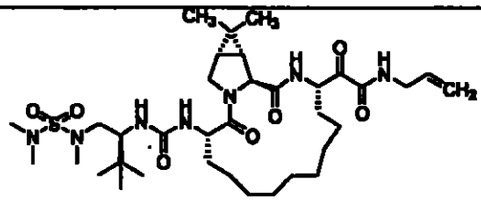
29		A
30		A

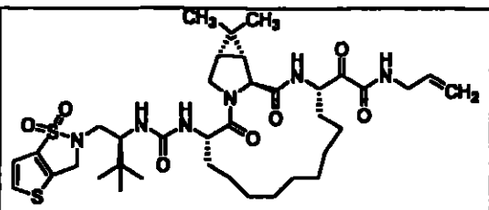
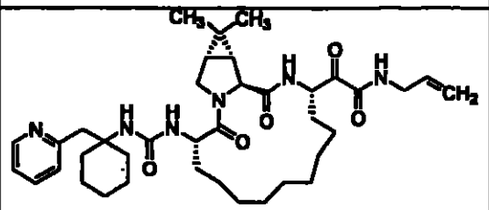
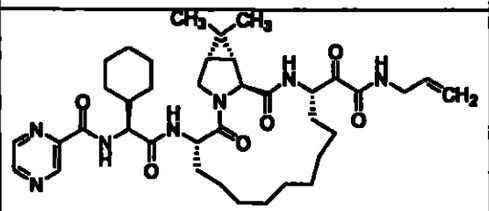
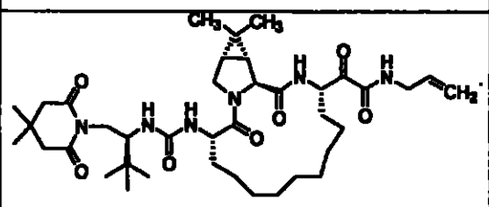
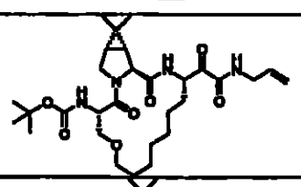
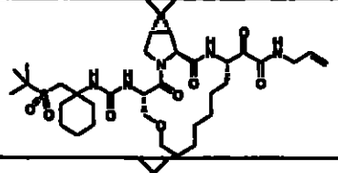
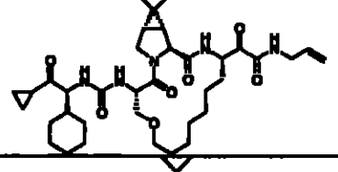
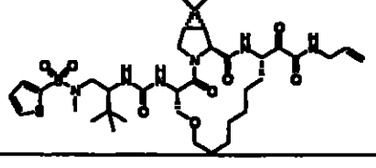
Additional representative compounds of the invention which exhibit excellent HCV protease inhibitory activity are listed below in **Table 2.**

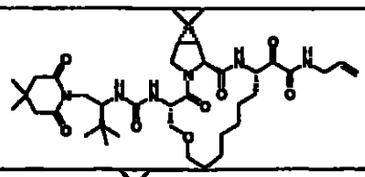
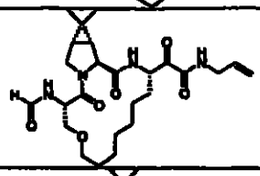
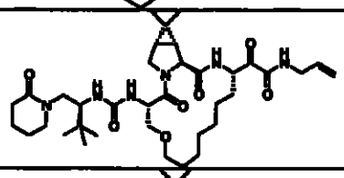
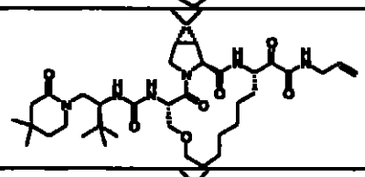
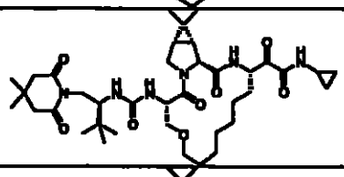
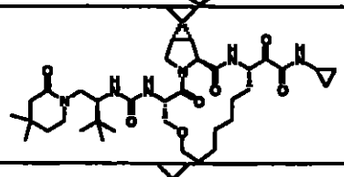
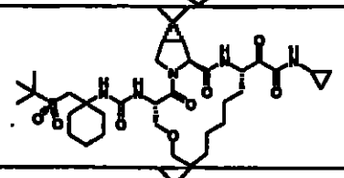
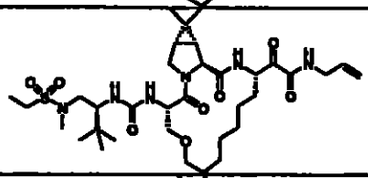
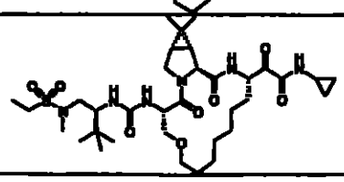
Table 2

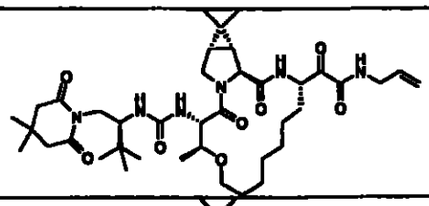
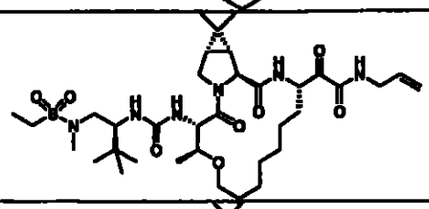
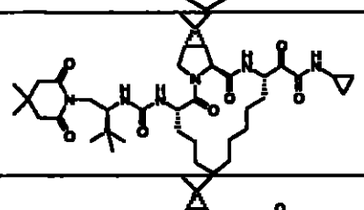
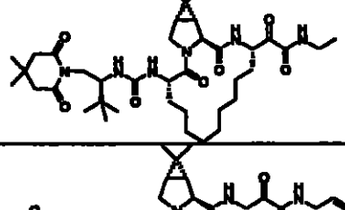
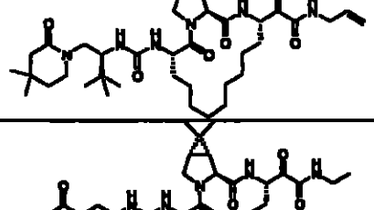
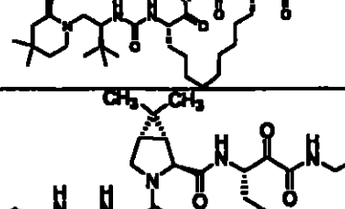
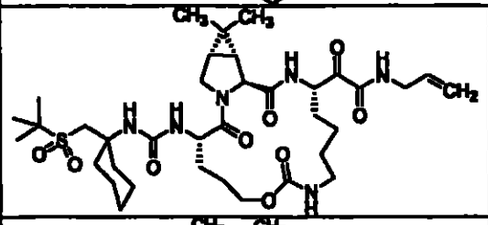
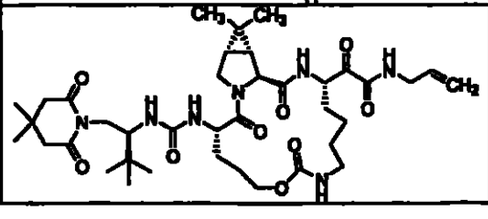
Entry	Structure	Activity K_i* (nM)
31		–
32		B
33		A

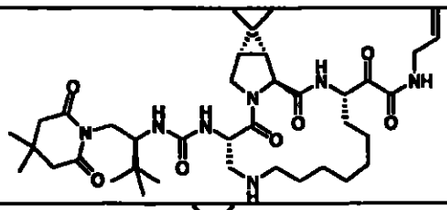
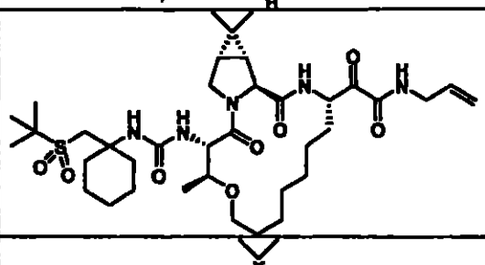
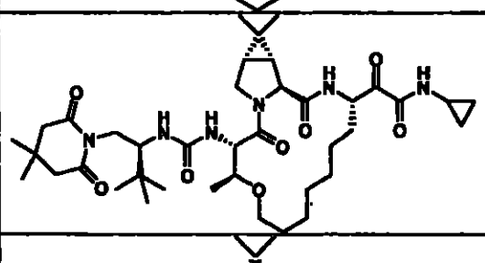
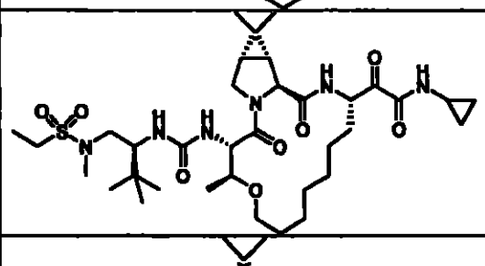
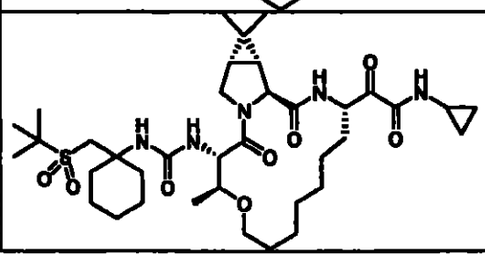
34		A
35		A
36		A
37		A
38		A
39		A
40		A

41		NA
42		A
43		A
44		A
45		A
46		A
47		A

48		A
49		A
50		A
51		A
52		B
53		A
54		B
55		A

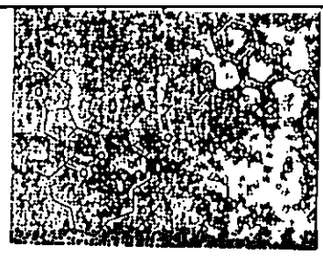
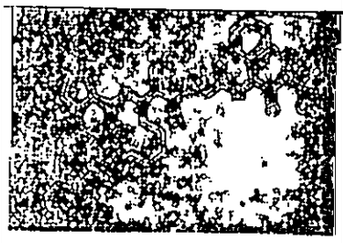
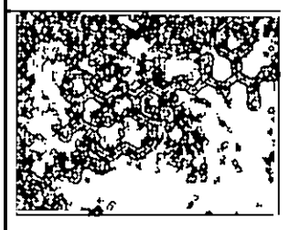
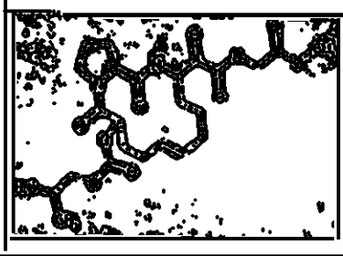
56		A
57		C
58		A
59		A
60		A
61		A
62		A
63		A
64		A

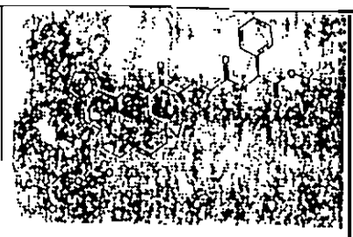
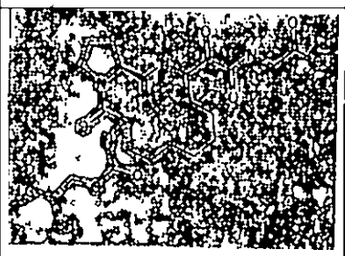
65		A
66		A
67		A
68		A
69		A
70		A
71		A
72		A

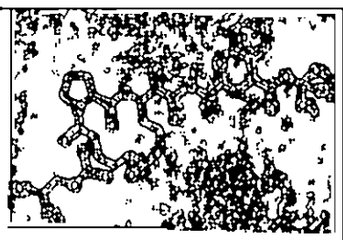
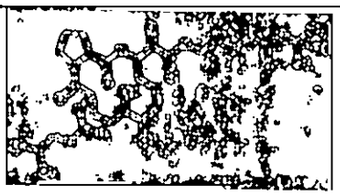
73		NA
74		A
75		A
76		A
77		A

Still additional compounds are shown in Table 2A:

Table 2A

Example	Structure	Binding Activity
78		C
79		C
80		C
81		C
82		C

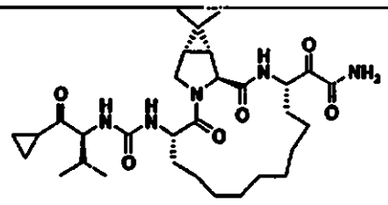
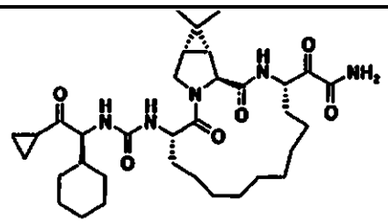
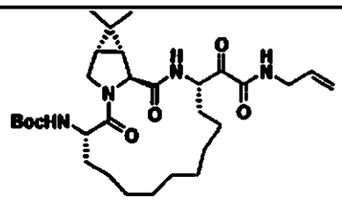
83		C
84		B
85		C
86		C

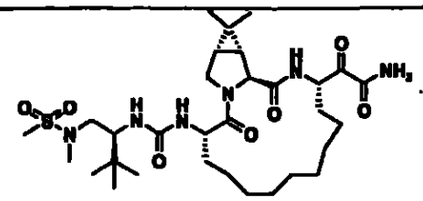
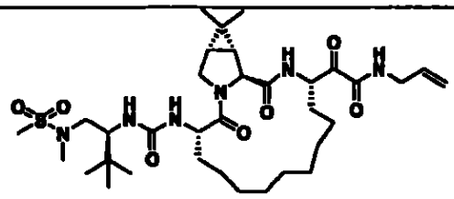
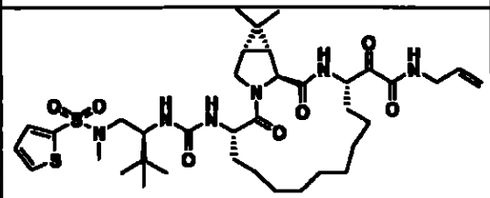
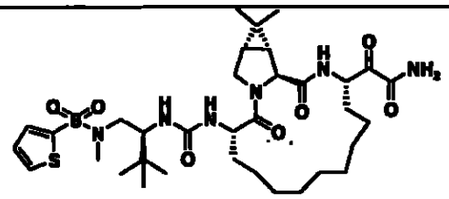
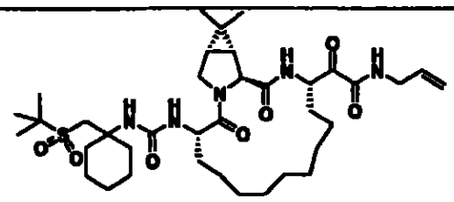
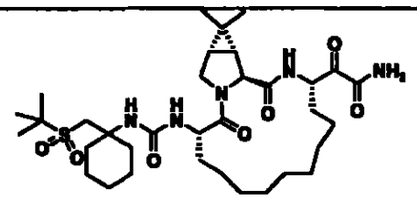
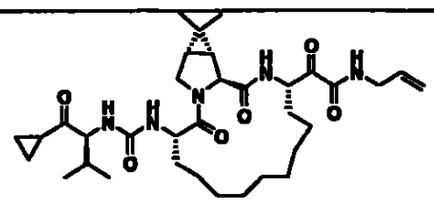
87		C
88		C

89		C
90		B

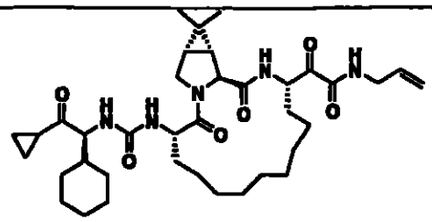
Table 3 shows the activities (Ki*) of certain representative compounds of the invention:

Table 3. Representative compounds with inhibitory activity

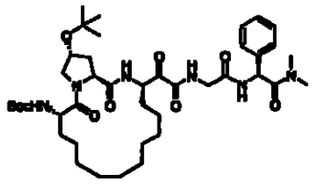
Entry	Compound number	Structure	Activity K_i* (nM)
1	20		11
2	21		11
3	22		36

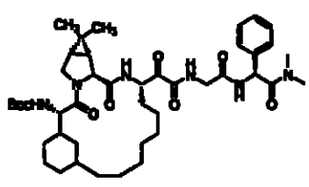
4	23		3
5	24		3
6	25		3
7	26		2
8	27		5
9	28		5
10	29		20

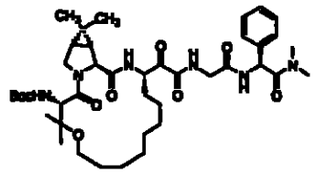
291
289

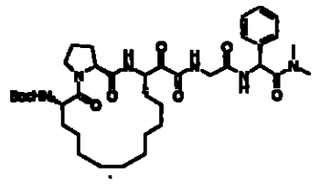
11	30		5

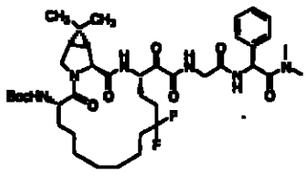
Following generally the procedures described above, the following compounds can also be prepared and used as HCV protease inhibitors:

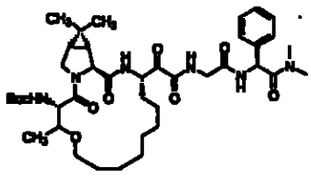


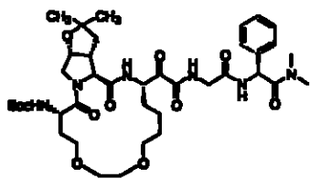


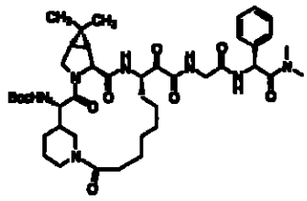


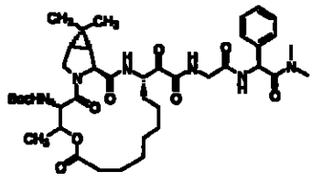


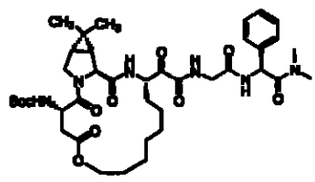




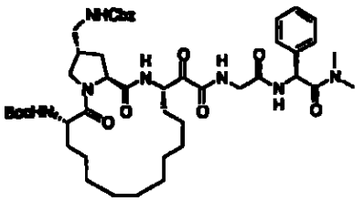
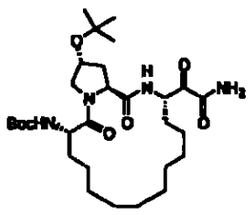
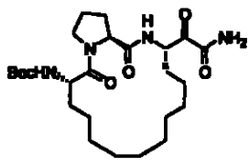
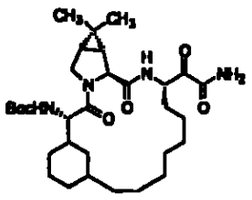
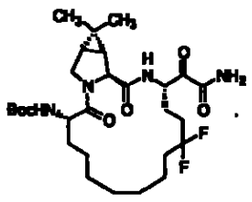
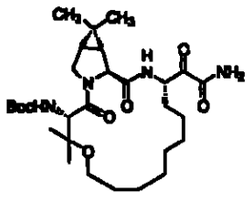
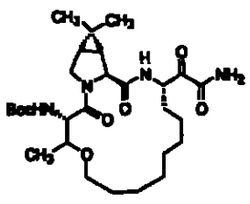
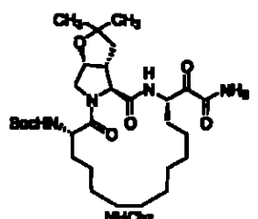
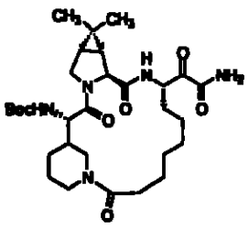
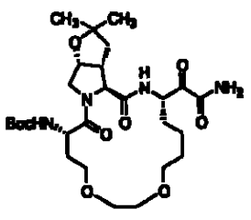
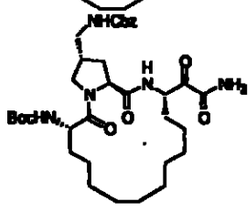




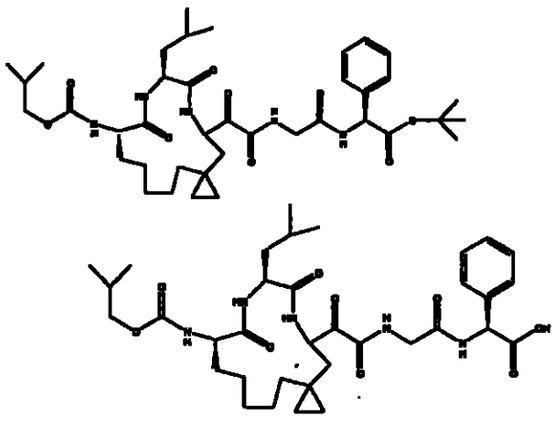




5

5



The present invention relates to novel HCV protease inhibitors. This utility is manifested in their ability to inhibit the HCV NS2/NS4a serine protease as demonstrated by the following *in vitro* assays.

Assay for HCV Protease Inhibitory Activity:

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

Materials and Methods:

Materials: Chemical reagents for assay related buffers were obtained from Sigma Chemical Company (St. Louis, Missouri). Reagents for peptide synthesis were from Aldrich Chemicals, Novabiochem (San Diego, California), Applied Biosystems (Foster City, California) and Perseptive Biosystems

(Framingham, Massachusetts). Peptides were synthesized manually or on an automated ABI model 431A synthesizer (from Applied Biosystems). UV/VIS Spectrometer model LAMBDA 12 was from Perkin Elmer (Norwalk, Connecticut) and 96-well UV plates were obtained from Corning (Corning, New York). The prewarming block was from USA Scientific (Ocala, Florida) and the 96-well plate vortexer was from Labline Instruments (Melrose Park, Illinois). A Spectramax Plus microtiter plate reader with monochrometer was obtained from Molecular Devices (Sunnyvale, California).

Enzyme Preparation: Recombinant heterodimeric HCV NS3/NS4A protease (strain 1a) was prepared by using the procedures published previously (D. L. Sali *et al*, *Biochemistry*, 37 (1998) 3392-3401). Protein concentrations were determined by the Biorad dye method using recombinant HCV protease standards previously quantified by amino acid analysis. Prior to assay initiation, the enzyme storage buffer (50 mM sodium phosphate pH 8.0, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside and 10 mM DTT) was exchanged for the assay buffer (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 µM EDTA and 5 µM DTT) utilizing a Biorad Bio-Spin P-6 prepacked column.

Substrate Synthesis and Purification: The synthesis of the substrates was done as reported by R. Zhang *et al*, (*ibid.*) and was initiated by anchoring Fmoc-Nva-OH to 2-chlorotrityl chloride resin using a standard protocol (K. Barlos *et al*, *Int. J. Pept. Protein Res.*, 37 (1991), 513-520). The peptides were subsequently assembled, using Fmoc chemistry, either manually or on an automatic ABI model 431 peptide synthesizer. The N-acetylated and fully protected peptide fragments were cleaved from the resin either by 10% acetic acid (HOAc) and 10% trifluoroethanol (TFE) in dichloromethane (DCM) for 30 min, or by 2% trifluoroacetic acid (TFA) in DCM for 10 min. The combined filtrate and DCM wash was evaporated azeotropically (or repeatedly extracted by aqueous Na_2CO_3 solution) to remove the acid used in cleavage. The DCM phase was dried over Na_2SO_4 and evaporated.

The ester substrates were assembled using standard acid-alcohol coupling procedures (K. Holmber *et al*, *Acta Chem. Scand.*, B33 (1979) 410-

412). Peptide fragments were dissolved in anhydrous pyridine (30-60 mg/ml) to which 10 molar equivalents of chromophore and a catalytic amount (0.1 eq.) of para-toluenesulfonic acid (pTSA) were added. Dicyclohexylcarbodiimide (DCC, 3 eq.) was added to initiate the coupling reactions. Product formation was monitored by HPLC and found to be complete following 12-72 hour reaction at room temperature. Pyridine solvent was evaporated under vacuum and further removed by azeotropic evaporation with toluene. The peptide ester was deprotected with 95% TFA in DCM for two hours and extracted three times with anhydrous ethyl ether to remove excess chromophore. The deprotected substrate was purified by reversed phase HPLC on a C3 or C8 column with a 30% to 60% acetonitrile gradient (using six column volumes). The overall yield following HPLC purification was approximately 20-30%. The molecular mass was confirmed by electrospray ionization mass spectroscopy. The substrates were stored in dry powder form under desiccation.

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

Protease Assay: HCV protease assays were performed at 30°C using a 200 µl reaction mix in a 96-well microtiter plate. Assay buffer conditions (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 µM EDTA and 5 µM DTT) were optimized for the NS3/NS4A heterodimer (D. L. Sali *et al*, *ibid.*)). Typically, 150 µl mixtures of buffer, substrate and inhibitor were placed in wells (final concentration of DMSO ≤4 % v/v) and allowed to preincubate at 30 °C for approximately 3 minutes. Fifty µls of prewarmed protease (12 nM, 30°C) in assay buffer, was then used to initiate the reaction (final volume 200 µl).The plates were monitored over the length of the assay

(60 minutes) for change in absorbance at the appropriate wavelength (340 nm for 3-Np and HMC, 370 nm for PAP, and 400 nm for 4-Np) using a Spectromax Plus microtiter plate reader equipped with a monochrometer (acceptable results can be obtained with plate readers that utilize cutoff filters). Proteolytic cleavage of the ester linkage between the Nva and the chromophore was monitored at the appropriate wavelength against a no enzyme blank as a control for non-enzymatic hydrolysis. The evaluation of substrate kinetic parameters was performed over a 30-fold substrate concentration range (~6-200 μM). Initial velocities were determined using linear regression and kinetic constants were obtained by fitting the data to the Michaelis-Menten equation using non-linear regression analysis (Mac Curve Fit 1.1, K. Raner). Turnover numbers (k_{cat}) were calculated assuming the enzyme was fully active.

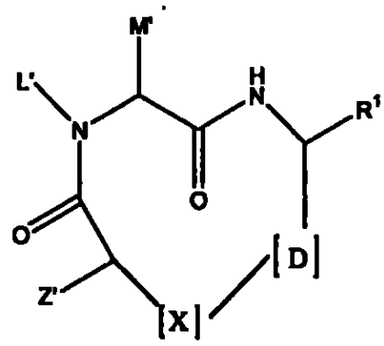
Evaluation of Inhibitors and Inactivators: The inhibition constants (Ki*) for the competitive inhibitors Ac-D-(D-Gla)-L-I-(Cha)-C-OH (27), Ac-DTEDVVA(Nva)-OH and Ac-DTEDVVP(Nva)-OH were determined experimentally at fixed concentrations of enzyme and substrate by plotting v_o/v_i vs. inhibitor concentration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

The obtained K_i values for the various macrocycles of the present invention are given in Tables 1, 2 and 2A, where the compounds have been arranged in the order of ranges of Ki* values, as well as in Table 3. From these test results, it would be apparent to the skilled artisan that the compounds of the invention have excellent utility as NS3-serine protease inhibitors.

CLAIMS

What is claimed is:

1. A compound having the general structure shown in Formula 1:



Formula 1

or pharmaceutically acceptable salts, solvates or esters of said compound wherein:

(1) R^1 is $-C(O)R^5$ or $-B(OR)_2$;

(2) R^5 is H, -OH, $-OR^8$, $-NR^9R^{10}$, $-C(O)OR^8$, $-C(O)NR^9R^{10}$, $-CF_3$; $-C_2F_5$, $-C_3F_7$, $-CF_2R^8$, $-R^8$, $-C(O)R^7$ or $NR^7SO_2R^8$;

(3) R^7 is H, -OH, $-OR^8$,or $-CHR^9R^{10}$;

(4) R^8, 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, aryl, heteroalkyl, heteroaryl, cycloalkyl, arylalkyl, heteroarylalkyl, R^{14},
$-CH(R^{1'})CH(R^{1'})C(O)OR^{11}$,
$-[CH(R^{1'})]_pC(O)OR^{11}$,
$-[CH(R^{1'})]_pC(O)NR^{12}R^{13}$,
$-[CH(R^{1'})]_pS(O_2)R^{11}$,
$-[CH(R^{1'})]_pC(O)R^{11}$,
$-[CH(R^{1'})]_pS(O_2)NR^{12}R^{13}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$,

$-CH(R^{1'})CH(R^{1'})C(O)NR^{12}R^{13}$,
$-CH(R^{1'})CH(R^{1'})S(O_2)R^{11}$,
$-CH(R^{1'})CH(R^{1'})S(O_2)NR^{12}R^{13}$,
$-CH(R^{1'})CH(R^{1'})C(O)R^{11}$,
$-[CH(R^{1'})]_pCH(OH)R^{11}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$,
$-C(O)N(H)CH(R^{2'})C(O)OR^{11}$,
$-C(O)N(H)CH(R^{2'})C(O)R^{11}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)NR^{12}R^{13}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})R'$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)OR^{11}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)CH(R^{3'})NR^{12}R^{13}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)NR^{12}R^{13}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)OR^{11}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)NR^{12}R^{13}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)N(H)CH(R^{5'})C(O)OR^{11}$,
and
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)N(H)CH(R^{5'})C(O)NR^{12}R^{13}$;

wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, R^{12} and R^{13} can be the same or different, each being independently selected from the group consisting of: H, halogen, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkoxy, aryloxy, alkenyl, alkynyl, alkyl-aryl, alkyl-heteroaryl, heterocycloalkyl, aryl-alkyl and heteroaralkyl;

or R^{12} and R^{13} are linked together such that the combination is cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

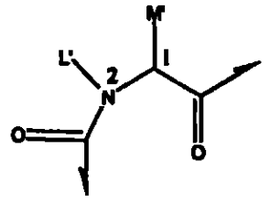
R^{14} is present or not and if present is selected from the group consisting of: H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, allyl, alkyl-heteroaryl, alkoxy, aryl-alkyl, alkenyl, alkynyl and heteroaralkyl;

(5) R and R' are present or not and if present can be the same or different, each being independently selected from the group consisting of: H, OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, alkylamino, arylamino, amino, amido, arylthioamino, arylcarbonylamino, arylaminocarboxy, alkylaminocarboxy, heteroalkyl, alkenyl, alkynyl, (aryl)alkyl, heteroarylalkyl, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen, (cycloalkyl)alkyl, aryl, heteroaryl, (alkyl)aryl, alkylheteroaryl, alkyl-heterocyclyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms;

(6) L' is H, OH, alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl;

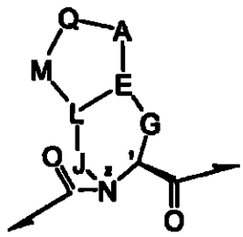
(7) M' is H, alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, arylalkyl, heterocyclyl or an amino acid side chain;

or L' and M' are linked together to form a ring structure such that the portion of structural Formula 1 represented by



(the numbers 1 and 2 having been added to show the location of a certain carbon atom and a certain nitrogen atom respectively)

is represented by structural Formula 2:



Formula 2

wherein in Formula 2:

E is present or absent and if present is C, CH, N or C(R);

J is present or absent, and when J is present, J is $(CH_2)_p$, (CHR-CHR')$_p$, $(CHR)_p$, $(CRR')_p$, $S(O_2)$, N(H), N(R) or O; when J is absent and G is present, L is directly linked to the nitrogen atom marked position 2;

p is a number from 0 to 6;

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

G is present or absent, and when G is present, G is $(CH_2)_p$, $(CHR)_p$, (CHR-CHR')$_p$ or $(CRR')_p$; when G is absent, J is present and E is directly connected to the carbon atom marked position 1;

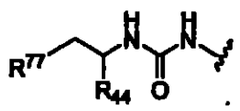
Q is present or absent, and when Q is present, Q is NR, PR, (CR=CR), $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, (CHR-CHR')$_p$, O, NR, S, SO, or SO_2; when Q is absent, M is (i) either directly linked to A or (ii) an independent substituent on L, said independent substituent being selected from -OR, -CH(R)(R'), $S(O)_{0-2}R$ or –NRR' or (iii) absent; when both Q and M are absent, A is either directly linked to L, or A is an independent substituent on E, said independent substituent being selected from -OR, -CH(R)(R'), $S(O)_{0-2}R$ or –NRR' or A is absent;

A is present or absent and if present A is O, O(R), $(CH_2)_p$, $(CHR)_p$, (CHR-CHR')$_p$, $(CRR')_p$, N(R), NRR', S, $S(O_2)$, -OR, CH(R)(R') or NRR'; or A is linked to M to form an cycloalkyl, aliphatic or heterocyclic bridge;

M is present or absent, and when M is present, M is halogen, O, OR, N(R), S, $S(O_2)$, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$, or $(CRR')_p$; or M is linked to A to form a cycloalkyl, aliphatic or heterocycloalkyl bridge;

(8) Z' is represented by either (i), (ii), (iii), (iv) or (v) shown below:

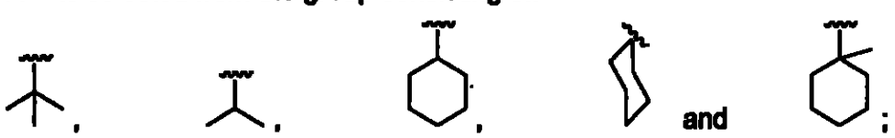
(i)



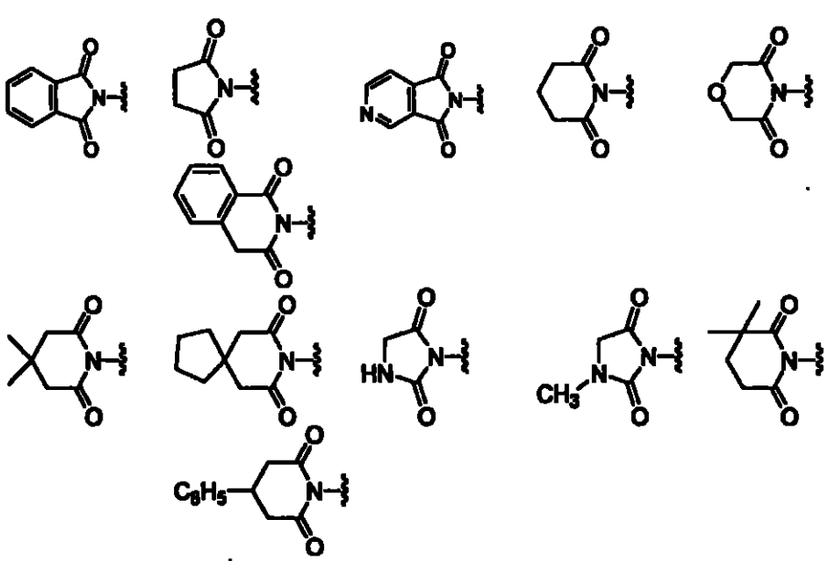
Formula A

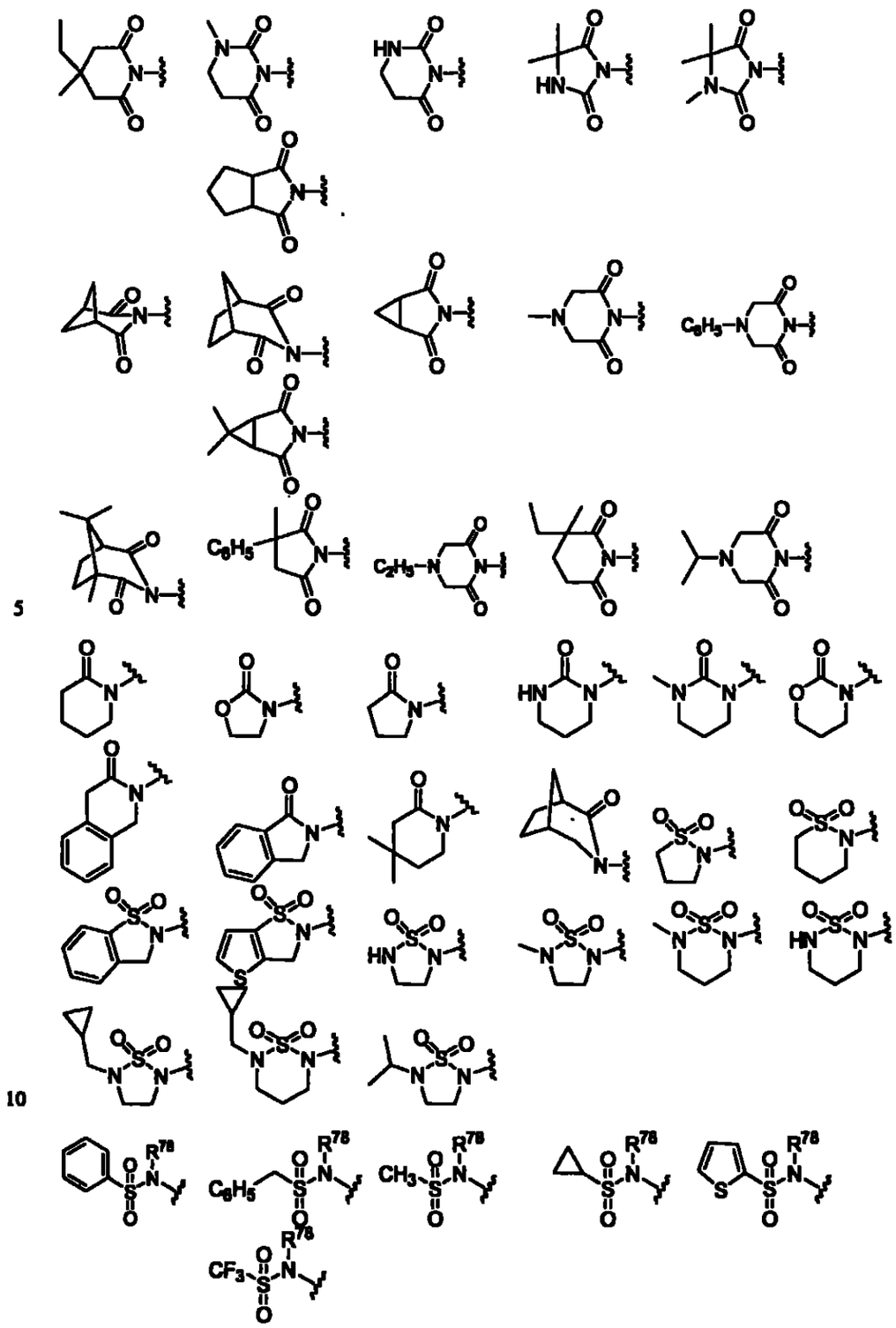
wherein:

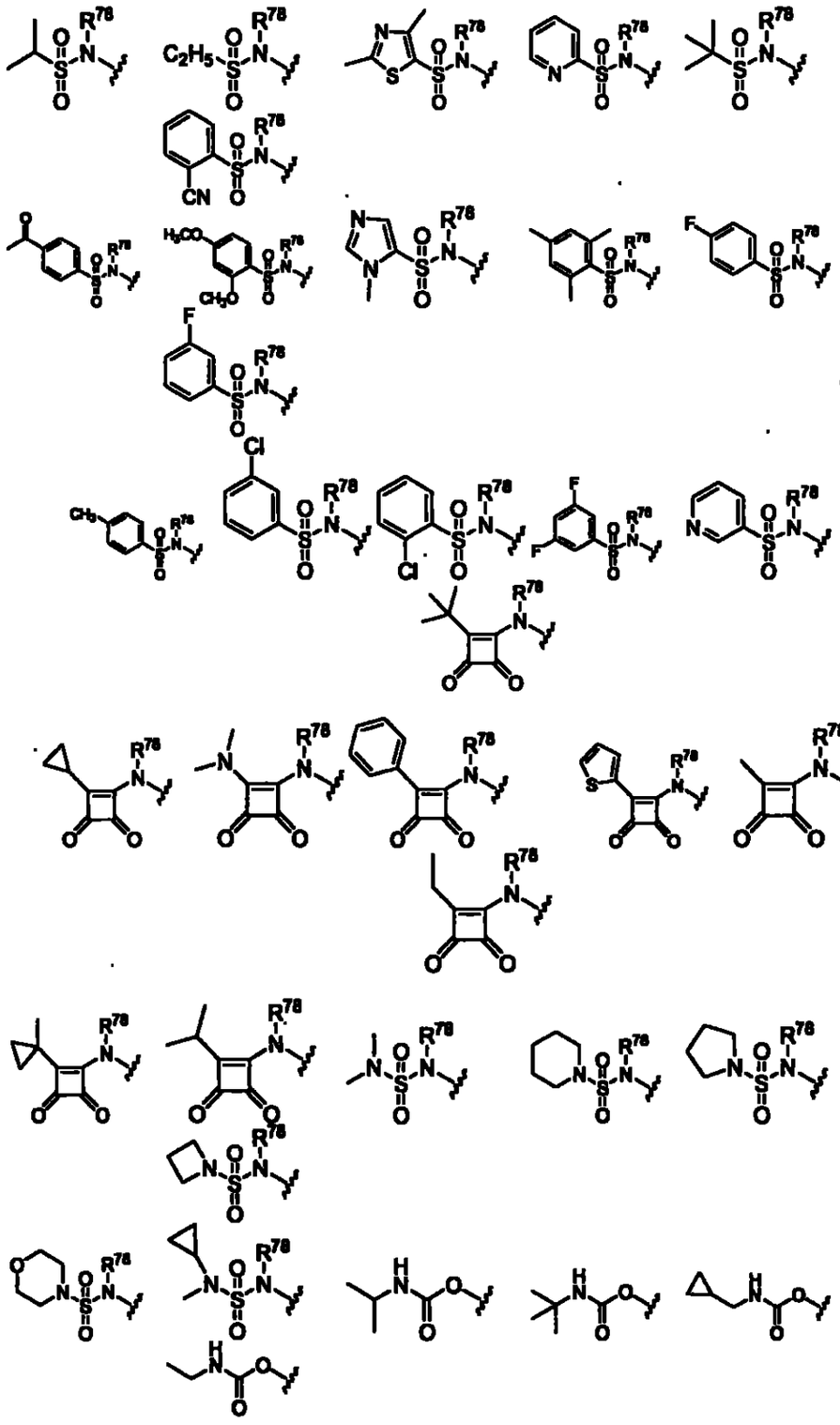
R^{44} is selected from the group consisting of:

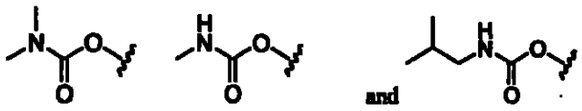


and R^{77} is selected from the group consisting of:



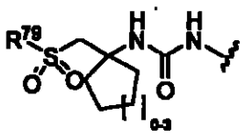






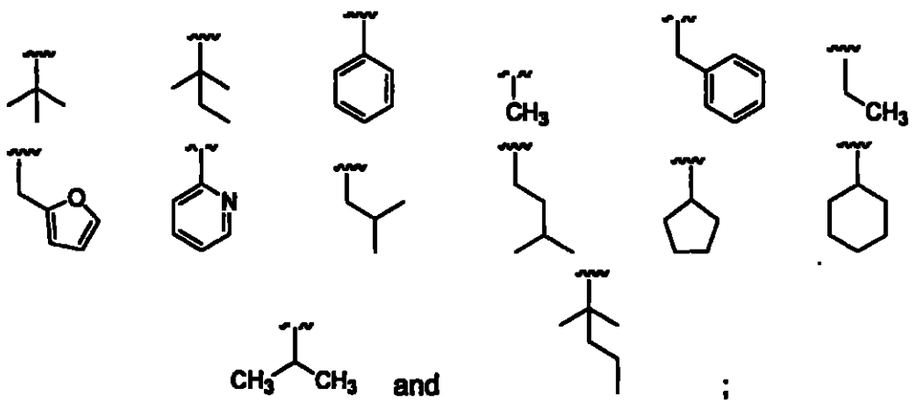
where R^{79} is selected from methyl, ethyl, isopropyl, tert-butyl and phenyl;

(ii)

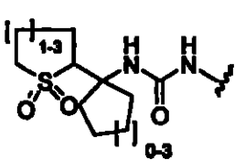


Formula B

where R^{79} is selected from the group consisting of:



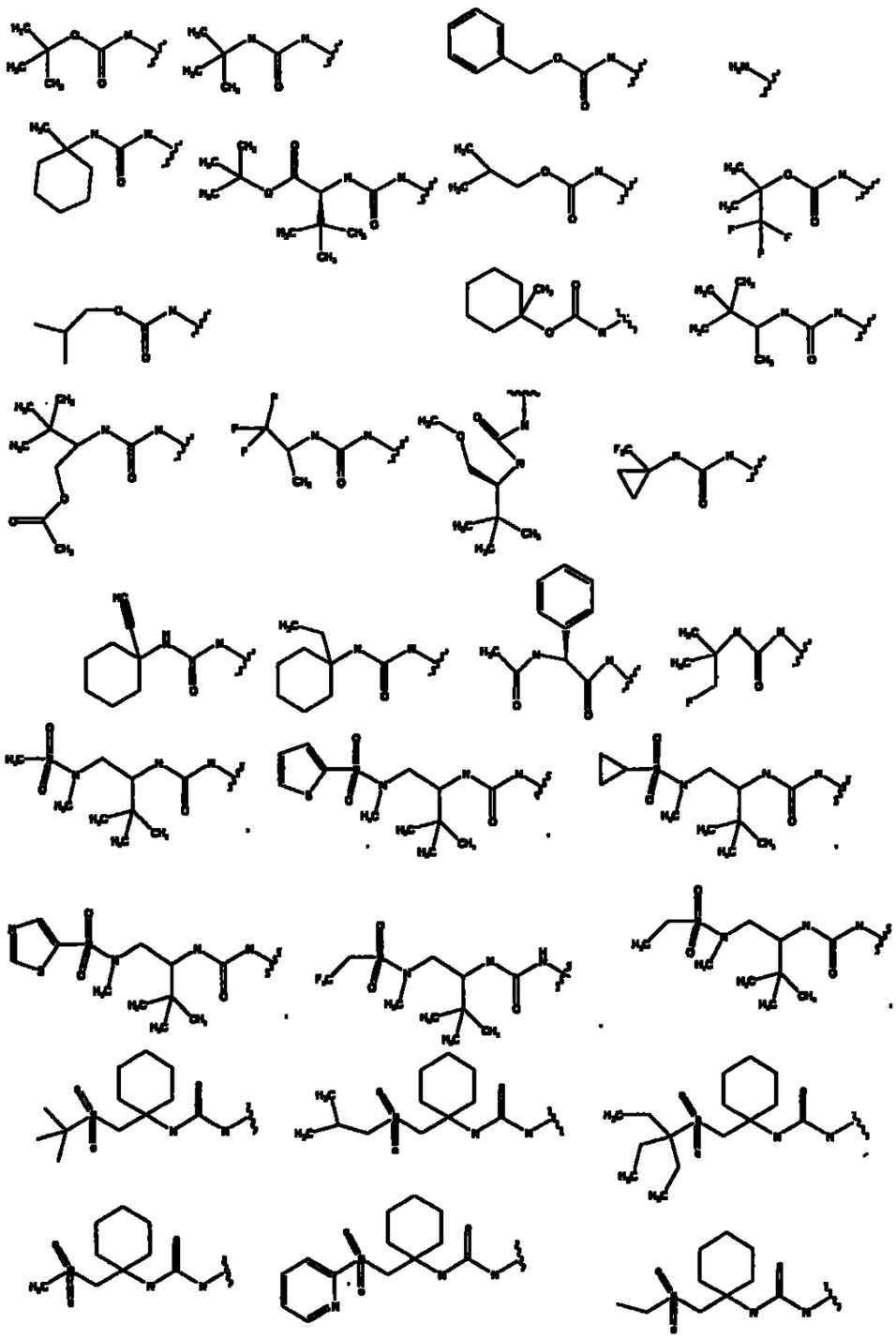
(iii)



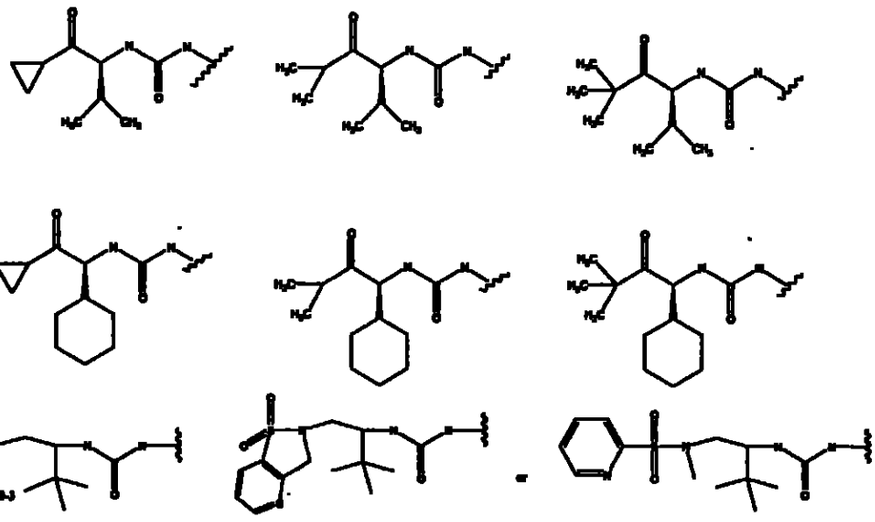
Formula C

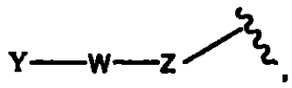
wherein the sulfone ring is optionally substituted with alkyl and cycloalkyl;

(iv) the moiety:



5

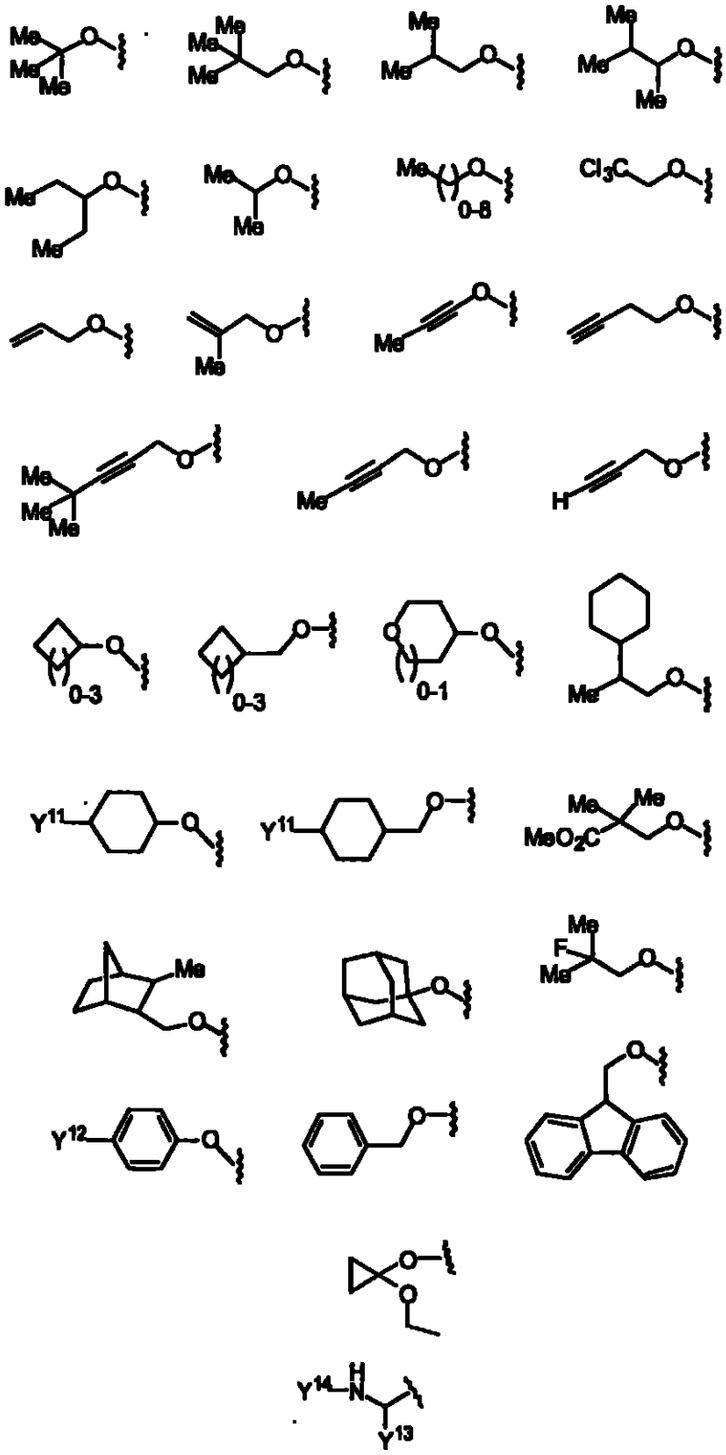


(v) the moiety:  ,

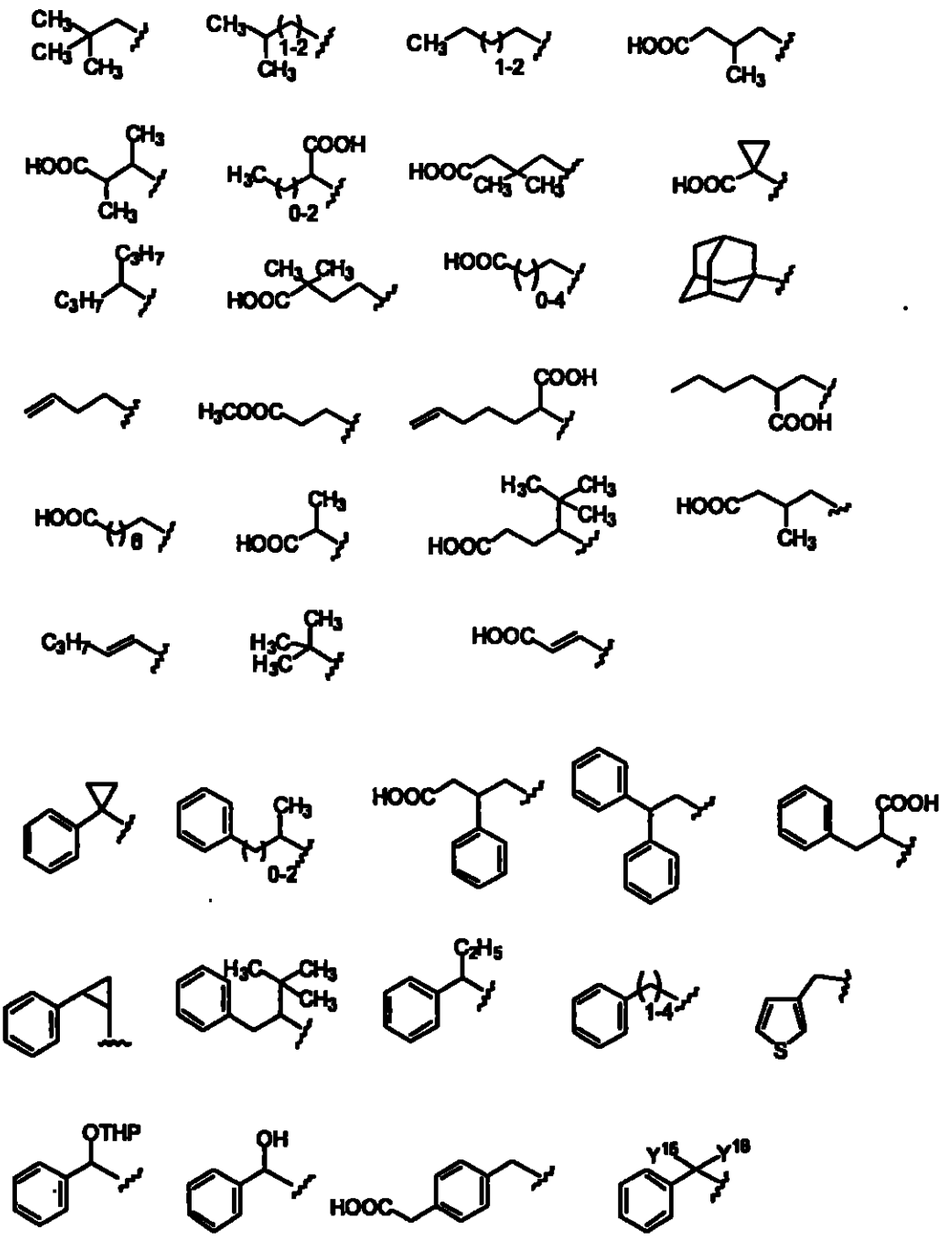
wherein W is –C(=O)- or -S(O_2)- ;

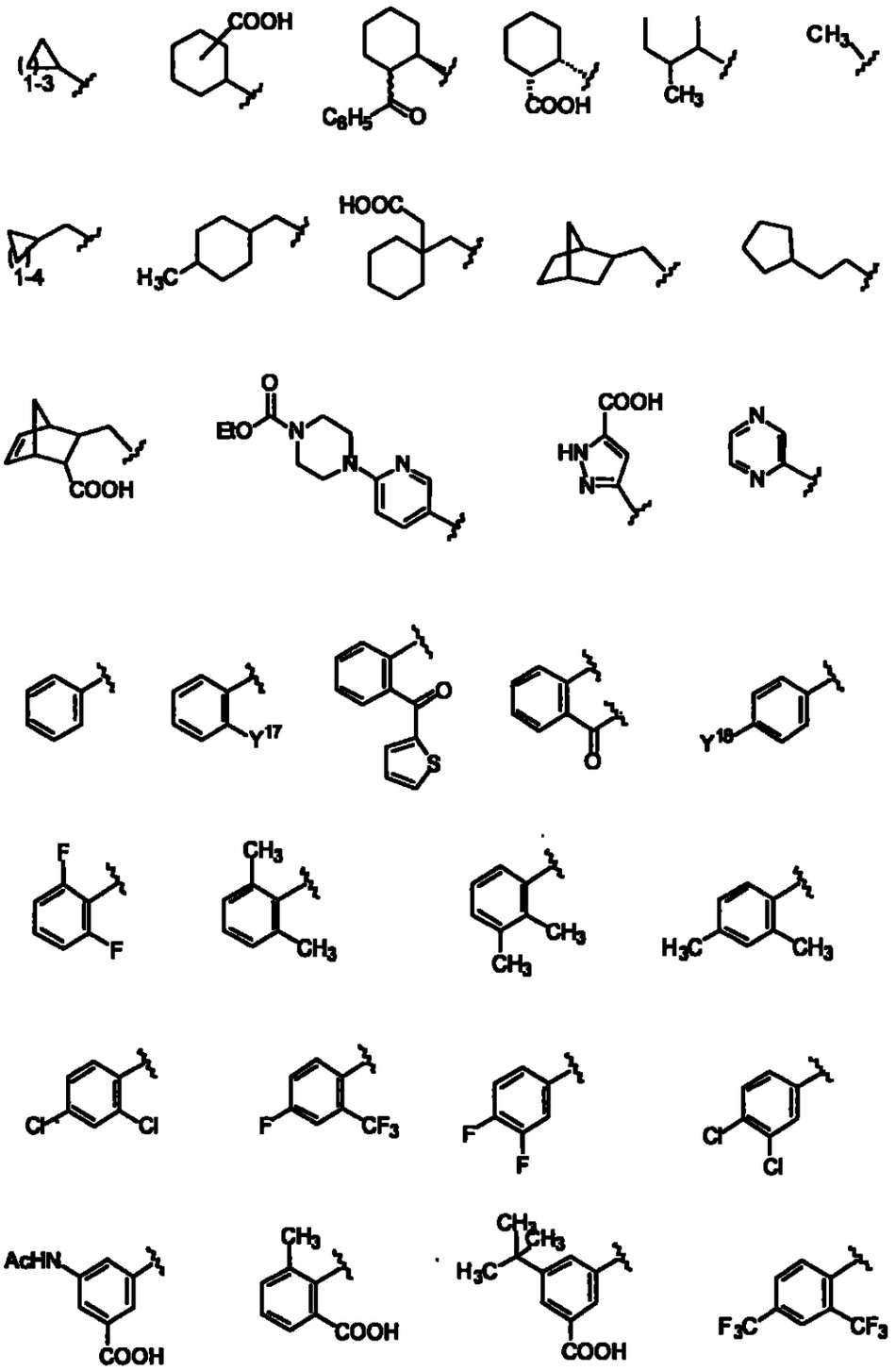
Z is O or N;

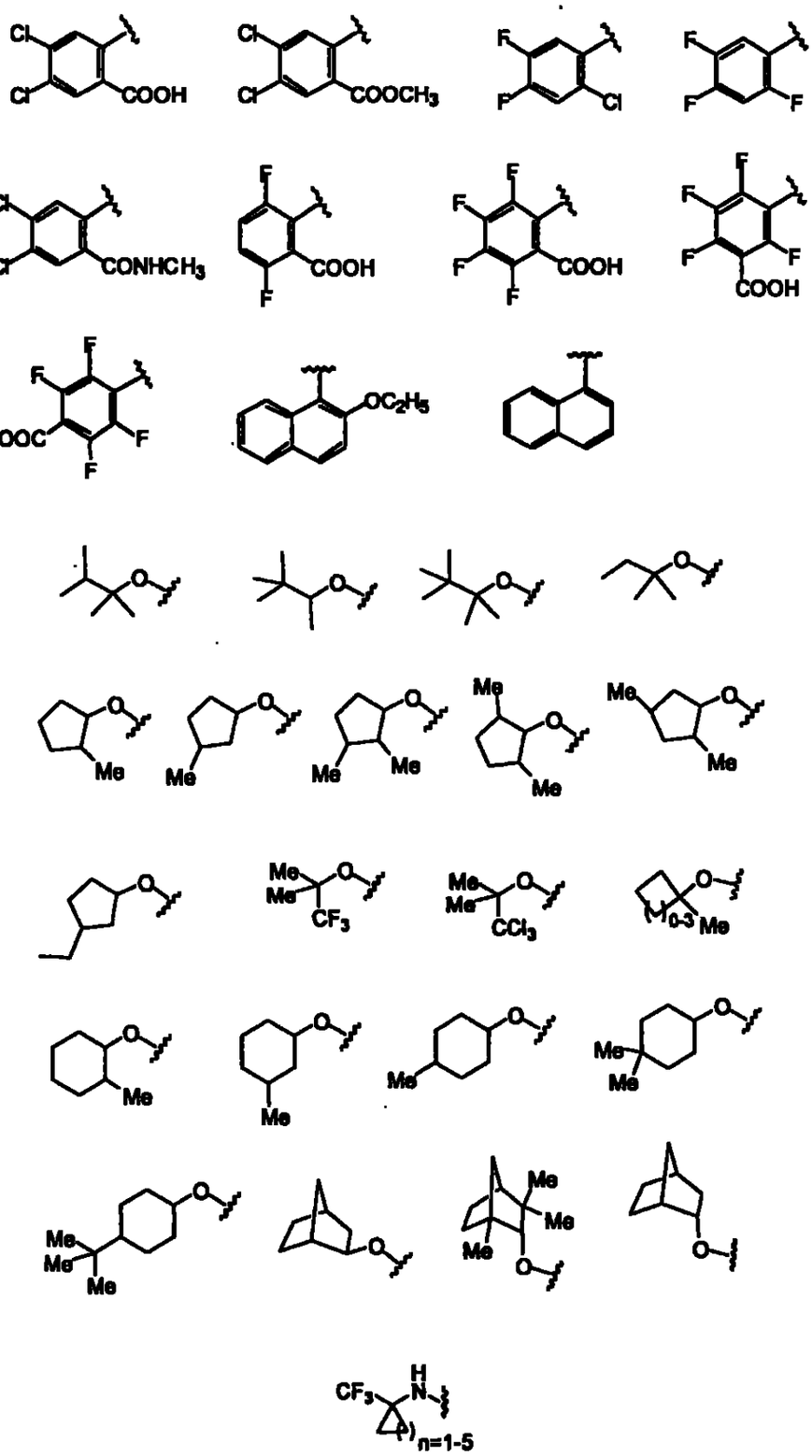
and Y is selected from the group consisting of:


Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
0-8
Cl3C
Me
Me
Me
Me
Me
Me
Me
H
0-3
0-3
0-1
Me
Y11
Y11
Me
MeO2C
Me
Me
F
Me
Y12
O
Y14
H
N
Y13

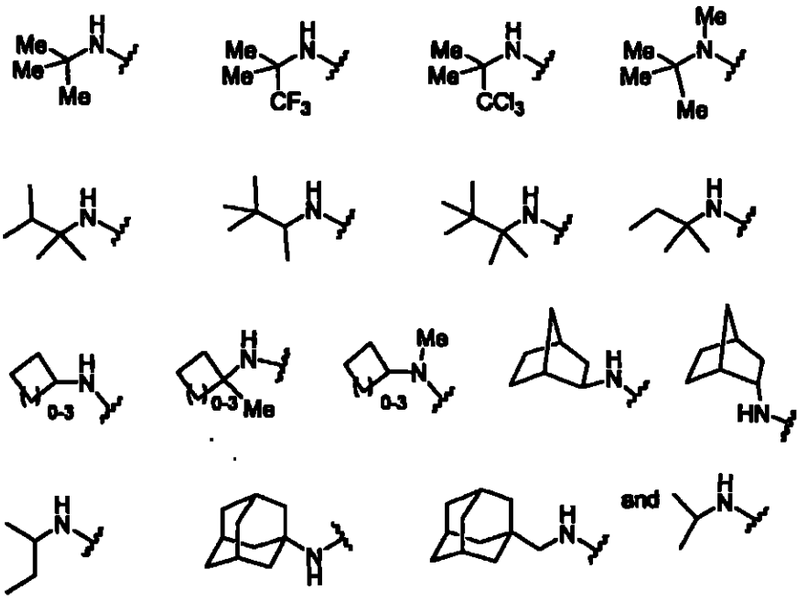
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CH3
CH3
CH3
1-2
CH3
CH3
1-2
HOOC
CH3
HOOC
CH3
CH3
COOH
H3C
0-2
HOOC
CH3
CH3
HOOC
C3H7
C3H7
CH3
CH3
HOOC
HOOC
0-4
H3COOC
COOH
COOH
HOOC
6
CH3
HOOC
H3C
CH3
CH3
HOOC
HOOC
CH3
C3H7
H3C
H3C
HOOC
0-2
HOOC
COOH
H3C
CH3
CH3
C2H5
1-4
S
OTHP
OH
HOOC
Y15
Y16


1-3
COOH
C_6H_5
O
COOH
CH_3
CH_3
1-4
H_3C
HOOC
EtO
N
N
N
COOH
HN
N
N
N
COOH
O
S
Y^{17}
Y^{18}
F
F
CH_3
CH_3
CH_3
CH_3
H_3C
CH_3
Cl
Cl
F
CF_3
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H_3C
COOH
F_3C
CF_3



5

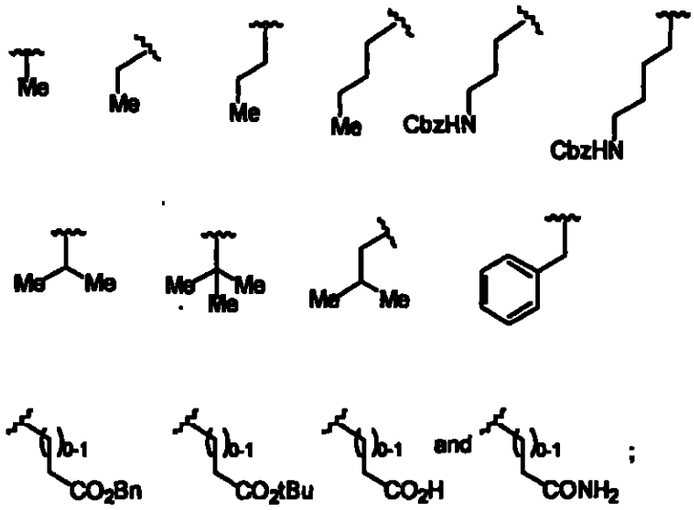


wherein:

Y^{11} is selected from the group consisting of: H, -C(O)OH, -C(O)OEt, -OMe, -Ph, -OPh, -NHMe, -NHAc, -NHPh, $-CH(Me)_2$, 1-triazolyl, 1-imidazolyl and $-NHCH_2COOH$;

Y^{12} is selected from the group consisting of: H, -C(O)OH, -C(O)OMe, -OMe, F, Cl and Br;

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



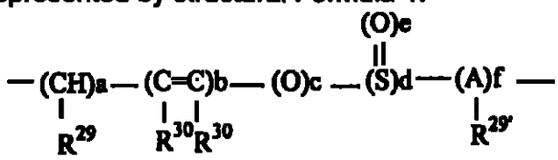
Y^{14} is $MeS(O_2)$-, -Ac, -Boc, -iBoc, -Cbz, or -Alloc;

Y^{15} and Y^{16} can be the same or different and are independently selected from the group consisting of: alkyl, aryl, heteroalkyl, and heteroaryl;

Y^{17} is $-CF_3$, $-NO_2$, $-C(O)NH_2$, -OH, $-C(O)OCH_3$, $-OCH_3$, $-OC_6H_5$, $-C_6H_5$, $-C(O)C_6H_5$, $-NH_2$, or –C(O)OH; and

Y^{18} is $-C(O)OCH_3$, $-NO_2$, $-N(CH_3)_2$, F, $-OCH_3$, $-C(H_2)C(O)OH$, $-C(O)OH$, $-S(O_2)NH_2$, or $-N(H)C(O)CH_3$;

(9) X is represented by structural Formula 4:



Formula 4

wherein in Formula 4, a is 2, 3, 4, 5, 6, 7, 8 or 9;

b, c, d, e and f can be the same or different, each being independently 0, 1, 2, 3, 4 or 5;

A is C, N, S or O;

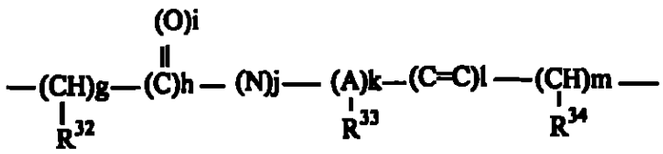
R^{29} and $R^{29'}$ are independently present or absent and if present can be the same or different, each being independently one or two substituents independently selected from the group consisting of: H, halo, alkyl, aryl, cycloalkyl, cycloalkylamino, cycloalkylaminocarbonyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), $-N(alkyl)_2$, carboxyl, –C(O)O-alkyl, heteroaryl, aralkyl, alkylaryl, aralkenyl, heteroaralkyl, alkylheteroaryl, heteroaralkenyl, hydroxyalkyl, aryloxy, aralkoxy, acyl, aroyl, nitro, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkenyl, heterocyclyl, heterocyclenyl, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$- and $Y_1Y_2NSO_2$-, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl;

or

R^{29} and $R^{29'}$ are linked together such that the combination is an aliphatic or heteroaliphatic chain of 0 to 6 carbons;

R^{30} is present or absent and if present is one or two substituents independently selected from the group consisting of: H, alkyl, aryl, heteroaryl and cycloalkyl;

(10) D in Formula 1 is represented by structural Formula 5:



Formula 5

wherein in Formula 5, R^{32}, R^{33} and R^{34} are present or absent and if present are independently one or two substituents independently selected from the group consisting of: H, halo, alkyl, aryl, cycloalkyl, cycloalkylamino, spiroalkyl, cycloalkylaminocarbonyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -$N(alkyl)_2$, carboxyl, –C(O)O-alkyl, heteroaryl, aralkyl, alkylaryl, aralkenyl, heteroaralkyl, alkylheteroaryl, heteroaralkenyl, hydroxyalkyl, aryloxy, aralkoxy, acyl, aroyl, nitro, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkenyl, heterocyclyl, heterocyclenyl, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$- and $Y_1Y_2NSO_2$-, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl;

or

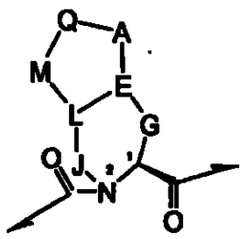
R^{32} and R^{34} are linked together such that the combination forms a portion of a cycloalkyl group;

g is 1, 2, 3, 4, 5, 6, 7, 8 or 9;

h, i, j, k, l and m can be the same or different, each being independently 0, 1, 2, 3, 4 or 5; and

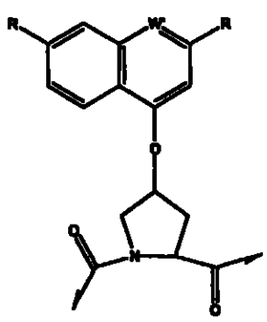
A is C, N, S or O,

(11) provided that in Formula 1 when structural Formula 2:



Formula 2

is



and

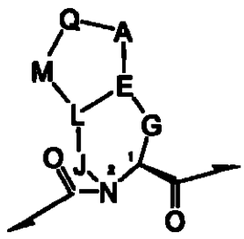
W' is CH or N, both the following conditional exclusions (i) and (ii) apply:

conditional exclusion (i): Z' is not –NH–R^{38}, wherein R^{38} is H, C_6 aryl, C_{10} aryl, heteroaryl, –C(O)–R^{37}, –C(O)–OR^{37} or –C(O)–NHR^{37}, wherein R^{37} is C_{1-6} alkyl or C_{3-6} cycloalkyl;

and

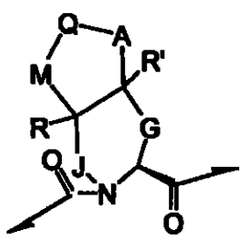
conditional exclusion (ii): R^1 is not –C(O)OH, a pharmaceutically acceptable salt of –C(O)OH, an ester of –C(O)OH or –C(O)NHR^{38} wherein R^{38} is selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, C_6 aryl, C_{10} aryl, or C_{7-16} aralkyl.

2. The compound according to Claim 1, wherein the portion of structural Formula 1 represented by structural Formula 2:



is

Formula 2



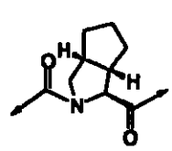
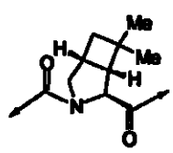
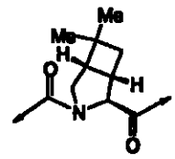
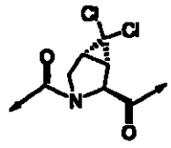
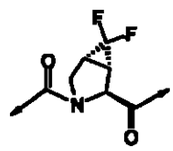
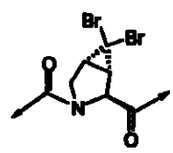
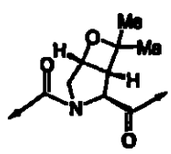
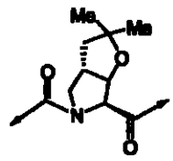
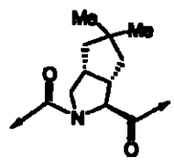
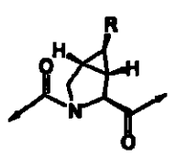
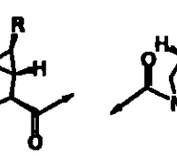
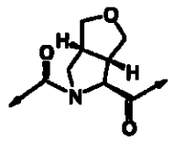
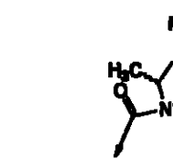
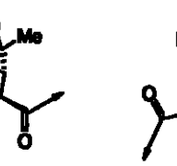
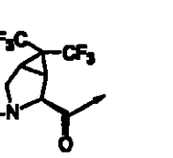
;

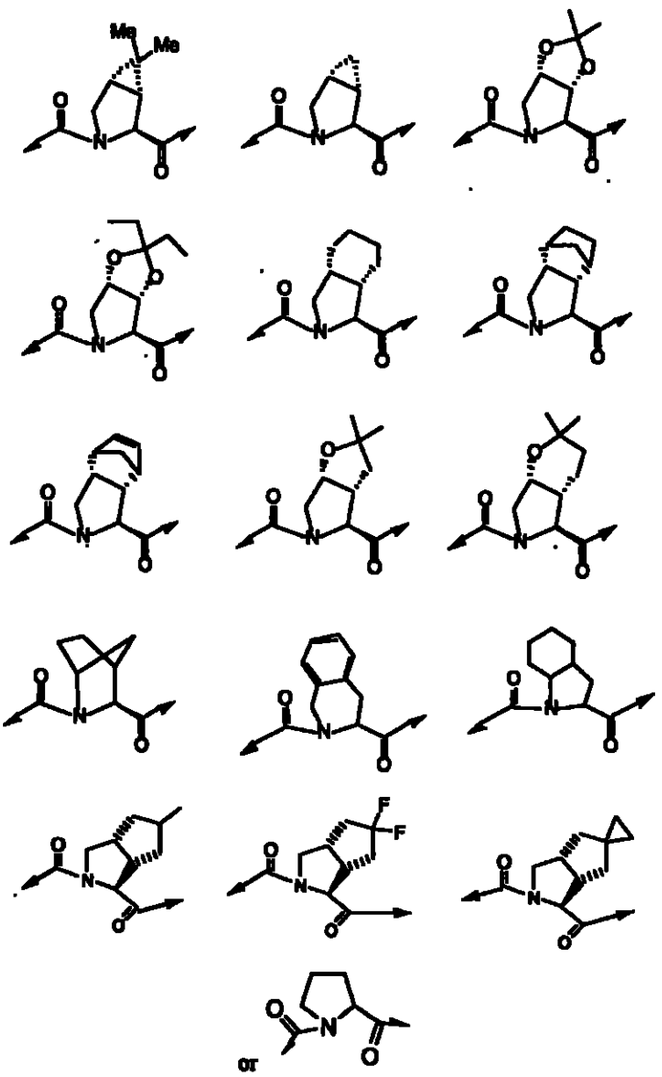
G and J independently may or may not be present and if present can be the same or different and are independently selected from the group consisting of $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$;

A and M independently may or may not be present and if present can be the same or different and are independently selected from the group consisting of O, S, $S(O_2)$, N(R), $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$; or A and M are linked together to form an cycloalkyl or heterocyclyl bridge; and

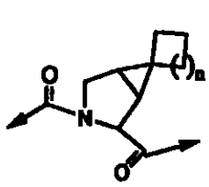
Q may or may not be present and if present is $(CH_2)_p$, N(R), O, S, $S(O_2)$, $(CHR)_p$, or $(CRR')_p$.

3. The compound according to Claim 2, wherein the portion represented by structural Formula 2 is selected from the following structures:

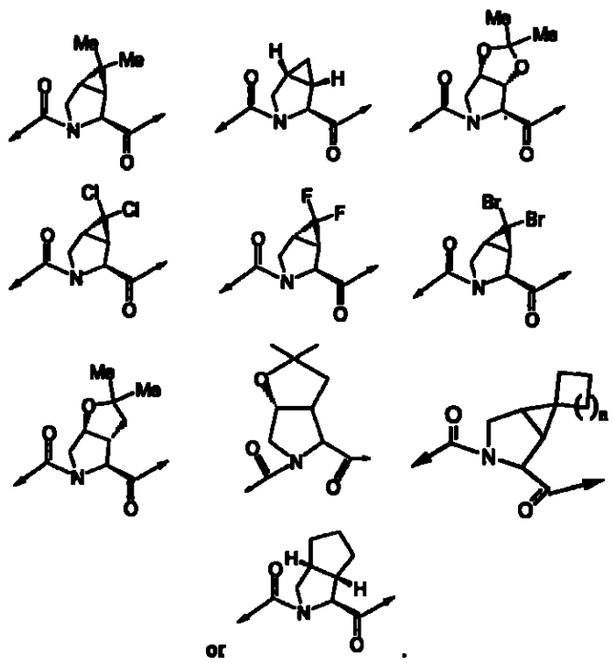


and



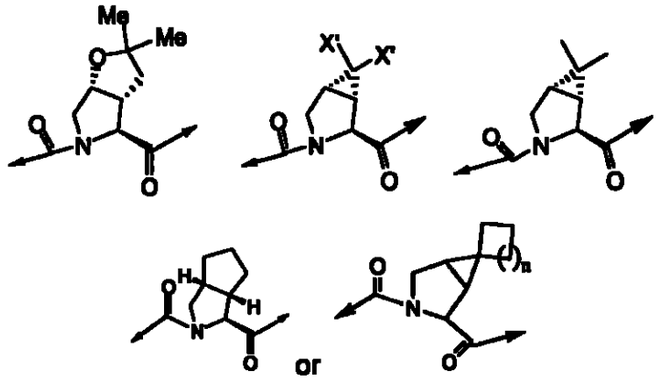
wherein n= 0-4.

4. The compound according to Claim 3, wherein the portion of structural Formula 1 represented by structural Formula 2 is selected from the following structures:



or

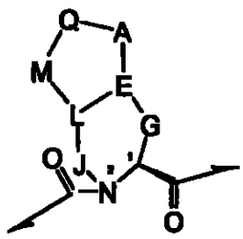
5. The compound according to Claim 4, wherein the portion of structural Formula 1 represented by structural Formula 2 is selected from the following structures:



or

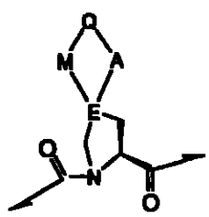
wherein X' is H, F, Cl or Br.

6. The compound according to Claim 1, wherein the portion of structural Formula 1 represented by structural Formula 2:



is

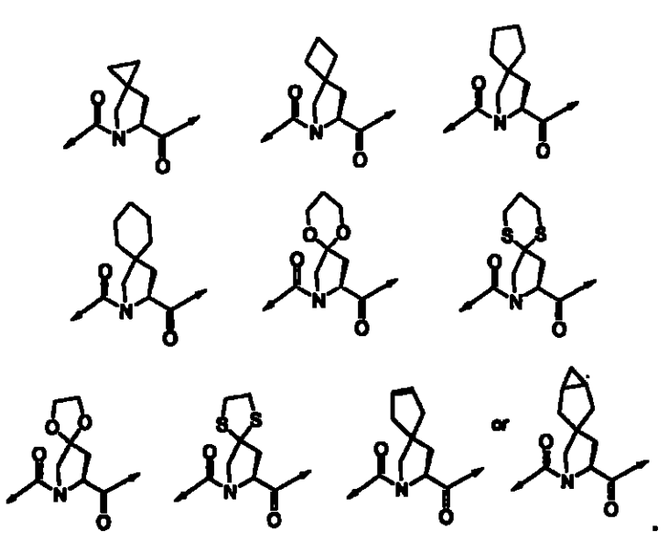
Formula 2



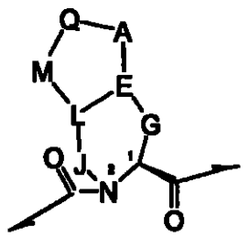
; and

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

7. The compound according to Claim 6, wherein the portion of structural Formula 1 represented by structural Formula 2 is selected from the following structures:

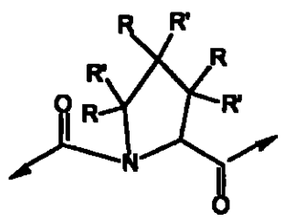


8. The compound according to Claim 1, wherein the portion of structural Formula 1 represented by structural Formula 2:

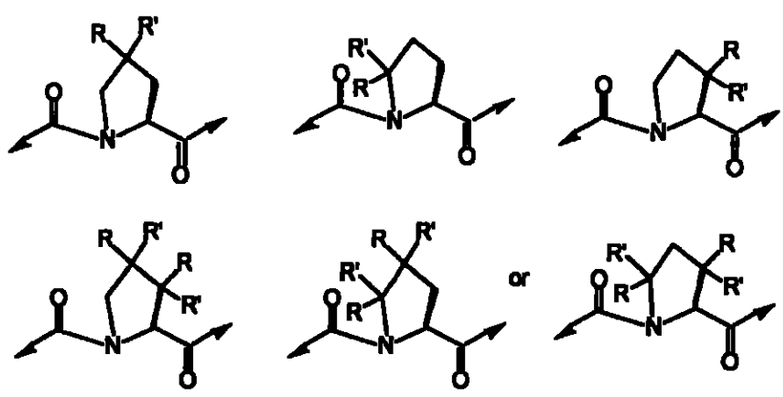


is

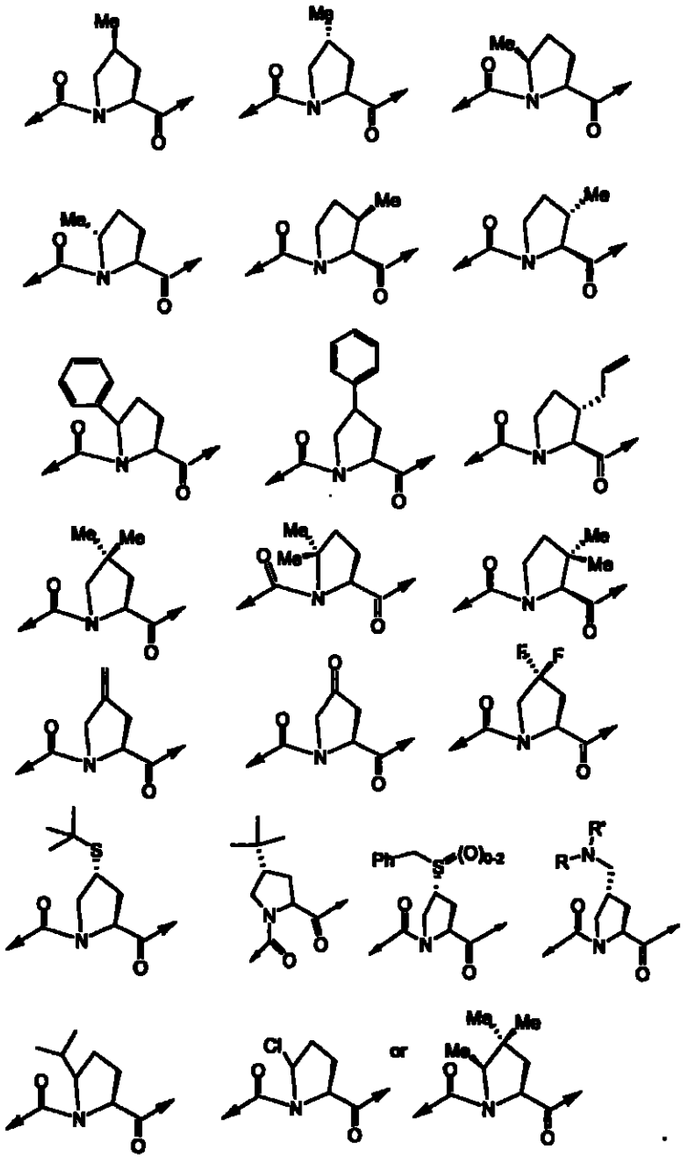
Formula 2



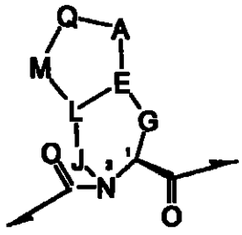
9. The compound according to Claim 8, wherein the portion of structural Formula 1 represented by structural Formula 2 is selected from the following structures:



10. The compound according to Claim 9, wherein the portion of structural Formula 1 represented by structural Formula 2 is selected from the following structures:

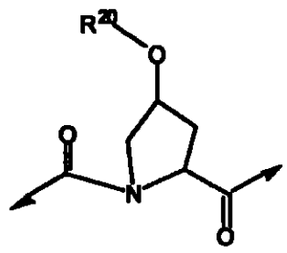


11. The compound according to Claim 1, wherein the portion of structural Formula 1 represented by structural Formula 2:



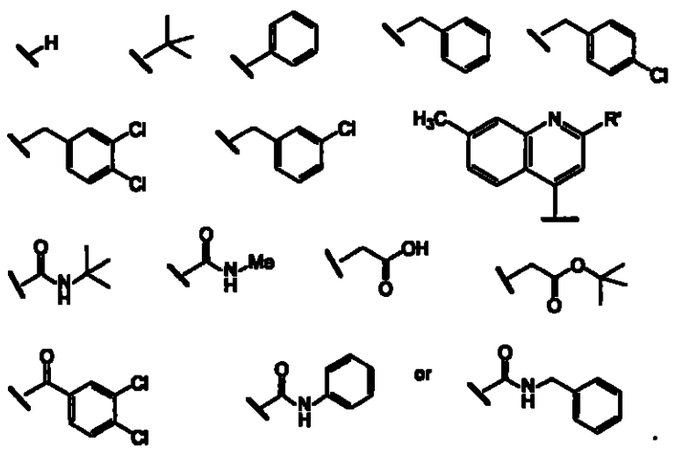
is

Formula 2

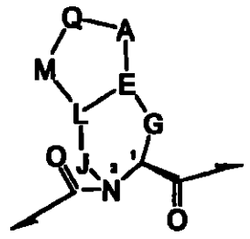


; and

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

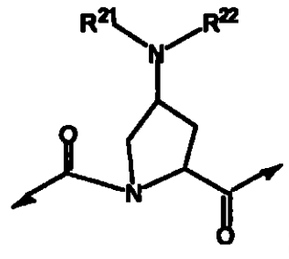


12. The compound according to Claim 1, wherein the portion of structural Formula 1 represented by structural Formula 2:



is

Formula 2

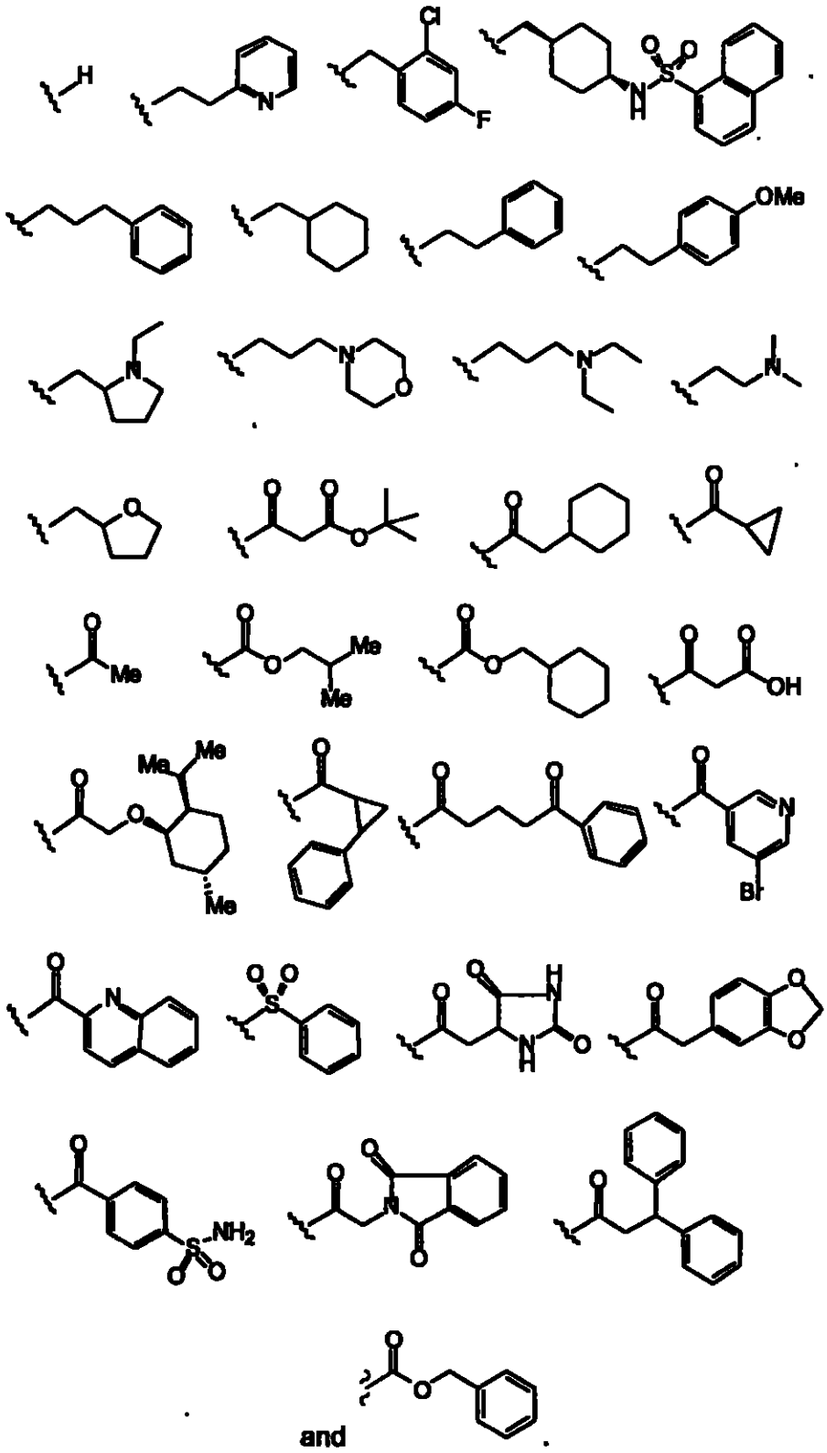


; and

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321

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



and

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13. The compound according to Claim 1, wherein L and M are absent, and J is directly linked to E.

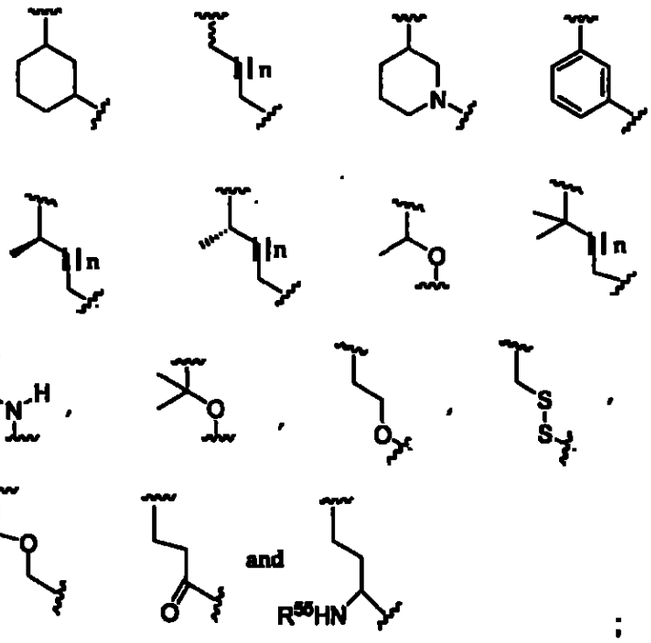
14. The compound according to Claim 1, wherein L, J and M are absent and E is directly linked to N.

15. The compound according to Claim 1, wherein G and M are absent.

16. The compound according to Claim 1, wherein M' is

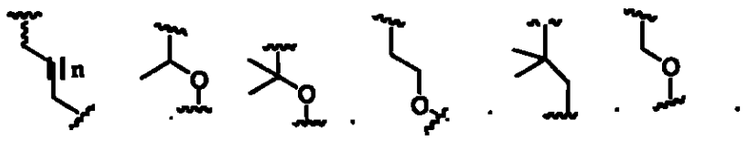


17. The compound according to Claim 1, wherein X is selected from the group consisting of the following structures:



and R^{55} is alkyl, cycloalkyl, carbamate or urea; and n= 0-5.

18. The compound according to Claim 17, wherein X is selected from the group consisting of the following structures:



19. The compound according to Claim 1, wherein R^1 is a ketoamide, ketoaldehyde, diketone, ketoacid or ketoester.

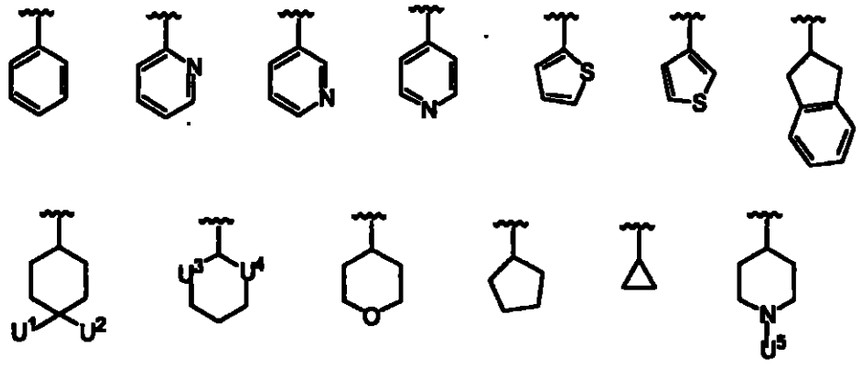
20. The compound according to Claim 19, wherein R^1 is $-C(O)C(O)NR^9R^{10}$;
R^9 is H; and
R^{10} is H, $-R^{14}$, $-[CH(R^{1'})]_pC(O)OR^{11}$,
$-[CH(R^{1'})]_pC(O)NR^{12}R^{13}$,
$-[CH(R^{1'})]_pS(O_2)R^{11}$,
$-[CH(R^{1'})]_pS(O_2)NR^{12}R^{13}$,
$-[CH(R^{1'})]_pC(O)R^{11}$,
$-CH(R^{1'})C(O)N(H)C(H)(R^{2'})C(O)OR^{11}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)NR^{12}R^{13}$, or
$-CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$.

21. The compound according to Claim 20, wherein:
R^{10} is H, $-R^{14}$, $-CH(R^{1'})C(O)OR^{11}$,
$-CH(R^{1'})CH(R^{1'})C(O)OR^{11}$,
$-CH(R^{1'})C(O)NR^{12}R^{13}$,
$-CH(R^{1'})CH(R^{1'})C(O)NR^{12}R^{13}$,
$-CH(R^{1'})CH(R^{1'})S(O_2)R^{11}$,
$-CH(R^{1'})CH(R^{1'})S(O_2)NR^{12}R^{13}$,
$-CH(R^{1'})CH(R^{1'})C(O)R^{11}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$,
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)NR^{12}R^{13}$, or
$-CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$;
$R^{1'}$ is H or alkyl; and
$R^{2'}$ is phenyl, substituted phenyl, hetero atom-substituted phenyl, cycloalkyl, heterocycloalkyl, piperidyl or pyridyl.

22. The compound according to Claim 21, wherein $R^{1'}$ is H.

23. The compound according to Claim 20, wherein
R^{11} is H, methyl, ethyl, allyl, *tert*-butyl, benzyl, α-methylbenzyl, α,α-dimethylbenzyl, 1-methylcyclopropyl or 1-methylcyclopentyl;
R' is hydroxymethyl or $-CH_2C(O)NR^{12}R^{13}$;

R^Z is independently selected from the group consisting of the following structures:



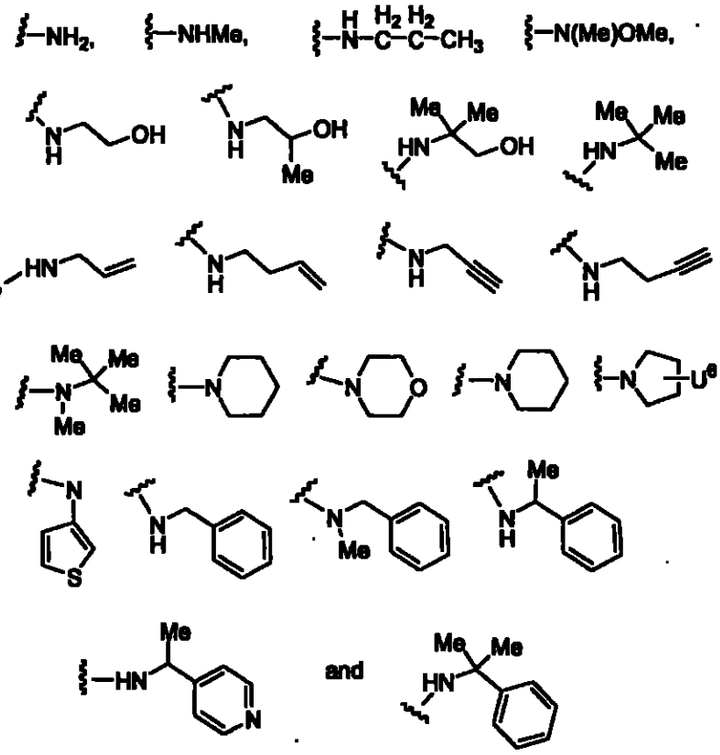
wherein U^1 and U^2 may be same or different and are independently selected from the group consisting of: H, F, $-CH_2C(O)OH$, $-CH_2C(O)OMe$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, $-CH_2C(O)NMe_2$, azido, amino, hydroxyl, substituted amino and substituted hydroxyl ;

U^3 and U^4 are the same or different and are independently O or S;

U^5 is alkyl sulfonyl, aryl sulfonyl, heteroalkyl sulfonyl, heteroaryl sulfonyl, alkyl carbonyl, aryl carbonyl, heteroalkyl carbonyl, heteroaryl carbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl or a combination thereof;

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

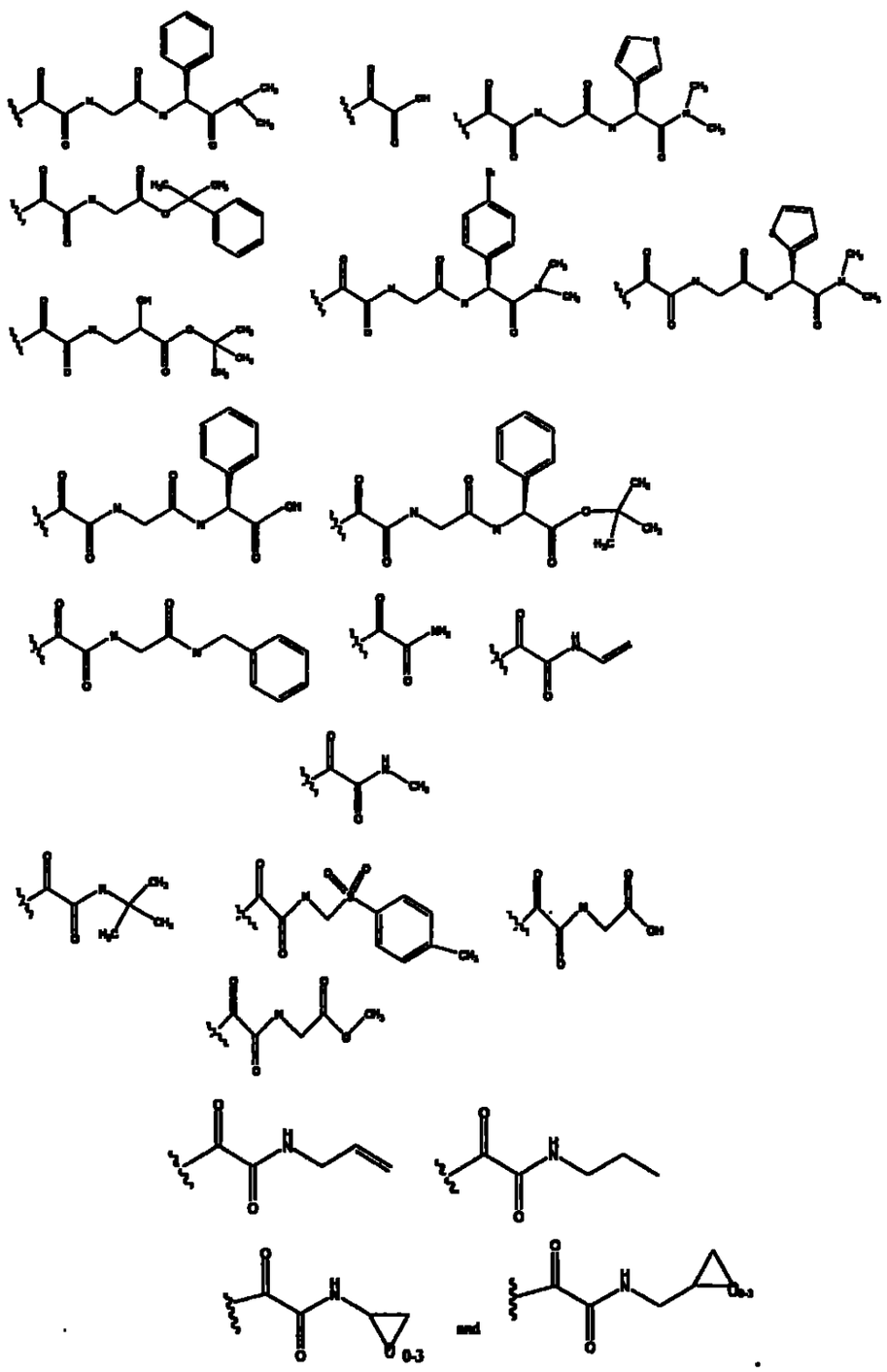
325



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

R^{14} is selected from the group consisting of: H, $-CH_3$, Et, *n*-propyl, methoxy, cyclopropyl, *n*-butyl, 1-but-3-ynyl, benzyl, α-methylbenzyl, phenethyl, allyl, 1-but-3-enyl, $-OCH_3$ and cyclopropylmethyl.

24. The compound according to Claim 1, wherein R^1 is selected from the following structures:



25. The compound according to Claim 1, wherein D and X taken together form a divalent C7-C12 unbranched paraffinic linking chain forming a portion of a 14-19 member macrocycle.

330.
327

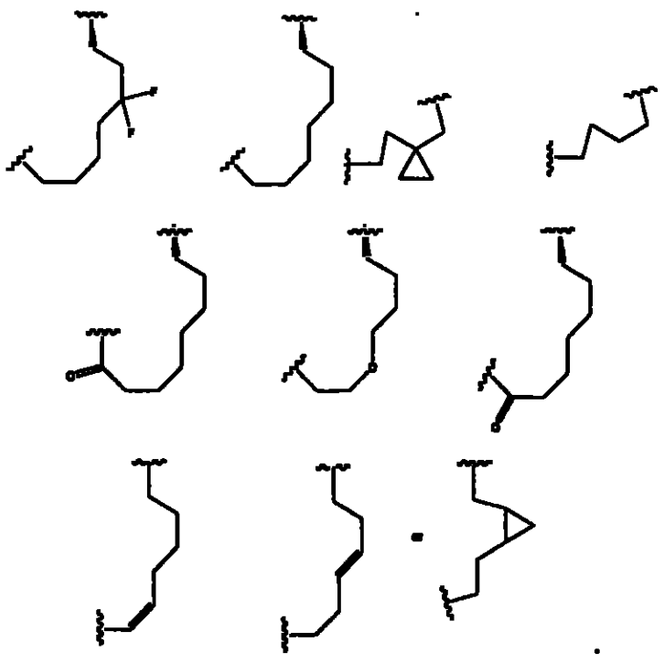
26. The compound according to Claim 25, wherein D and X taken together form a C8 or C9 unbranched paraffinic linking chain forming a portion of a 15 or 16 membered heterocycle.

27. The compound according to Claim 1, wherein D and X taken together form a divalent C7-C12 unbranched olefinic linking chain forming a portion of a 14-19 member macrocycle having a single degree of unsaturation.

28. The compound according to Claim 27, wherein D and X taken together form a C8 or C9 unbranched olefinic linking claim forming a portion of a 15 or 16 member heterocycle having a single degree of unsaturation.

29. The compound according to Claim 1, wherein D and X taken together form a divalent C2 – C12 unbranched aliphatic chain forming a portion of a 9-19 membered heterocycle.

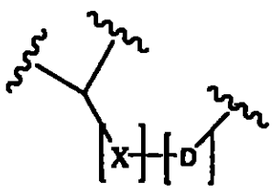
30. The compound according to Claim 1, wherein D is selected from the following structures:



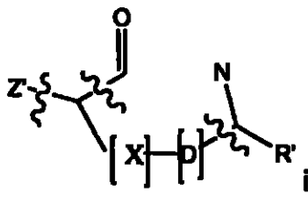
31. The compound according to Claim 1, wherein the portion represented by the part

331

328



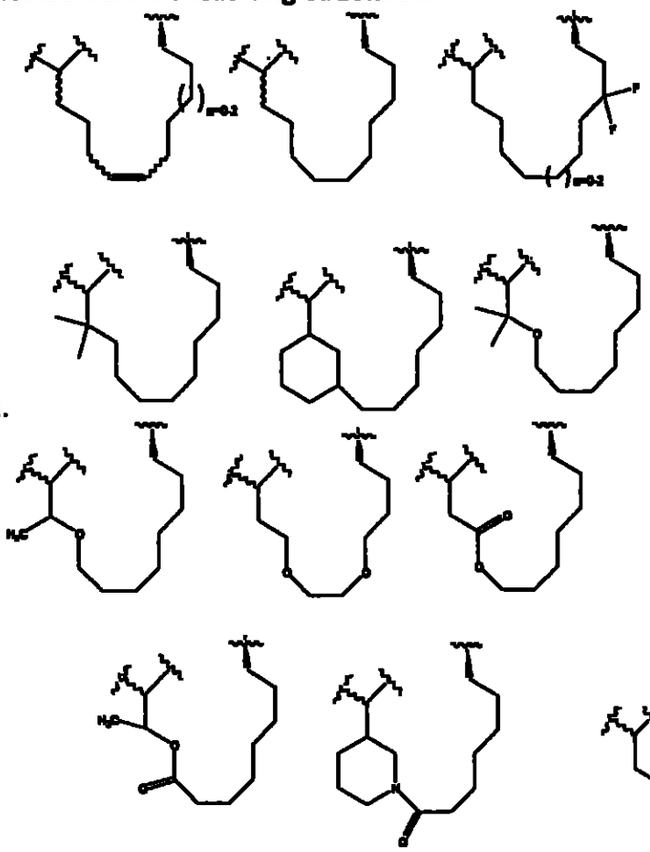
in the moiety

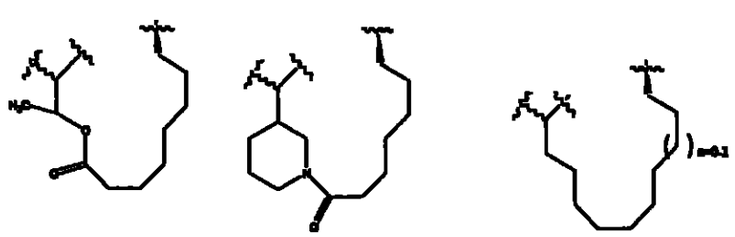


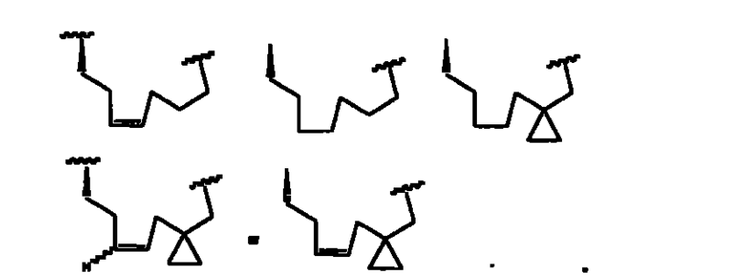
in Formula I

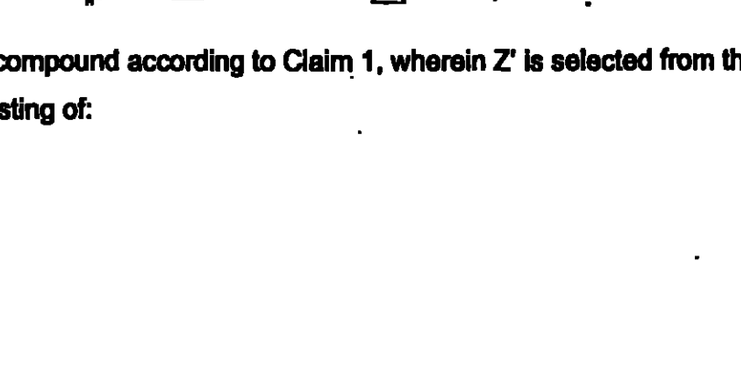
is selected from the following structures:

31.

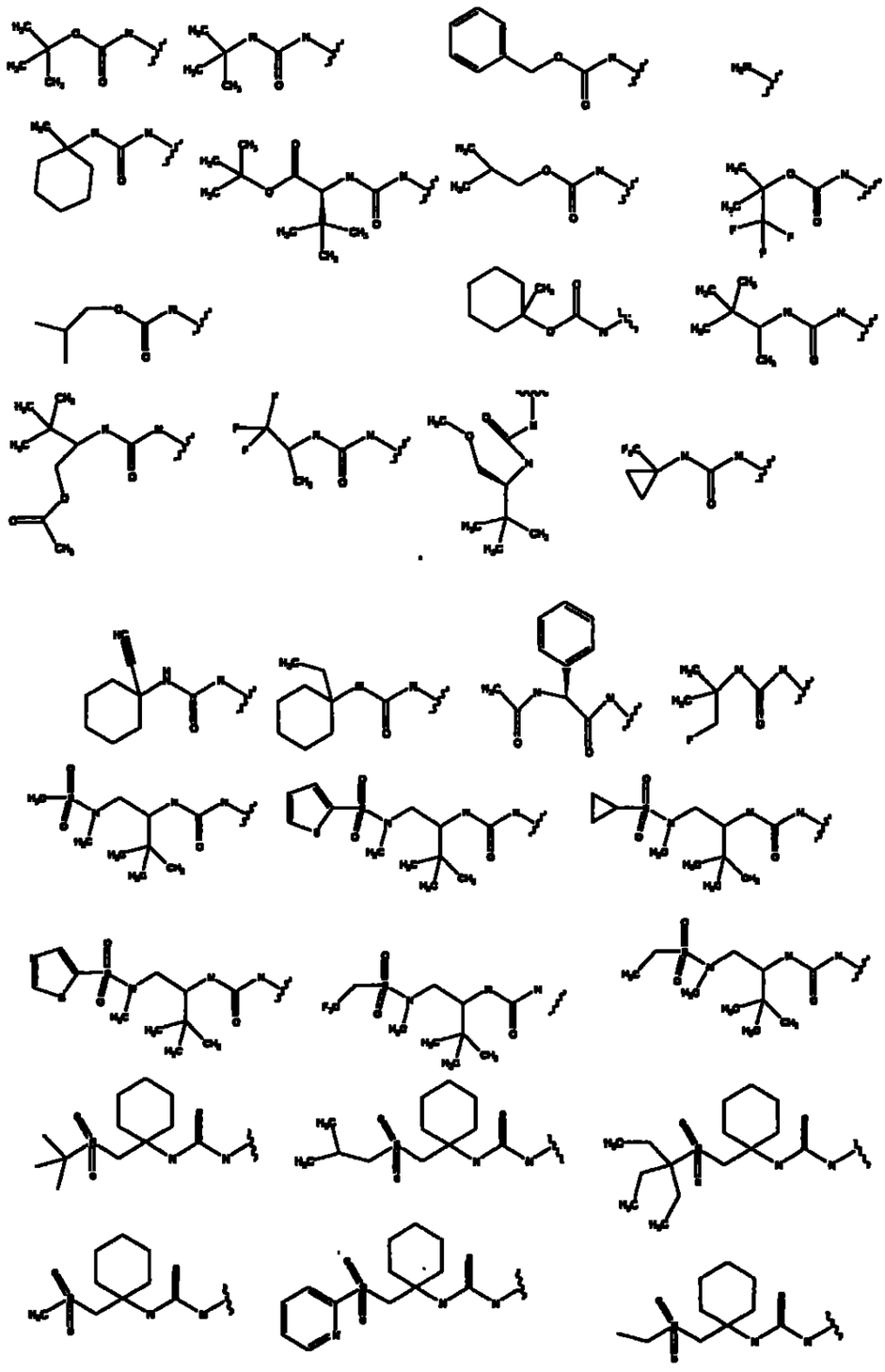


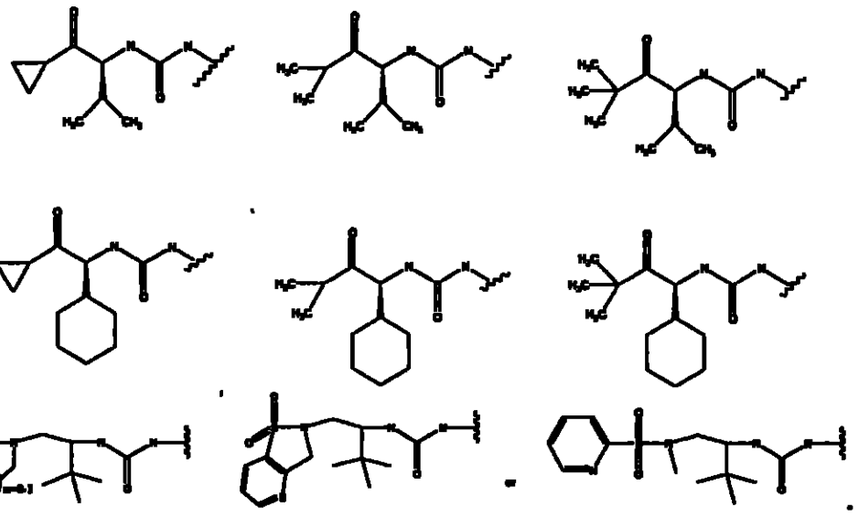






32. The compound according to Claim 1, wherein Z' is selected from the group consisting of:

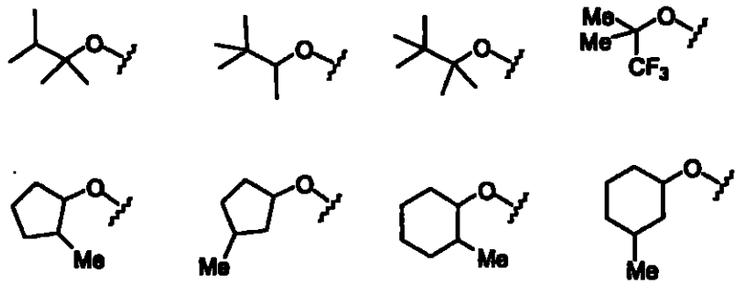


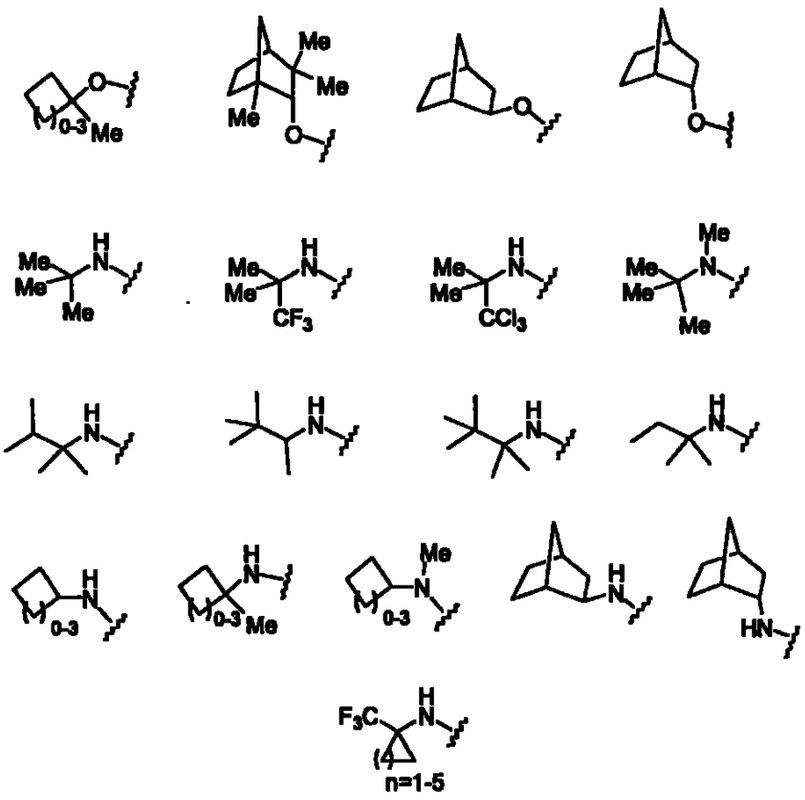


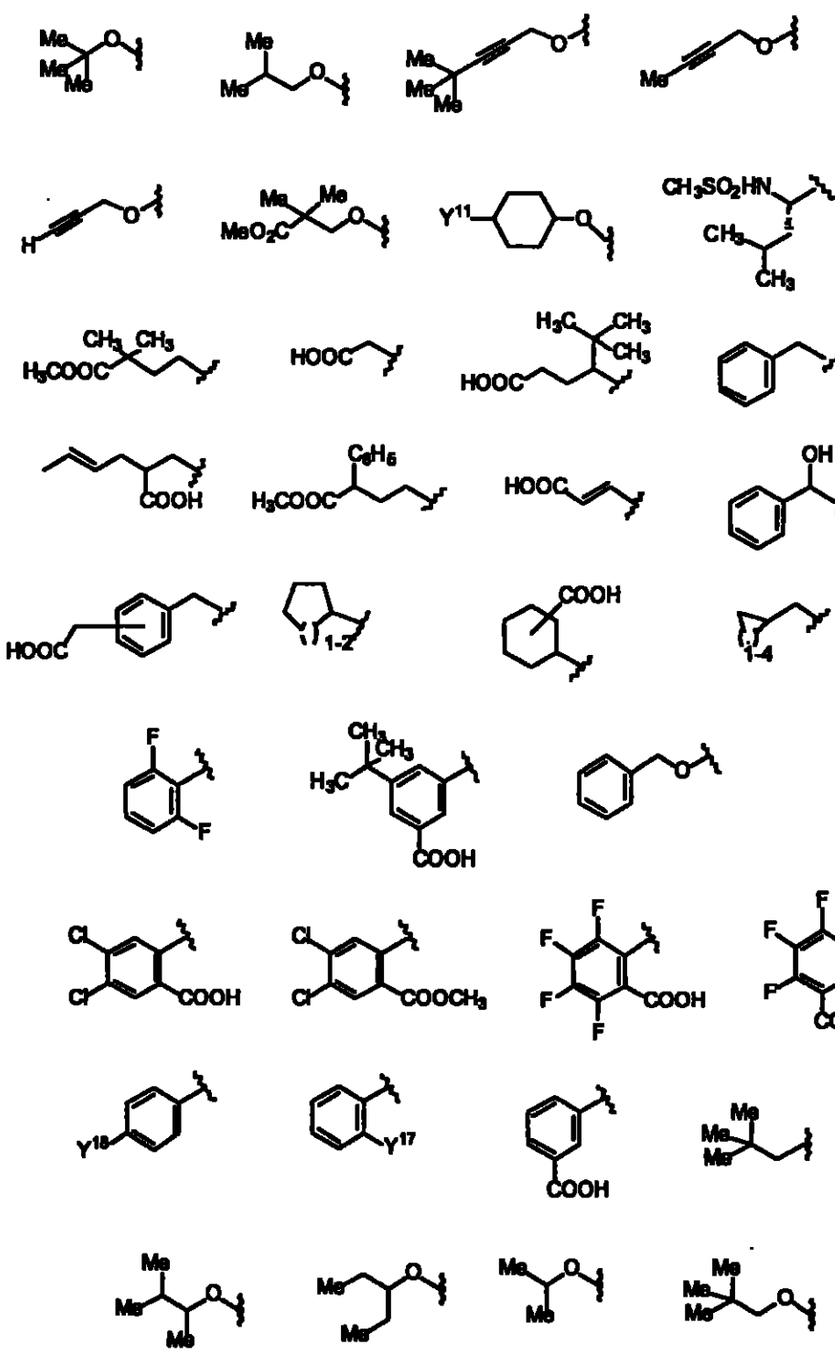
33. The compound according to Claim 1, wherein W is C=O.

34. The compound according to Claim 1, wherein Z is N.

35. The compound according to Claim 1, wherein Y is selected from the group consisting of the following structures:

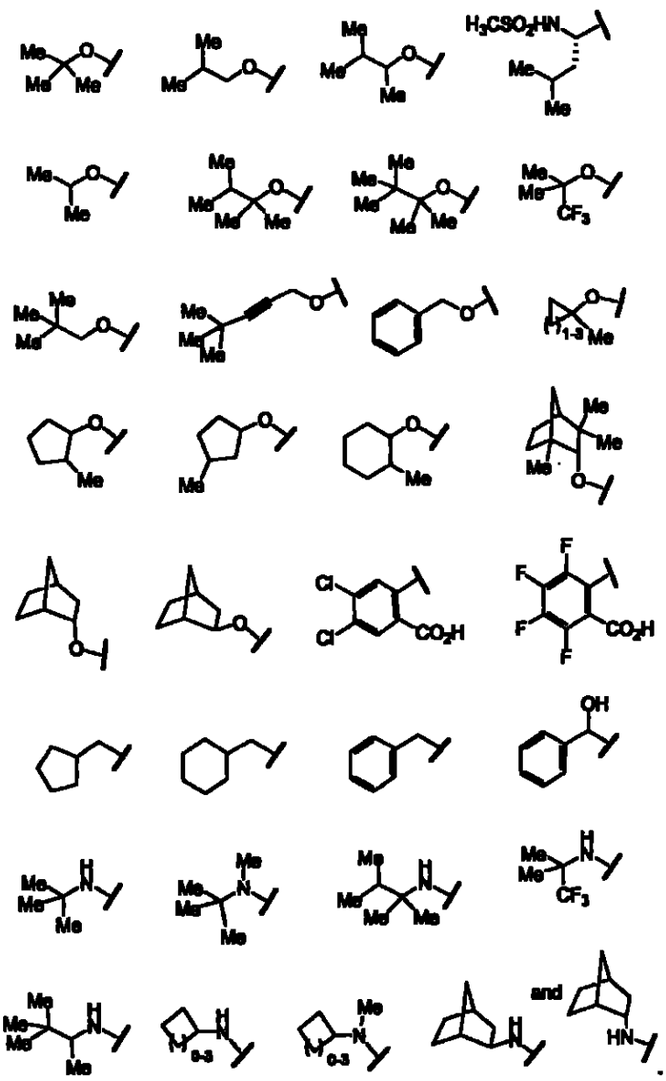



O
0-3
Me
Me
Me
Me
O
O
O
H
N
Me
Me
Me
Me
Me
CF3
Me
Me
CCl3
Me
Me
N
Me
Me
H
N
H
N
H
N
H
N
H
N
0-3
H
N
0-3
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N
0-3
H
N
H
N
HN
F3C
H
N
(4)
n=1-5

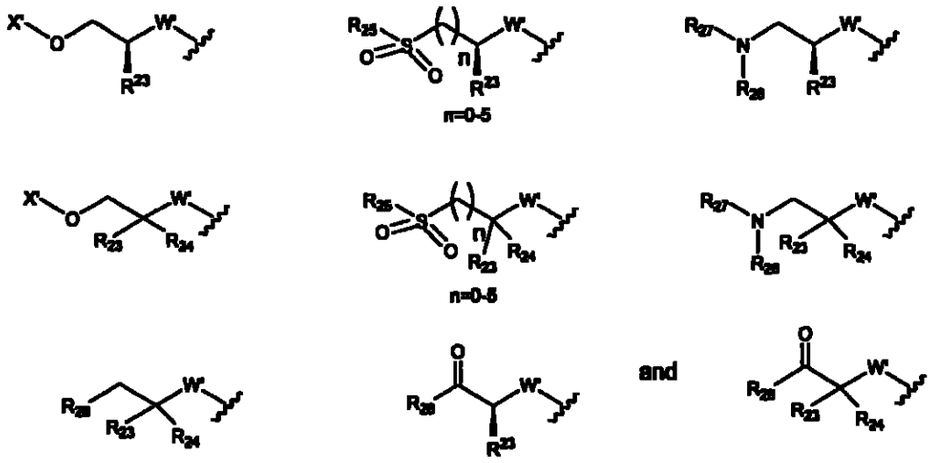

Me
Me
Me
O
Me
Me
Me
Me
Me
Me
O
Me
O
H
Me
Me
MeO2C
O
Y11
O
CH3SO2HN
CH3
CH3
CH3
CH3
H3COOC
HOOC
H3C
CH3
CH3
HOOC
COOH
C6H5
H3COOC
HOOC
OH
HOOC
1-2
COOH
1-4
F
F
CH3
CH3
H3C
COOH
O
Cl
Cl
COOH
Cl
Cl
COOCH3
F
F
F
COOH
F
F
F
F
COOH
Y18
Y17
COOH
Me
Me
Me
Me
Me
Me
O
Me
Me
O
Me
Me
Me
Me
Me
O

wherein Y^{17} is CF_3, NO_2, $C(O)NH_2$, OH, NH_2 or C(O)OH; and
Y^{18} is F or C(O)OH.

36. The compound according to Claim 37, wherein Y is selected from the group consisting of the following structures:



37. The compound according to Claim 1, wherein Y is selected from the group consisting of the following structures:



W' is N or O;

R^{23} is H, alkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl wherein each of said aryl, heteroaryl, cycloalkyl, heterocycloalkyl may be substituted with an alkyl moiety;

R^{24} is H, alkyl, aryl, heteroaryl, cycloalkyl or heterocycloalkyl wherein each of said aryl, heteroaryl, cycloalkyl, heterocycloalkyl may be substituted with an alkyl moiety;

or R^{23} and R^{24} taken together form a cyclic ring containing a carbocycle or heterocycle;

R^{25} is H, alkyl, heteroalkyl, aryl, heteroaryl, alkylamino, arylamino, heteroalkylamino or cycloalkyl,

R^{26} is selected from the group consisting of: H, carbamate, sulfonamides, alkylcarbonyl, alkylsulfonyl, arylsulfonyl, heteroaryl, sulfonyl, heteroalkylsulfonyl, aryloxycarbonyl, heteroalkoxycarbonyl, heteroaryloxycarbonyl, alkylaminoarbonyl, arylaminocarbonyl and urea;

R^{27} is H, alkyl, cycloalkyl, aryl or heteroaryl;

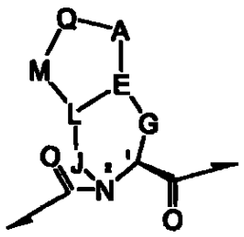
R^{28} is H, alkyl, heteroalkyl, aryl or heteroaryl; and

X'-O- is an ether, ester or carbamate.

38. The compound according to Claim 1, wherein:

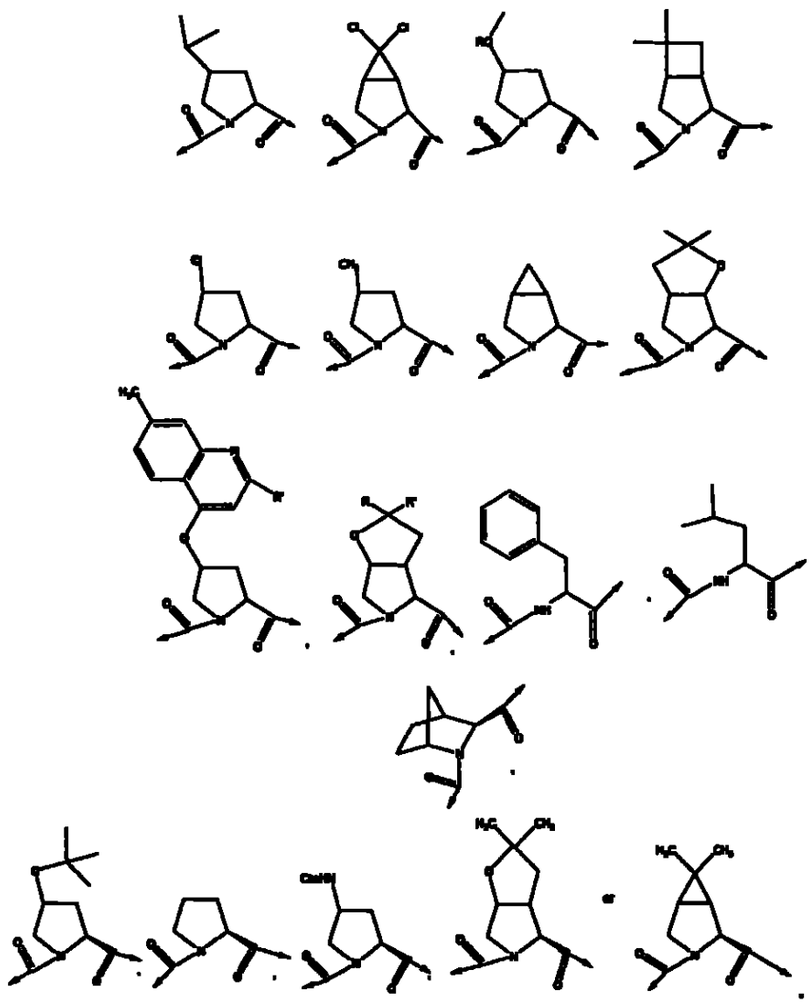
335

(a) the moiety:

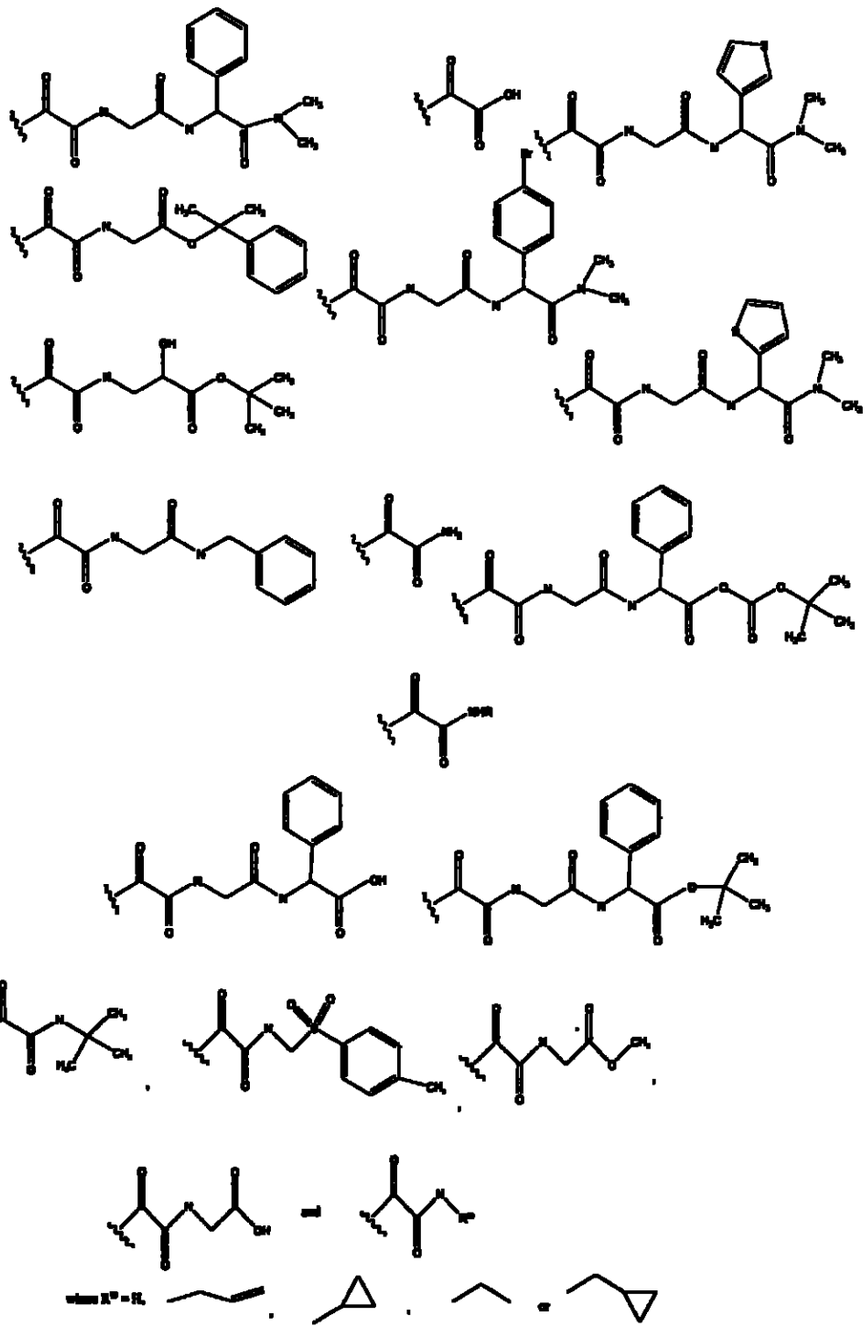


Formula 2

is

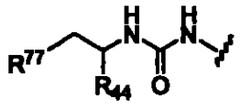


(b) R^1 is selected from the following structures:



(c) Z' is represented by either (i), (ii), or (iii) shown below:

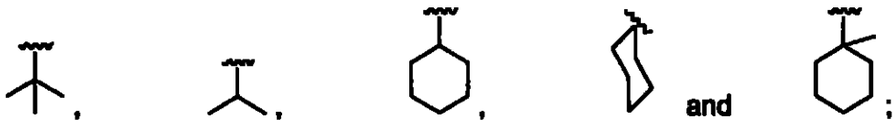
(i)



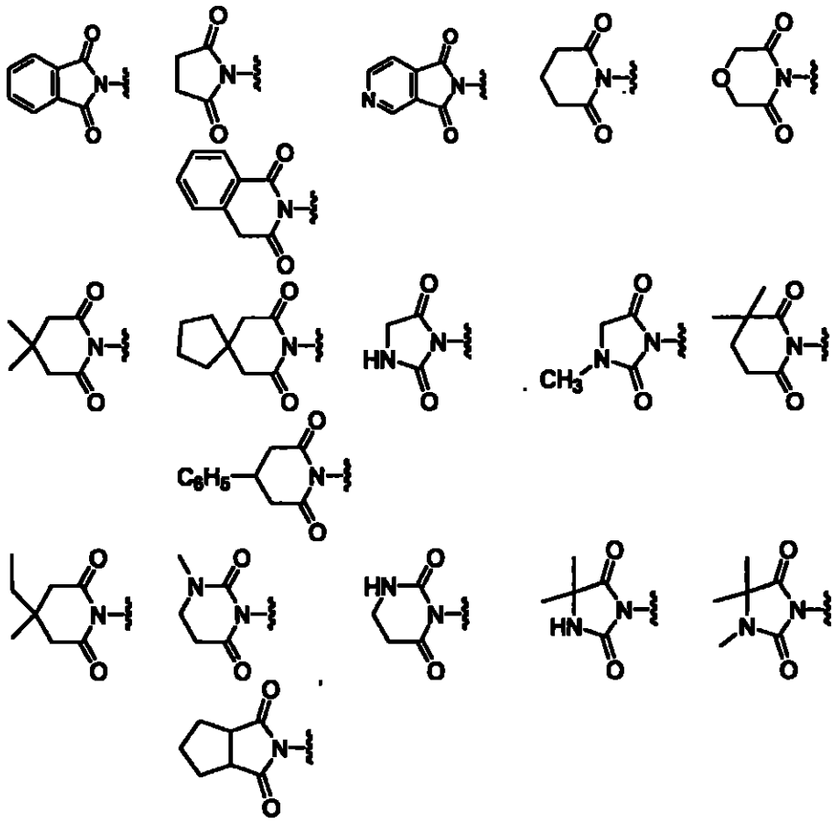
Formula A

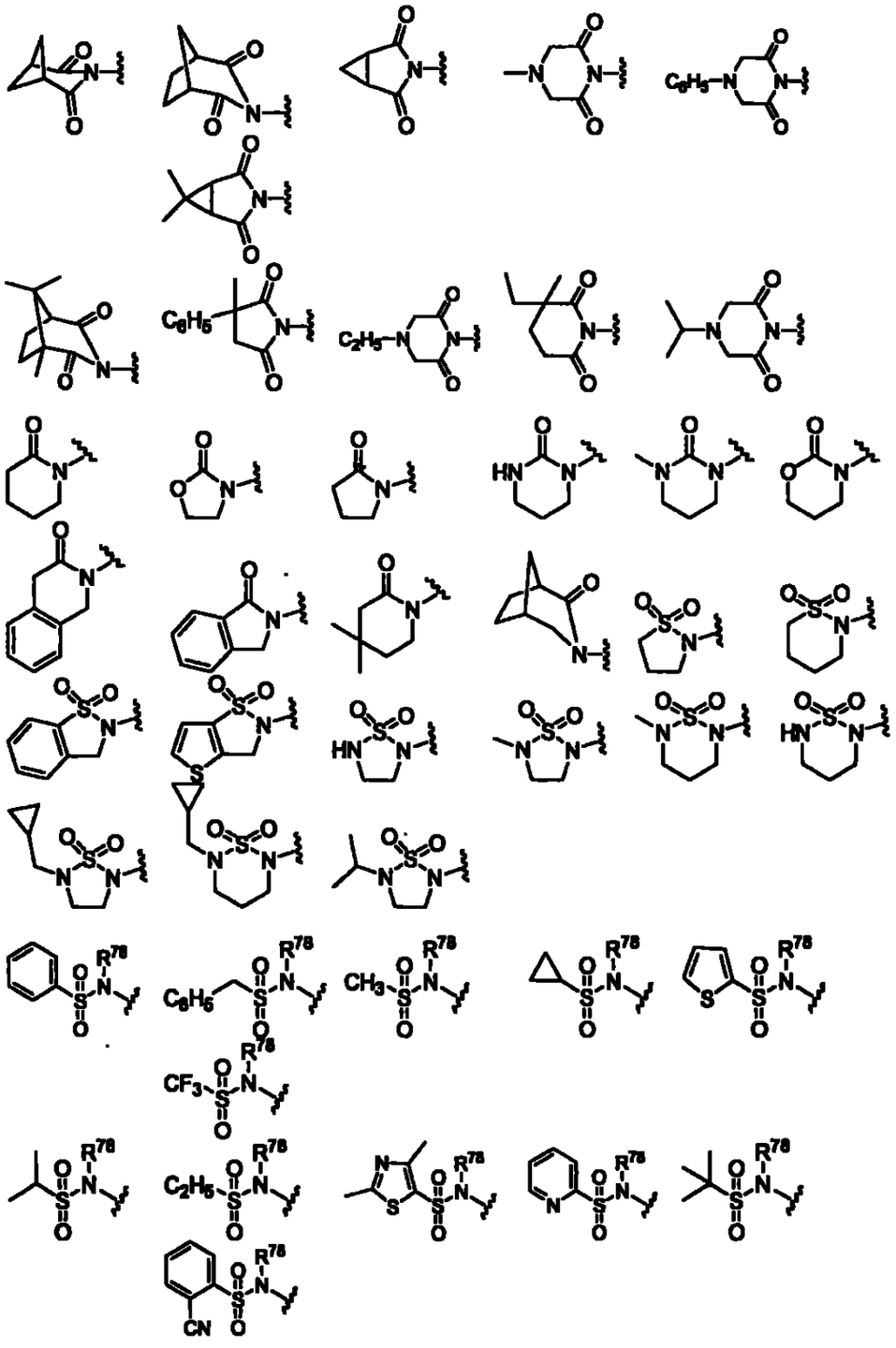
wherein:

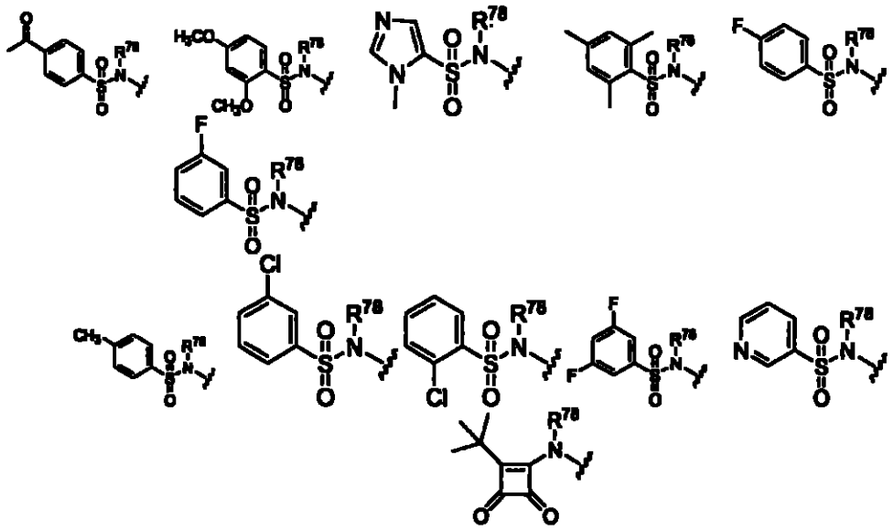
R^{44} is selected from the group consisting of:

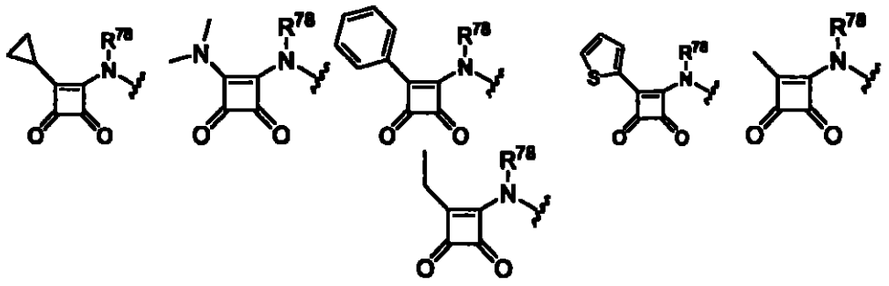


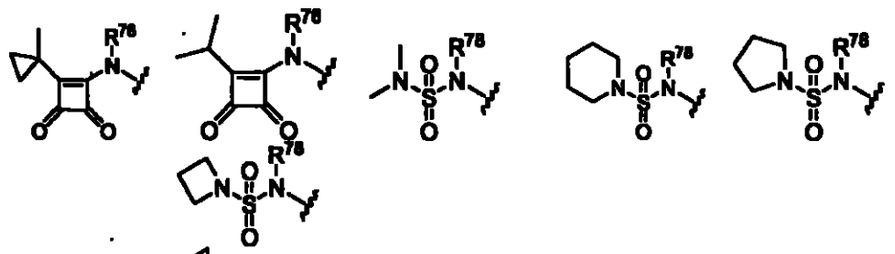
and R^{77} is selected from the group consisting of:

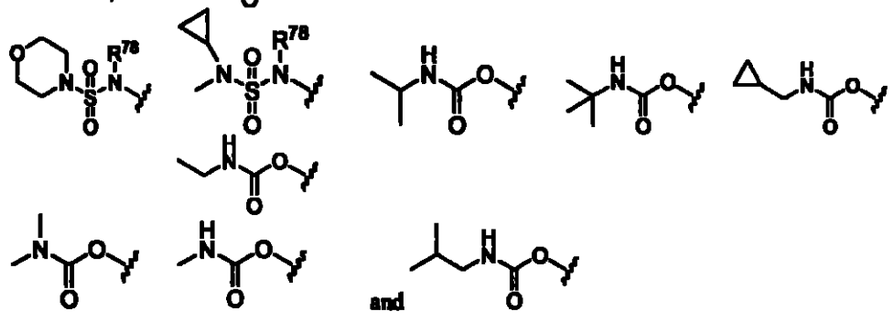








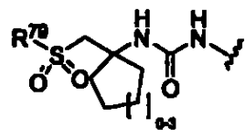




and

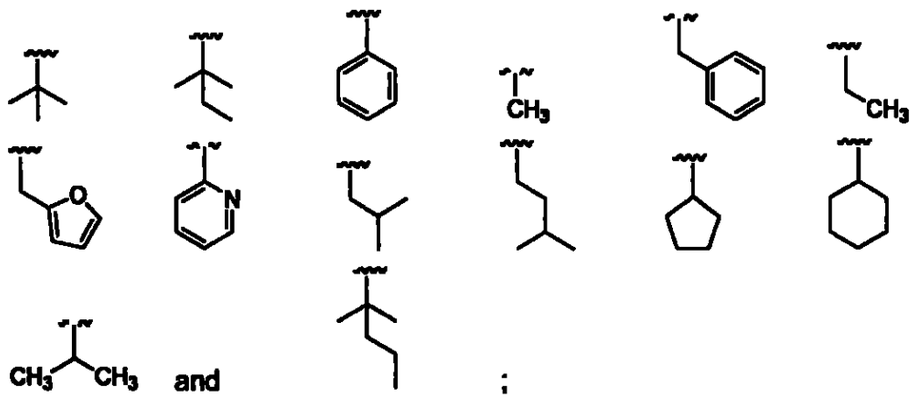
where R^{78} is selected from methyl, ethyl, isopropyl, tert-butyl and phenyl;

(II)



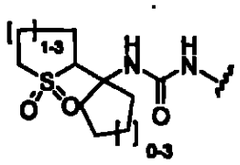
Formula B

where R^{79} is selected from the group consisting of:



; and

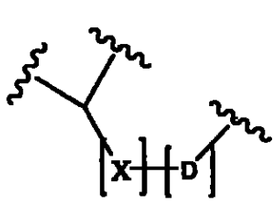
(iii)



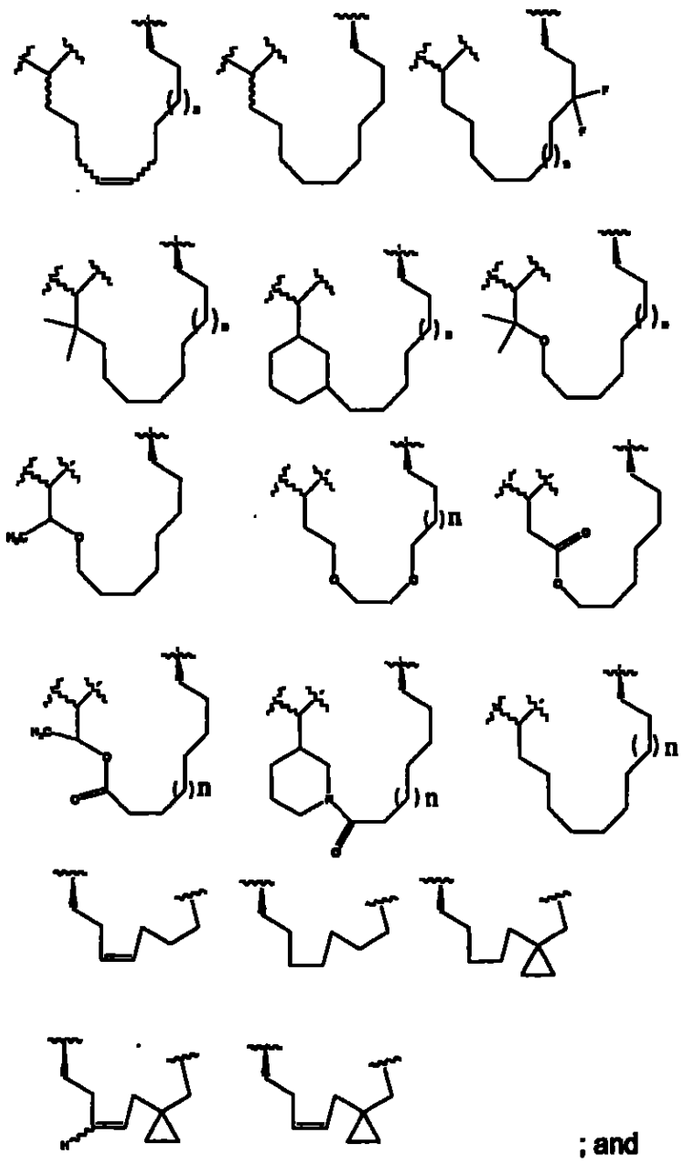
Formula C

wherein the sulfone ring is optionally substituted with alkyl and cycloalkyl; and

(d) the portion of Formula 1 represented by



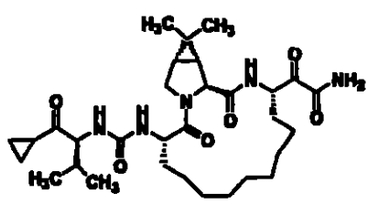
is selected from the following structures:

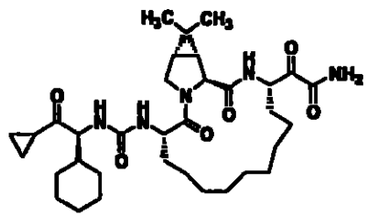


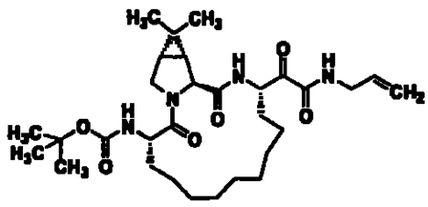
; and

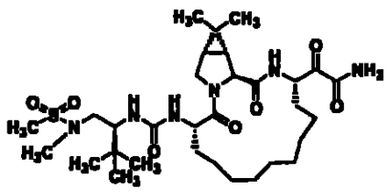
n= 0 to 3.

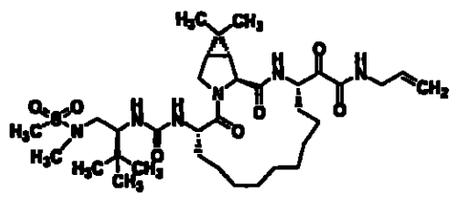
39. The compound according to Claim 1, selected from the group consisting of:

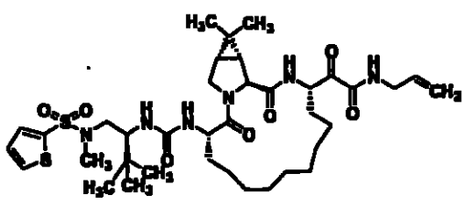


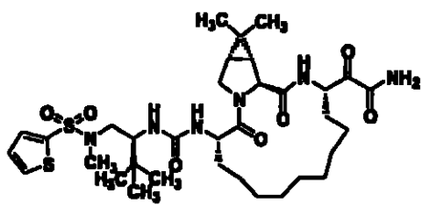


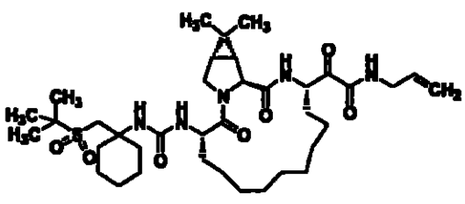


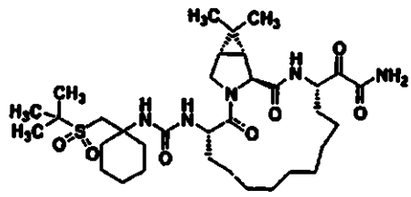


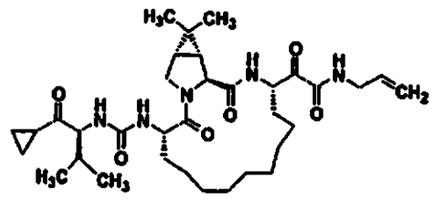


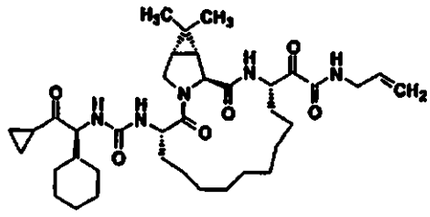






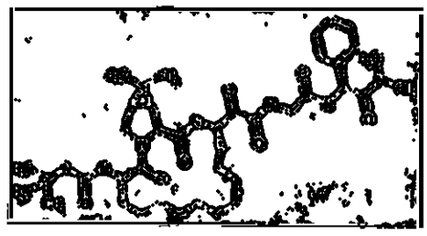


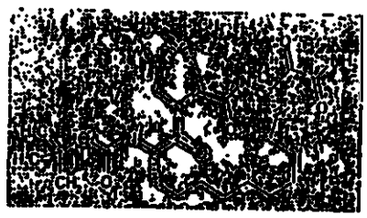




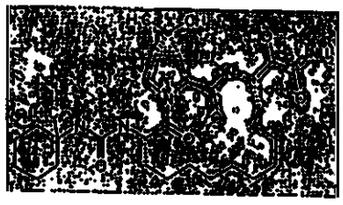


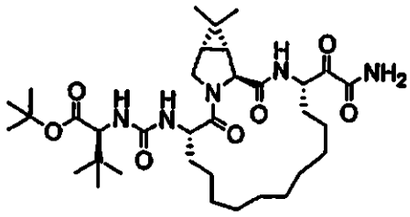




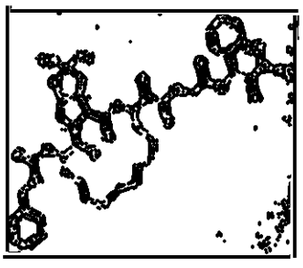


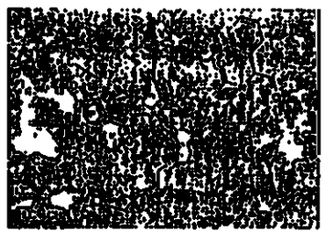




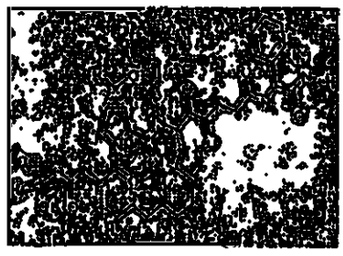


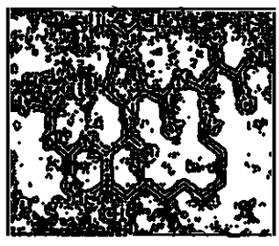


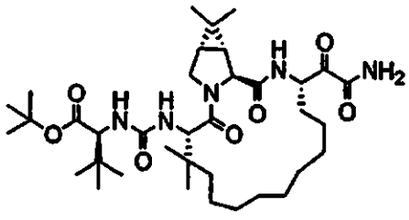




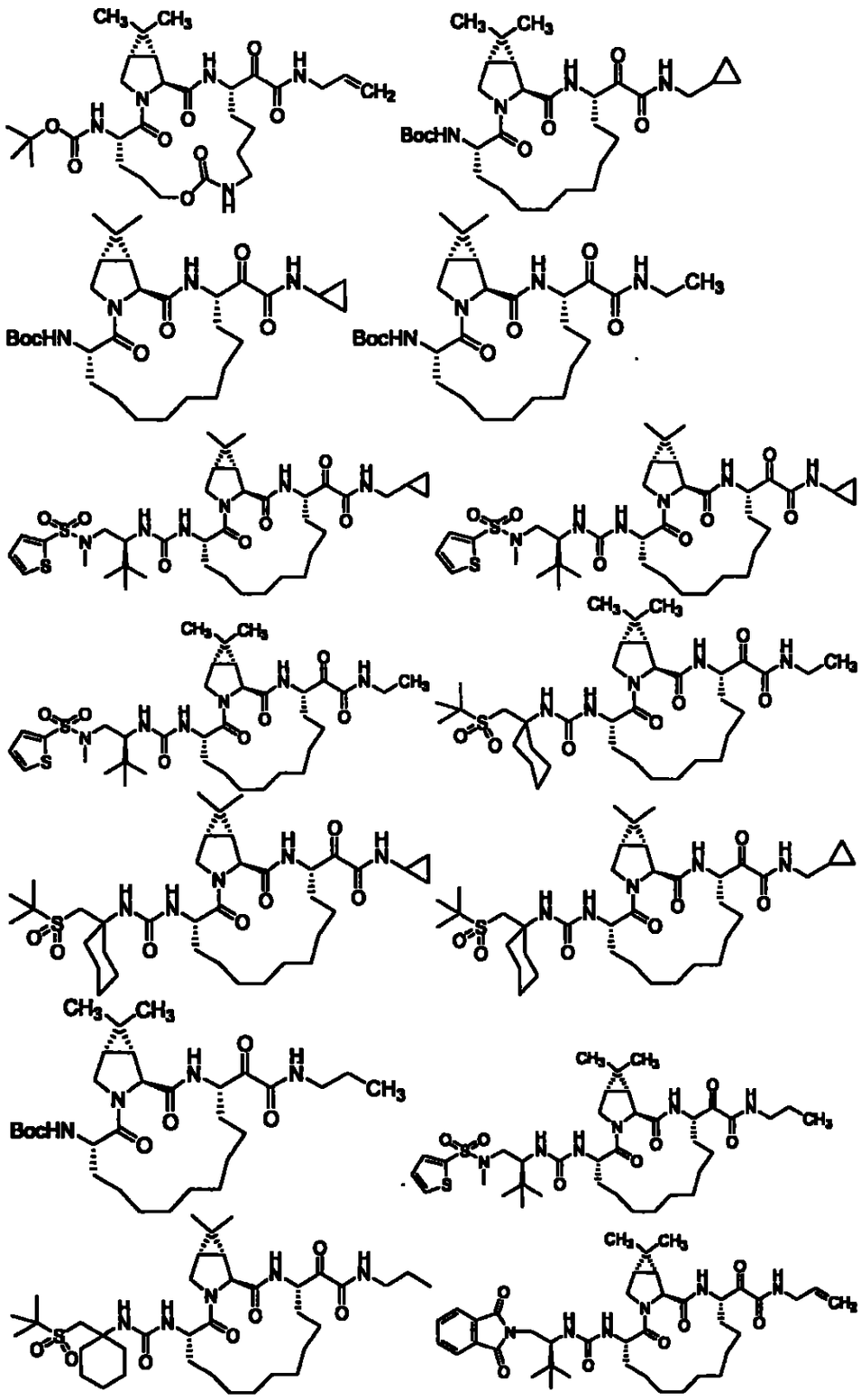


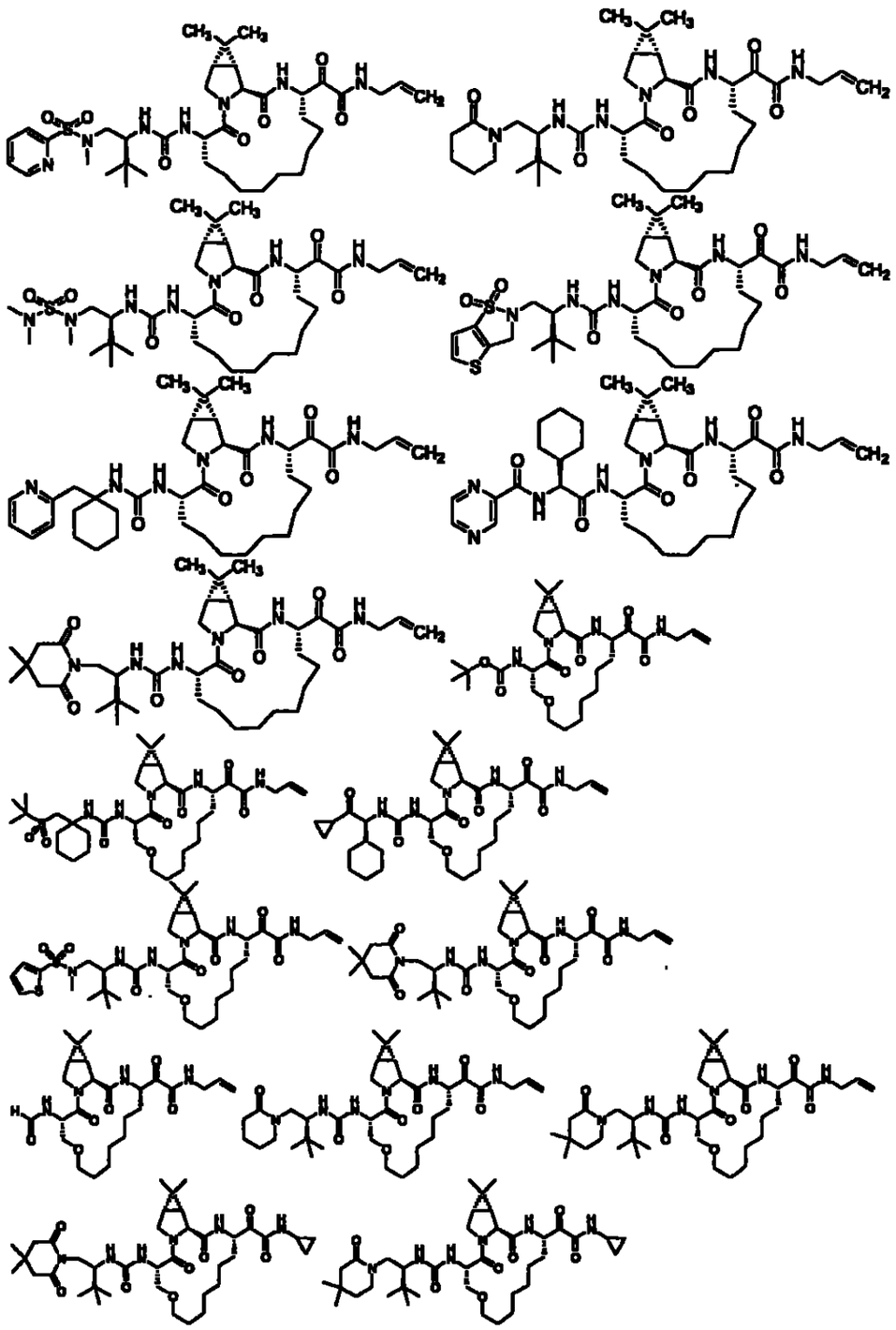


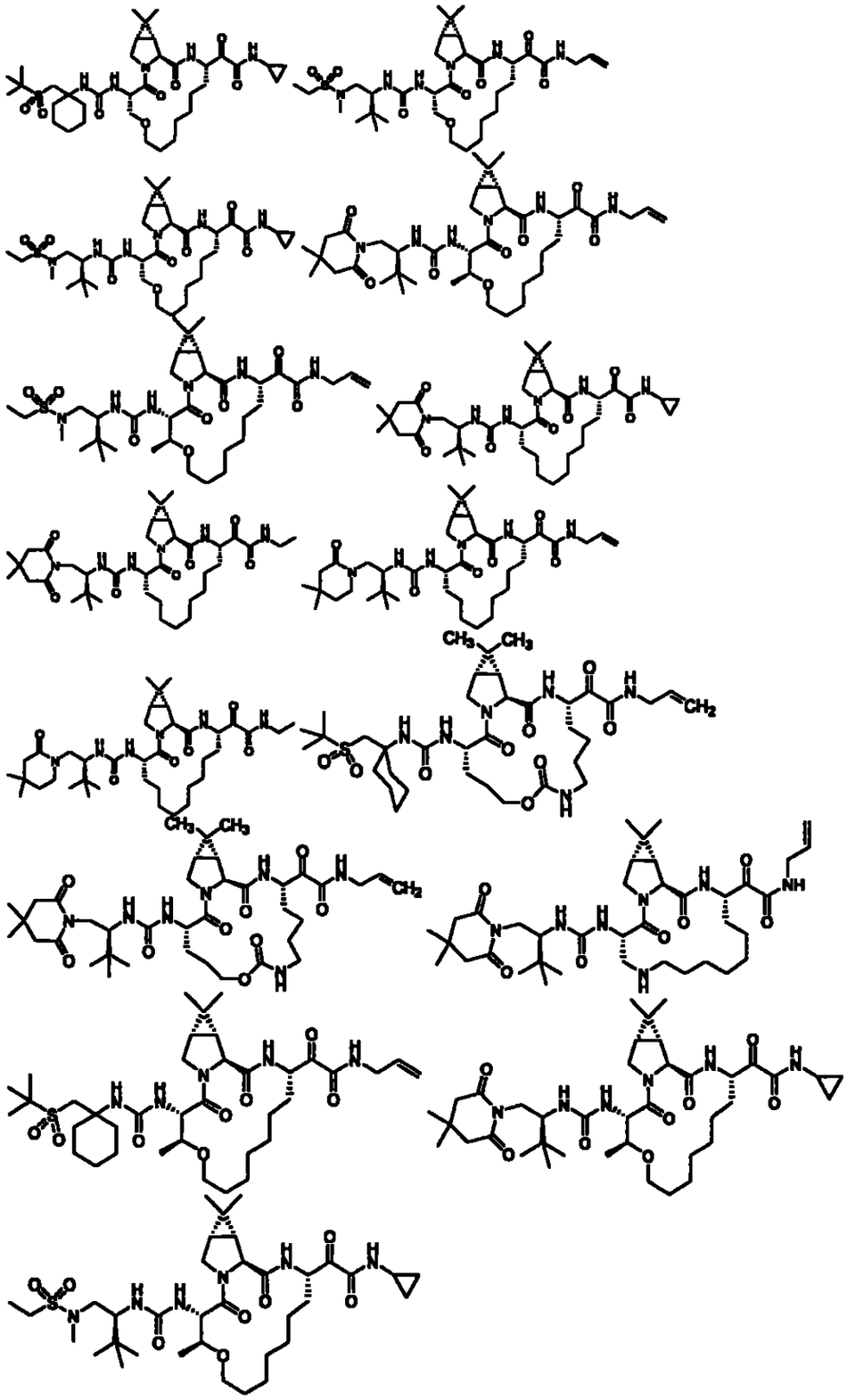


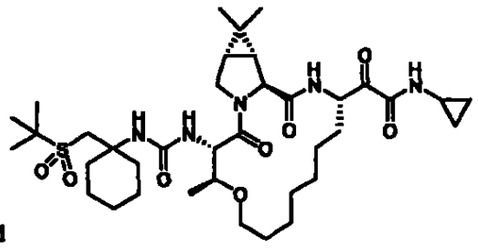

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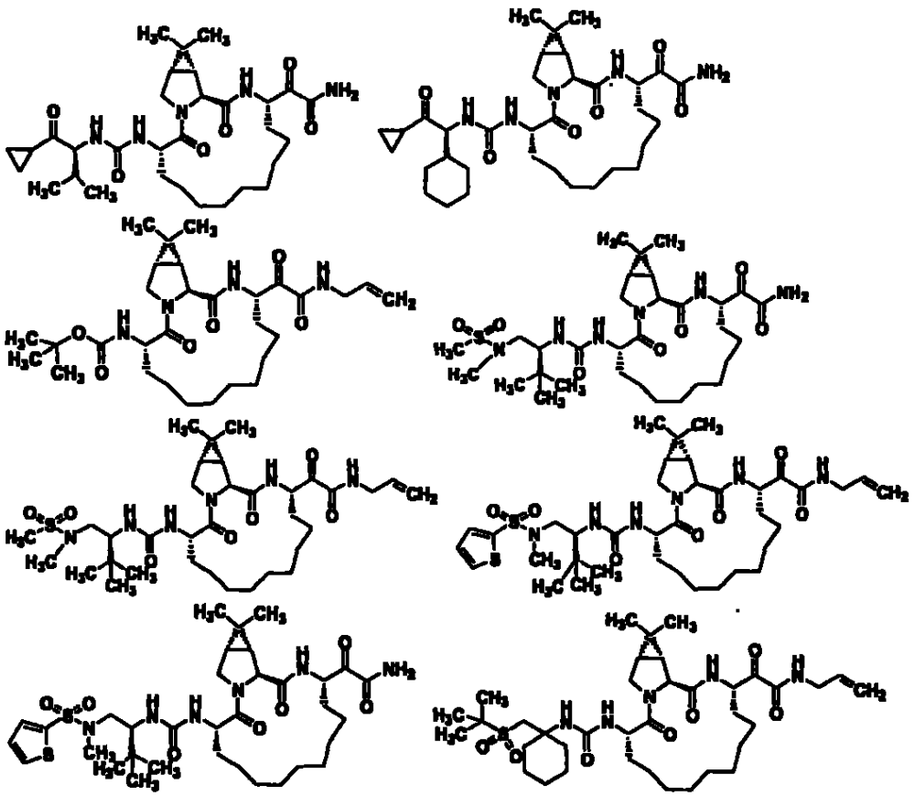


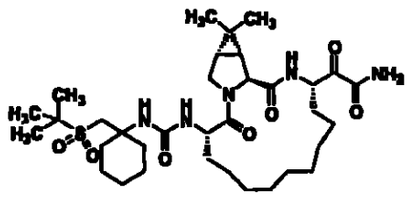
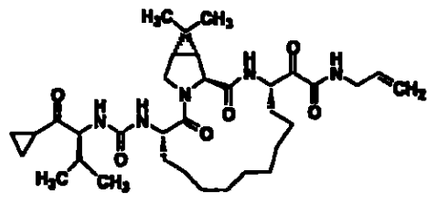
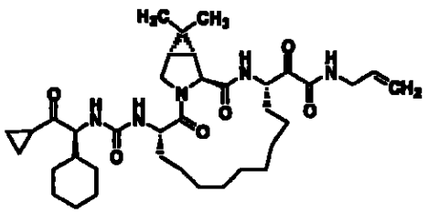


and

or pharmaceutically acceptable salts, solvates or esters of said compound.

40. The compound according to Claim 39, selected from the group consisting of:





and


or pharmaceutically acceptable salts, solvates or esters of said compound.

41. The compound of Claim 1, wherein R^1 is ketoamide, acid, ketoacid, ketoester, ketoaldehyde, diketone, boronic acid or trifluoroketone.

42. A pharmaceutical composition comprising as an active ingredient a compound according to Claim 1.

43. The pharmaceutical composition according to Claim 42 suitable for use in treating disorders associated with HCV.

44. The pharmaceutical composition according to Claim 42 additionally comprising a pharmaceutically acceptable carrier.

45. The pharmaceutical composition according to Claim 46, additionally containing an antiviral agent.

46. The pharmaceutical composition according to Claim 45, additionally containing an interferon or pegylated interferon.

47. The pharmaceutical composition according to Claim 46, wherein said antiviral agent is ribavirin and said interferon is α-interferon.

48. A method of treating disorders associated with the HCV protease, said method comprising administering to a patient in need of such treatment therapeutically effective amounts of a compound according to Claim 1.

49. A method of treating disorders associated with the HCV protease, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of a compound according to Claim 1.

50. The method according to Claim 49, wherein said administration is subcutaneous.

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51. The use of a compound according to Claim 1 for the manufacture of a medicament to treat disorders associated with the HCV protease.

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

53. The pharmaceutical composition according to Claim 52, additionally containing an antiviral agent.

54. The pharmaceutical composition according to Claim 53, still additionally containing an interferon or a pegylated interferon.

55. The pharmaceutical composition according to Claim 54, wherein said antiviral agent is ribavirin and said interferon is α-interferon.

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Memoria Descriptiva

de la

Patente de Invención

Sobre

"INHIBIDORES MACROCÍCLICOS DE LA SERINA PROTEASA NS3 DEL VIRUS DE LA HEPATITIS C"

Solicitada por:

SCHERING CORPORATION, *residente en* ***2000 Galloping Hill Road Kenilworth, Nueva Jersey 07033-0530, E. U. DE NORTEAMERICA.***

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US/RF

INHIBIDORES MACROCÍCLICOS DE LA SERINA PROTEASA NS3 DEL VIRUS DE LA HEPATITIS C

Campo de la Invención

La presente invención se refiere a inhibidores novedosos de proteasas del virus de la hepatitis C ("VHC"), a composiciones farmacéuticas que contienen uno o más de tales inhibidores, a métodos para preparar dichos inhibidores y a métodos para usar dichos inhibidores para tratar la hepatitis C y trastornos relacionados. La presente invención revela adicionalmente compuestos macrocíclicos novedosos como inhibidores de la serina proteasa NS3/NS4a del VHC. Esta solicitud reivindica el beneficio de prioridad de la solicitud de patente estadounidense provisional Acta No. 60/506.637, presentada el 26 de Septiembre de 2003.

Antecedentes de la Invención

El virus de la hepatitis C (VHC) es un virus de ARN mono-catenario de sentido positivo al que se ha vinculado como el mayor agente causal de la hepatitis no A no B (NANBH), en especial la NANBH asociada con sangre (BB-NANBH) (ver Publicación de Solicitud de Patente Internacional No. WO 89/04669, igual a US 2003162167). La NANBH se debe distinguir de otros tipos de enfermedad hepática inducida por virus, tal como el virus de la hepatitis A (VHA), el virus de la hepatitis B (VHB), el virus de la hepatitis delta (VHD), el citomegalovirus (CMV) y el virus de Epstein-Barr (VEB), al igual que otras formas de enfermedad hepática tales como el alcoholismo y la cirrosis biliar primaria.

Recientemente, se ha identificado, clonado y expresado una proteasa de VHC necesaria para el procesamiento de polipéptidos y la replicación viral; (ver, por ej., patente Estadounidense No. 5.712.145). Esta poliproteína de aproximadamente 3000 aminoácidos contiene, desde el extremo amino terminal hasta el carboxilo terminal, una proteína nucleocápside (C), proteínas de

envoltura (E1 y E2) y varias proteínas no estructurales (NS1, 2, 3, 4a, 5a y 5b). NS3 es una proteína de aproximadamente 68 kda, codificada por aproximadamente 1893 nucleótidos del genoma del VHC y posee dos dominios diferentes: (a) un dominio de serina proteasa que consiste en aproximadamente 200 de los aminoácidos N-terminales; y (b) un dominio de ATPasa dependiente de ARN en el extremo C-terminal de la proteína. La proteasa NS3 es considerada un miembro de la familia de las quimiotripsinas debido a las similitudes en la secuencia proteica, la estructura global tridimensional y el mecanismo de catálisis. Otras enzimas similares a las quimiotripsinas son la elastasa, el factor Xa, la trombina, la tripsina, la plasmina, la uroquinasa, la tPA y la PSA. La serina proteasa NS3 del VHC es responsable de la proteólisis del polipéptido (poliproteína) en las uniones NS3/NS4a, NS4a/NS4b, NS4b/NS5a y NS5a/NS5b y es de este modo responsable de la generación de cuatro proteínas virales durante la replicación viral. Esto ha convertido a la serina proteasa NS3 del VHC en un blanco atractivo para la quimioterapia antiviral. Los compuestos novedosos pueden inhibir dicha 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 auto-escisión de la unión NS3/NS4a por la serina proteasa NS3/NS4a ocurre intramolecularmente (es decir, en forma cis) mientras que los otros sitios de escición se procesan de manera intermolecular (es decir, en forma trans).

El análisis de los sitios de escisión natural para la proteasa del VHC reveló la presencia de cisteína en P1 y serina en P1' y que estos residuos se conservan estrictamente en las uniones NS4a/NS4b, NS4b/NS5a y NS5a/NS5b. La unión NS3/NS4a contiene una treonina en P1 y una serina en P1'. La sustitución Cys→Thr en NS3/NS4a se postula para explicar el requerimiento del

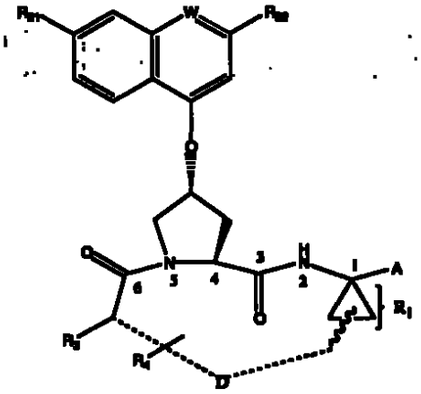
procesamiento en cis en lugar de trans en esta unión. Ver, por ej., Pizzi et al. (1994) Proc. Natl. Acad. Sci (USA) 91:888-892, Failla et al. (1996) Folding & Design 1:35-42. El sitio de escisión de NS3/NS4a es también más tolerante a la mutagénesis que los otros sitios. Ver, por ej., Kollykhalov et al. (1994) J. Virol. 68:7525-7533. También se descubrió que se requieren residuos acídicos en la región corriente arriba del sitio de ruptura para una ruptura eficiente. Ver, por ej., Komoda et al. (1994) J. Virol. 68:7351-7357.

Los inhibidores de proteasa de VHC que se han informado incluyen antioxidantes (ver Publicación de Solicitud de Patente Internacional No. WO 98/14181), ciertos péptidos y análogos de péptidos (ver Publicación de Solicitud de Patente Internacional No. WO 98/17679 (igual a US2002032175), 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 eglina c de 70 aminoácidos (Martin et al. (1998) Biochem. 37:11459-11468, afinidad de inhibidores seleccionados de inhibidores humanos de tripsina secretora pancreática (hPSTI-C3) y repertorios de mini-cuerpos (MBip) (Dimasi et al. (1997) J. Virol. 71:7461-7469), cVHE2 (un fragmento "camelizado" de anticuerpo de dominio variable) (Martin et al.(1997) Protein Eng. 10:607-614), y α1-antiquimiotripsina (ACT) (Elzouki et al.) (1997) J. Hepat. 27:42-28). Se reveló recientemente una ribozima diseñada para destruir selectivamente el ARN del virus de la hepatitis C (ver, BioWorld Today 9(217): 4 (10 de noviembre de 1998)).

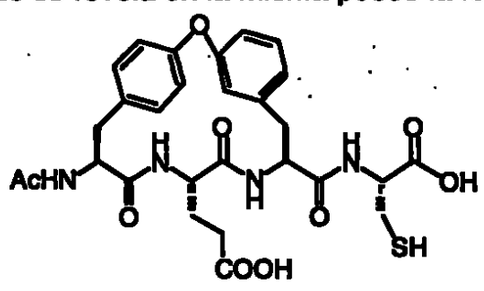
También se hace referencia a las Publicaciones de PCT No. WO 98/17679, publicada el 30 de Abril de 1998 (Vertex Pharmaceuticals Incorporated); WO 98/22496, publicada el 28 de mayo de 1998 (igual a U.S. 6.018.020 y U.S. 5.866.684; F. Hoffmann-La Roche AG); y WO 99/07734, publicada el 18 de febrero de 1999 (igual a U.S. 6.143.715; Boehringer Ingelheim Canada Ltd.).

Se ha vinculado al VHC con la cirrosis hepática y la inducción del carcinoma hepatocelular. El pronóstico para pacientes que padecen la infección por VHC, actualmente, es pobre. La infección por VHC es más difícil de tratar que otras formas de hepatitis debido a la falta de inmunidad o remisión asociada con la infección por VHC. Datos actuales indican una tasa de supervivencia de menos del 50% a los cuatro años posteriores al diagnóstico de cirrosis. A los pacientes que se les diagnosticó carcinoma localizado hepatocelular resecable poseen una tasa de supervivencia del 10-30%, mientras que aquellos con carcinoma localizable hepatocelular no resecable poseen una tasa de supervivencia de cinco años menor del 1%.

Se hace referencia a WO 00/59929 (igual a US2004002448 y U.S. 6.608.027; Apoderado: Boehringer Ingelheim (Canada) Ltd.; publicada el 12 de octubre de 2000) que revela derivados peptídicos de fórmula:



Se hace referencia a A. Marchetti et al, Synlett, S1, 1000-1002 (1999), que describe la síntesis de análogos bicíclicos de un inhibidor de la proteasa NS3 del VHC. Un compuesto que se revela en la misma posee la fórmula:

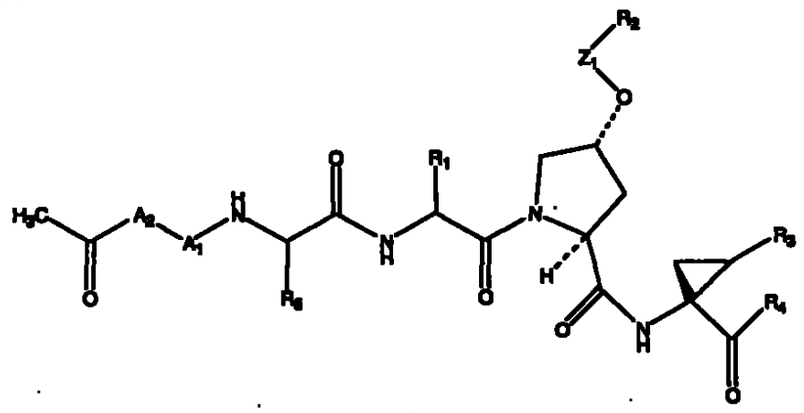


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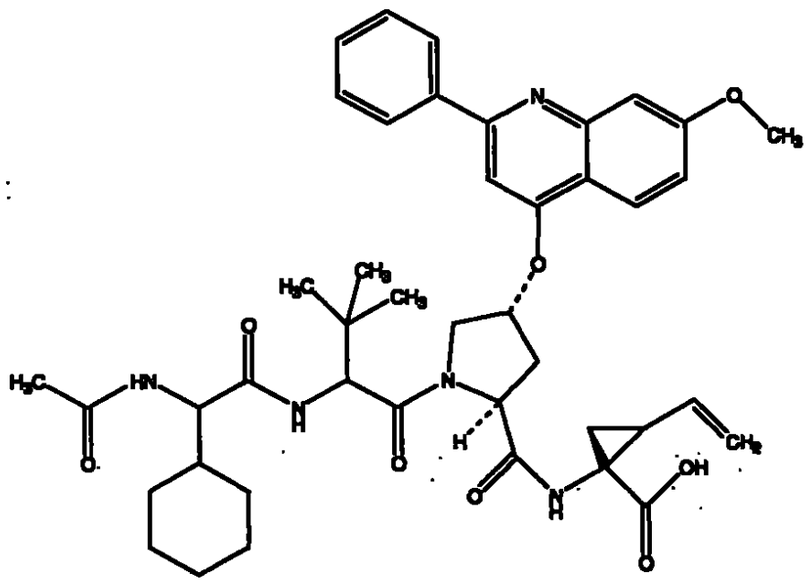
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También se hace referencia a W. Han *et al*, *Bioorganic & Medicinal Chem. Lett*, (2000) 10, 711-713, que describe la preparación de ciertas α-cetoamidas, α-cetoésteres y α-dicetonas que contienen grupos funcionales alilo y etilo.

También se hace referencia a WO 00/09558 (Apoderado: Boehringer Ingelheim Limited; publicada el 24 de febrero de 2000) que revela derivados peptídicos de fórmula:



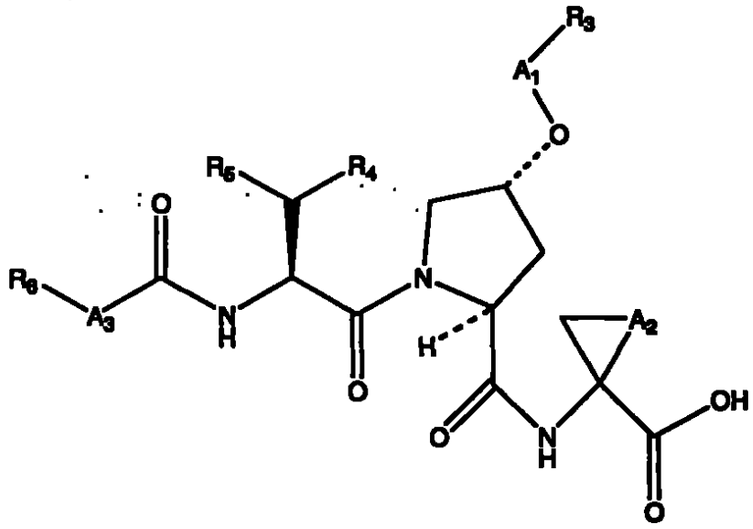
donde los diversos elementos se definen en la misma. Un compuesto ilustrativo de esa serie es:



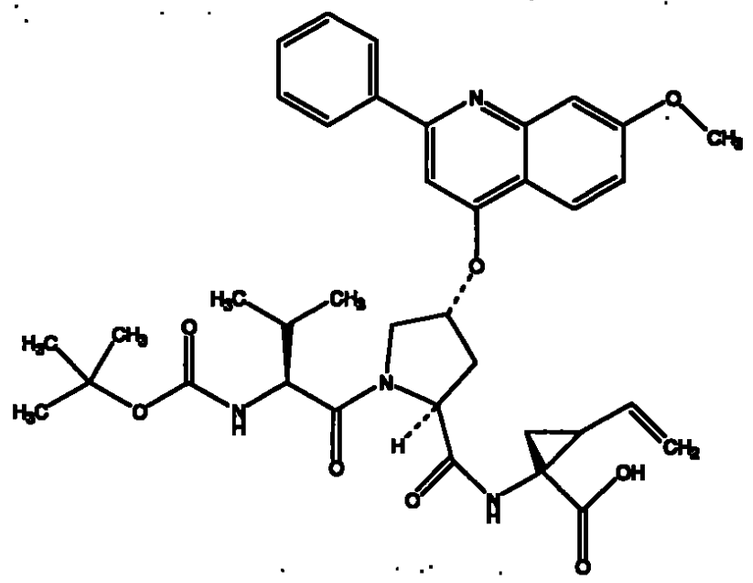
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También se hace referencia a WO 00/09543 (igual a US2002016442 y US 2002037998; Apoderado: Boehringer Ingelheim Limited; publicada el 24 de febrero de 2000) que revela derivados peptídicos de fórmula:



donde los diversos elementos se definen en la misma. Un compuesto ilustrativo de esa serie es:



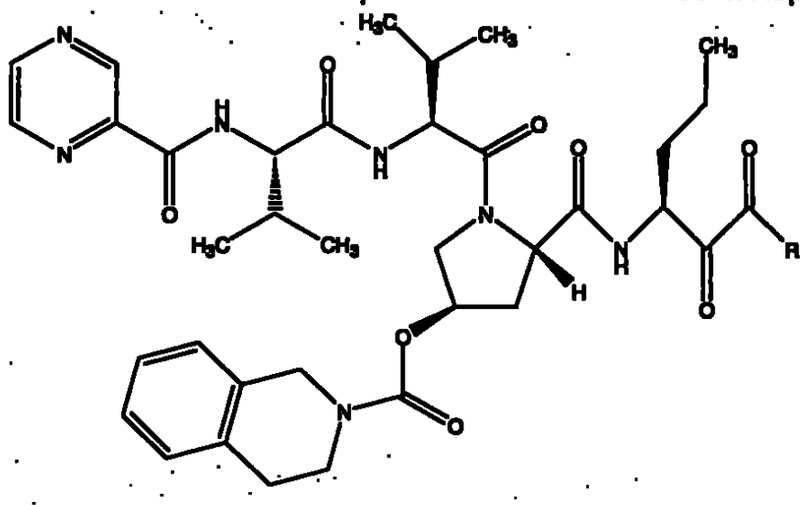
Las terapias actuales para la hepatitis C incluyen interferón-α (INF_α) y terapia de combinación con ribavirin e interferón. Ver, por ej., Beremguer et al. (1998) Proc. Assoc. Am. Physicians 110(2):98-112. Estas terapias adolecen de una baja tasa de respuesta sostenida y efectos secundarios frecuentes. Ver, por

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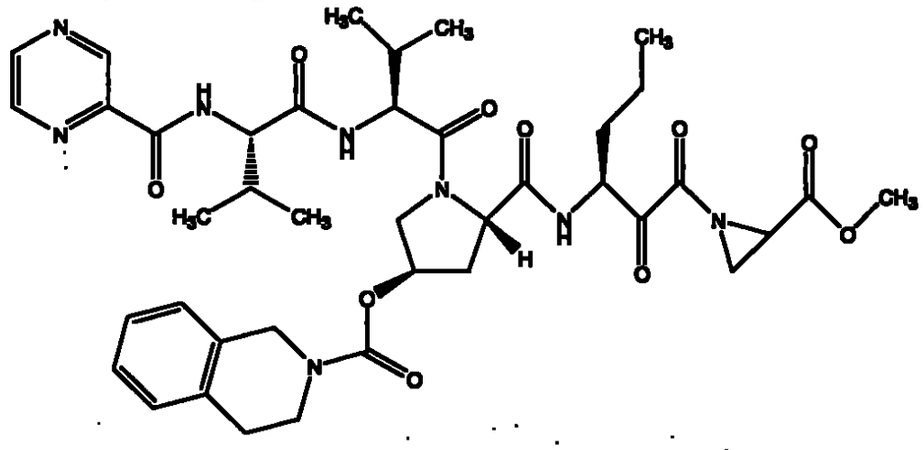
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ej., Hoofnagle et al. (1997) N. Engl. J. Med. 336:347. Actualmente, no hay vacuna disponible para la infección por VHC.

También se hace referencia a WO 01/74768 (igual a US 2003236242; Apoderado: Vertex Pharmaceuticals Inc) publicada el 11 de octubre de 2001, que revela ciertos compuestos de la siguiente fórmula general (R se define en la misma) como inhibidores de la serina proteasa NS3 del virus de la Hepatitis C:



Un compuesto específico revelado en la patente mencionada anteriormente WO 01/74768 posee la siguiente fórmula:



Las Publicaciones de PCT WO 01/77113 que corresponde a la solicitud de patente argentina Acta No. PO10101579; WO 01/081325 que corresponde a la solicitud de patente argentina Acta No. PO10101794; WO 02/08198 que

corresponde a la solicitud de patente argentina Acta No. PO10103435; WO 02/08256 que corresponde a la solicitud de patente argentina Acta No. PO101013434; WO 02/08187 que corresponde a la solicitud de patente argentina Acta No. PO10103451; WO 02/08244 que corresponde a la solicitud de patente argentina Acta No. PO10103450; WO 02/48172 que corresponde a la solicitud de patente argentina Acta No. PO10105721; WO 02/08251; y la solicitud de patente estadounidense pendiente, Acta No. 10/052.388, presentada el 18 de Enero de 2002, que corresponde a la solicitud de patente argentina Acta No. PO30100131, revelan varios tipos de péptidos y/u otros compuestos como inhibidores de la serina proteasa NS-3 del virus de la hepatitis C. Las revelaciones de aquellas solicitudes se incorporan a la presente a modo de referencia a las mismas.

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

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

Existe la necesidad de métodos para modular la actividad de serina proteasas, en especial la serina proteasa NS3/NS4a del VHC, usando los compuestos que se proveen en la presente.

Existe la necesidad de métodos para modular el procesamiento del polipéptido de VHC usando los compuestos que se proveen en la presente.

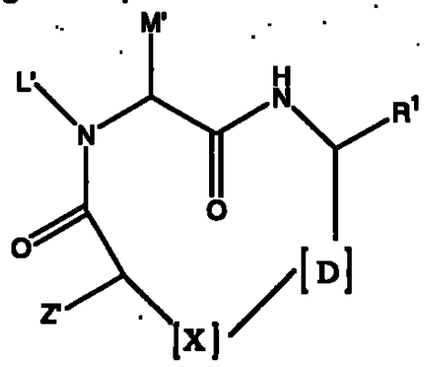
Síntesis de la Invención

En sus muchas realizaciones, la presente invención provee una clase novedosa de inhibidores de la proteasa de VHC, composiciones farmacéuticas que contienen uno o más de los compuestos, métodos para preparar formulaciones farmacéuticas que comprenden uno o más de dichos compuestos, y métodos para el tratamiento y prevención de VHC o el alivio de los síntomas de

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la hepatitis C usando uno o más de dichos compuestos o una o más de dichas formulaciones. También se proveen métodos para modular la interacción de un polipéptido de VHC con la proteasa del VHC. Entre los compuestos que se proveen en la presente, se prefieren los compuestos que inhiben la actividad de la serina proteasa NS3/NS4a del VHC. La presente invención revela compuestos que poseen la estructura general que se muestra en la Fórmula estructural 1:



Fórmula 1

o sales aceptables para uso farmacéutico o solvatos de dichos compuestos, en la cual:

(1) R^1 es $-C(O)R^5$ o $-B(OR)_2$;

(2) R^5 es H, -OH, $-OR^8$, $-NR^9R^{10}$, $-C(O)OR^8$, $-C(O)NR^9R^{10}$, $-CF_3$, $-C_2F_5$, $-C_3F_7$, $-CF_2R^8$, $-R^8$, $-C(O)R^7$ o $NR^7SO_2R^8$;

(3) R^7 es H, -OH, $-OR^8$ o $-CHR^9R^{10}$;

(4) R^6, R^8, R^9 y R^{10} pueden ser iguales o diferentes, seleccionándose cada uno independientemente del grupo que consiste en H, alquilo, alquenilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, arilalquilo, heteroarilalquilo, R^{14},

$-CH(R^{1'})CH(R^{1'})C(O)OR^{11}$,

$-[CH(R^{1'})]_pC(O)OR^{11}$,

$-[CH(R^{1'})]_pC(O)NR^{12}R^{13}$,

$-[CH(R^{1'})]_pS(O_2)R^{11}$,

$-[CH(R^{1'})]_pC(O)R^{11}$,

$-[CH(R^{1'})]_pS(O_2)NR^{12}R^{13}$,

$-CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$,

$-CH(R^{1'})CH(R^{1'})C(O)NR^{12}R^{13}$,

$-CH(R^{1'})CH(R^{1'})S(O_2)R^{11}$,

$-CH(R^{1'})CH(R^{1'})S(O_2)NR^{12}R^{13}$,

$-CH(R^{1'})CH(R^{1'})C(O)R^{11}$,

$-[CH(R^{1'})]_pCH(OH)R^{11}$,

$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$,

$-C(O)N(H)CH(R^{2'})C(O)OR^{11}$,

$-C(O)N(H)CH(R^{2'})C(O)R^{11}$,

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

$-CH(R^{1'})C(O)N(H)CH(R^{2'})R'$,

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

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

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

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

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

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

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

donde $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, R^{12} y R^{13} pueden ser iguales o diferentes, seleccionándose cada uno independientemente del grupo conformado por: H, halógeno, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, alcoxi, ariloxi, alquenilo, alquinilo, alquil-arilo, alquil-heteroarilo, heterocicloalquilo, aril-alquilo y heteroaralquilo;

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363

o R^{12} y R^{13} están unidos de manera que la combinación sea cicloalquilo, heterocicloalquilo, arilo o heteroarilo;

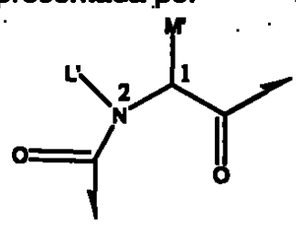
R^{14} se encuentra presente o no y si se encuentra presente se selecciona del grupo conformado por: H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, alquil-arilo, allilo, alquil-heteroarilo, alcoxi, aril-alquilo, alquenilo, alquinilo y heteroaralquilo;

(5) R y R' se encuentran presentes o no y si se encuentran presentes pueden ser iguales o diferentes, seleccionándose cada uno independientemente del grupo conformado por: H, OH, alquilo C_1-C_{10}, alquenilo C_2-C_{10}, cicloalquilo C_3-C_8, heterocicloalquilo C_3-C_8, alcoxi, ariloxi, alquiltio, ariltio, alquilamino, arilamino, amino, amido, ariltioamino, arilcarbonilamino, arilaminocarboxi, alquilaminocarboxi, heteroalquilo, alquenilo, alquinilo, (aril)alquilo, heteroarilalquilo, éster, ácido carboxílico, carbamato, urea, cetona, aldehído, ciano, nitro, halógeno, (cicloalquil)alquilo, arilo, heteroarilo, (alquil)arilo, alquilheteroarilo, alquil-heterociclilo y (heterocicloalquil)alquilo, donde cicloalquilo está compuesto por tres a ocho átomos de carbono, y de cero a 6 átomos de oxígeno, nitrógeno, azufre o fósforo y dicho alquilo es de uno a seis átomos de carbono;

(6) L' es H, OH, alquilo, heteroalquilo, arilo, heteroarilo, cicloalquilo, o heterociclilo;

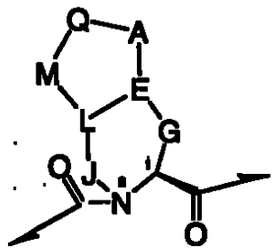
(7) M' es H, alquilo, heteroalquilo, arilo, heteroarilo, cicloalquilo, arilalquilo, heterociclilo o una cadena lateral de aminoácidos;

o L' y M' se unen para formar una estructura anular de manera que la parte de la Fórmula estructural 1 representada por



(los números 1 y 2 agregados para mostrar la ubicación de un cierto átomo de carbono y de cierto átomo de nitrógeno respectivamente)

se representa mediante la Fórmula estructural 2:



Fórmula 2

donde en la Fórmula 2:

E está presente o ausente y si se encuentra presente es C, CH, N o C(R);

J está presente o ausente, y cuando J se encuentra presente, J es $(CH_2)_p$, $(CHR\text{-}CHR')_p$, $(CHR)_p$, $(CRR')_p$, $S(O_2)$, N(H), N(R) o O; cuando J está ausente y G se encuentra presente, L se une directamente al átomo de nitrógeno marcado como posición 2;

p es un número de 0 a 6;

L está presente o ausente, y cuando L se encuentra presente, L es C(H) o C(R); cuando L está ausente, M está presente o ausente; si M se encuentra presente estando L ausente, entonces M se une está directa e independientemente a E, y J se une directa e independientemente a E;

G está presente o ausente, y cuando G se encuentra presente, G es $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$ o $(CRR')_p$; cuando G está ausente, J se encuentra presente y E se une directamente al átomo de carbono marcado como posición 1;

Q está presente o ausente, y cuando Q se encuentra presente, Q es NR, PR, (CR=CR), $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, $(CHR\text{-}CHR')_p$, O, NR, S, SO, o SO_2; cuando Q se encuentra ausente, M está (i) ya sea directamente unido a A o (ii) a un sustituyente independiente sobre L, seleccionándose dicho sustituyente independiente de -OR, -CH(R)(R'), $S(O)_{0\text{-}2}R$ o –NRR' o (iii) ausente; cuando

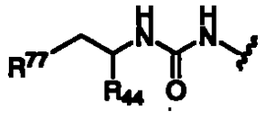
ambos Q y M están ausentes, A está ya sea unido directamente a L, o A es un sustituyente independiente sobre E, seleccionándose dicho sustituyente independiente de -OR, -CH(R)(R'), $S(O)_{0-2}R$ o –NRR' o A se encuentra ausente;

A está presente o ausente y si se encuentra presente A es O, O(R), $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, N(R), NRR', S, $S(O_2)$, -OR, CH(R)(R') o NRR'; o A está unido a M para formar un puente cicloalquilo, alifático o heterocíclico;

M está presente o ausente, y cuando M se encuentra presente, M es halógeno, O, OR, N(R), S, $S(O_2)$, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$, o $(CRR')_p$; o M está unido a A para formar un puente cicloalquilo, alifático o heterocicloalquilo;

(8) Z' está representado por cualquiera de (i), (ii), (iii), (iv) o (v) que se muestran a continuación:

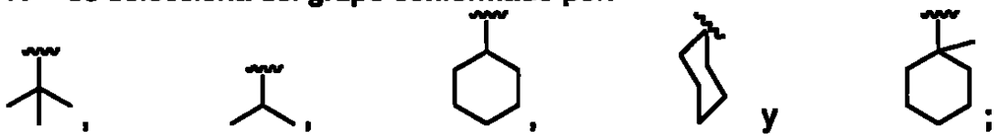
(i)



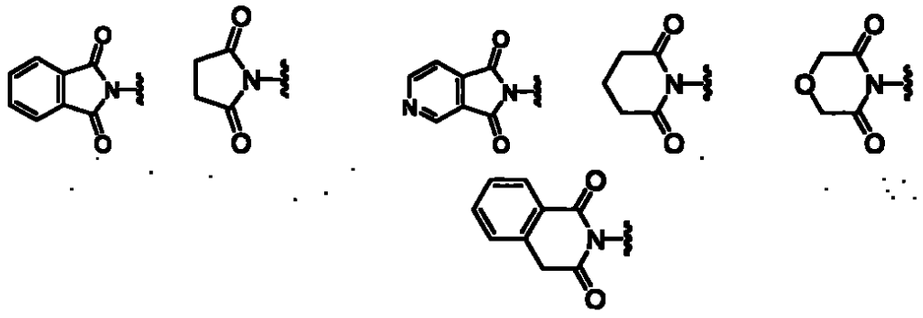
Fórmula A'

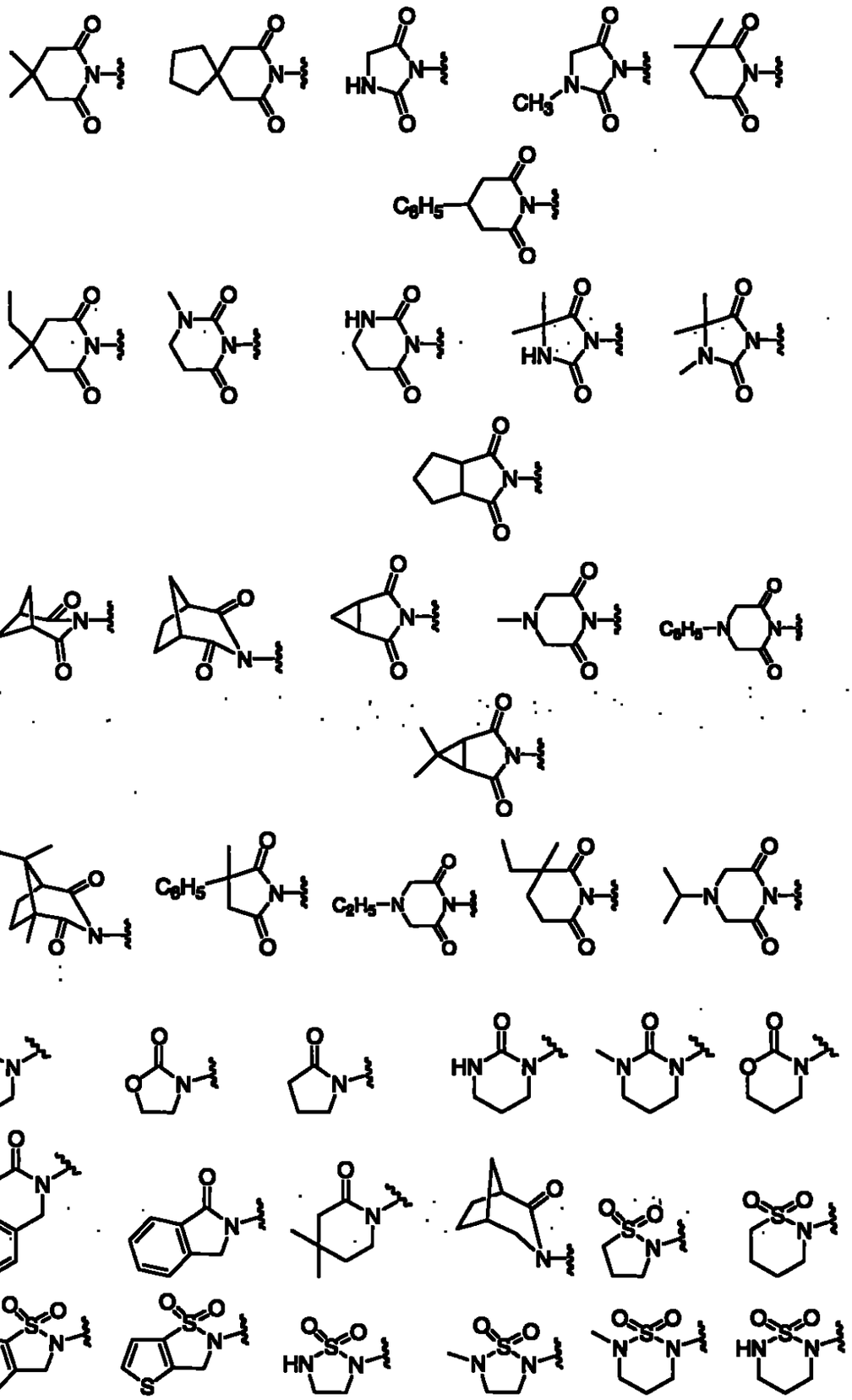
en la cual:

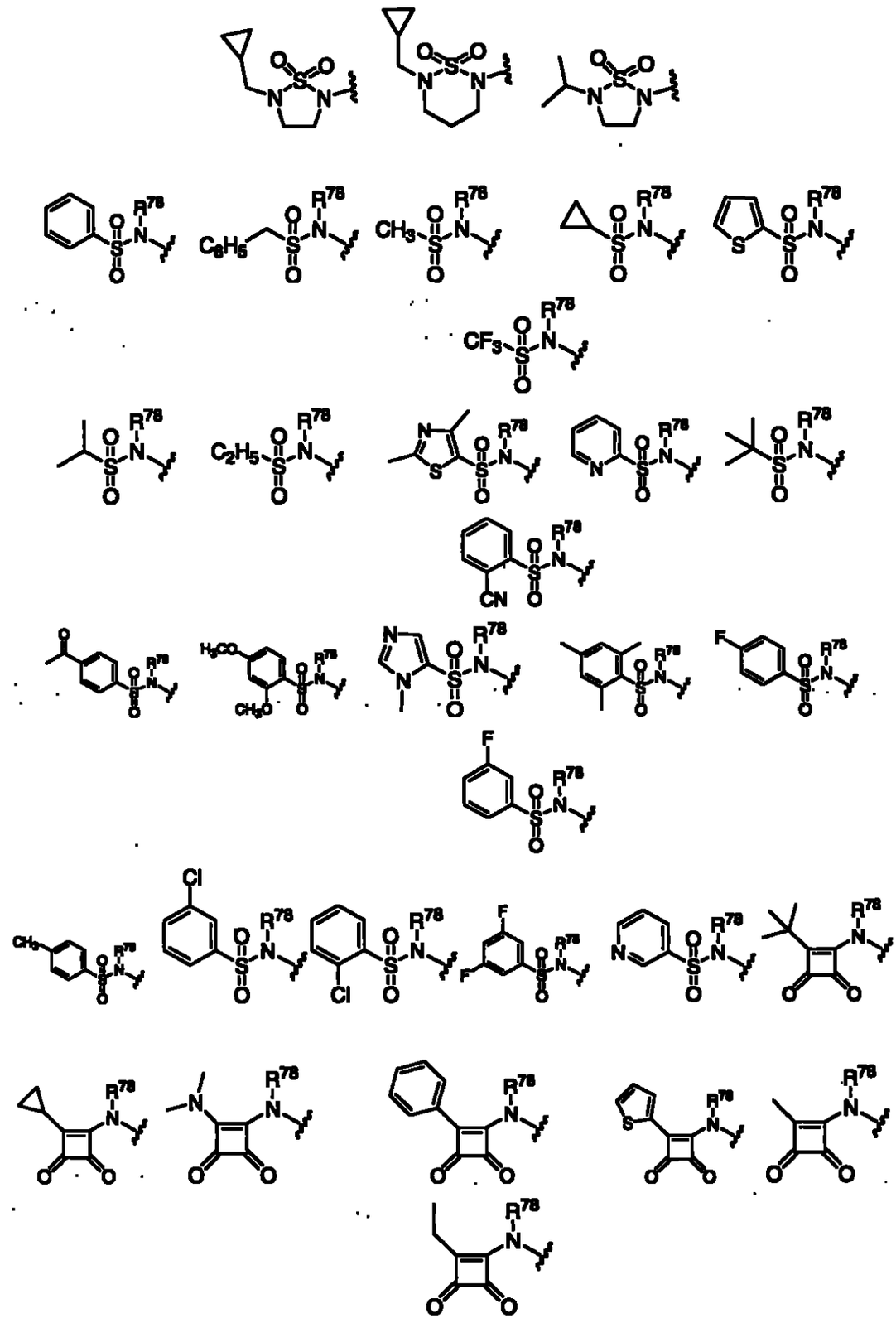
R^{44} se selecciona del grupo conformado por:

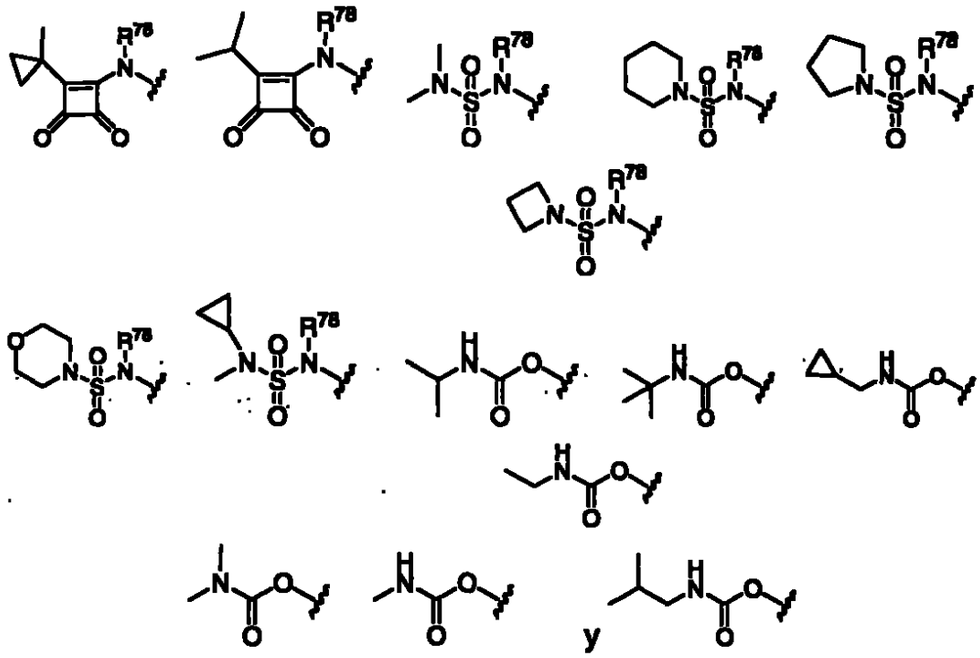


y R^{77} se selecciona del grupo conformado por:



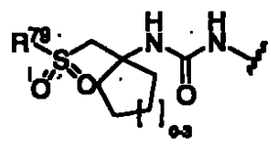






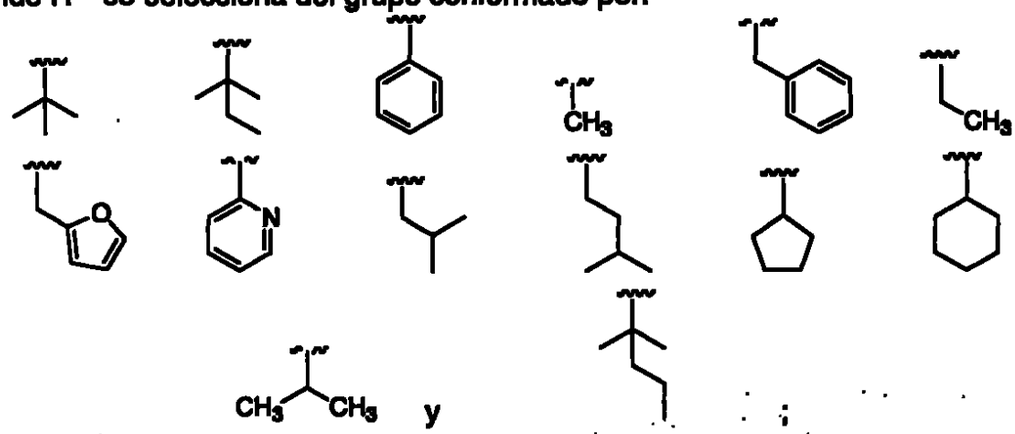
donde R^{78} se selecciona de metilo, etilo, isopropilo, ter-butilo y fenilo;

(ii)

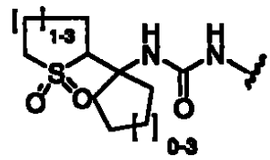


Formula B

donde R^{79} se selecciona del grupo conformado por:



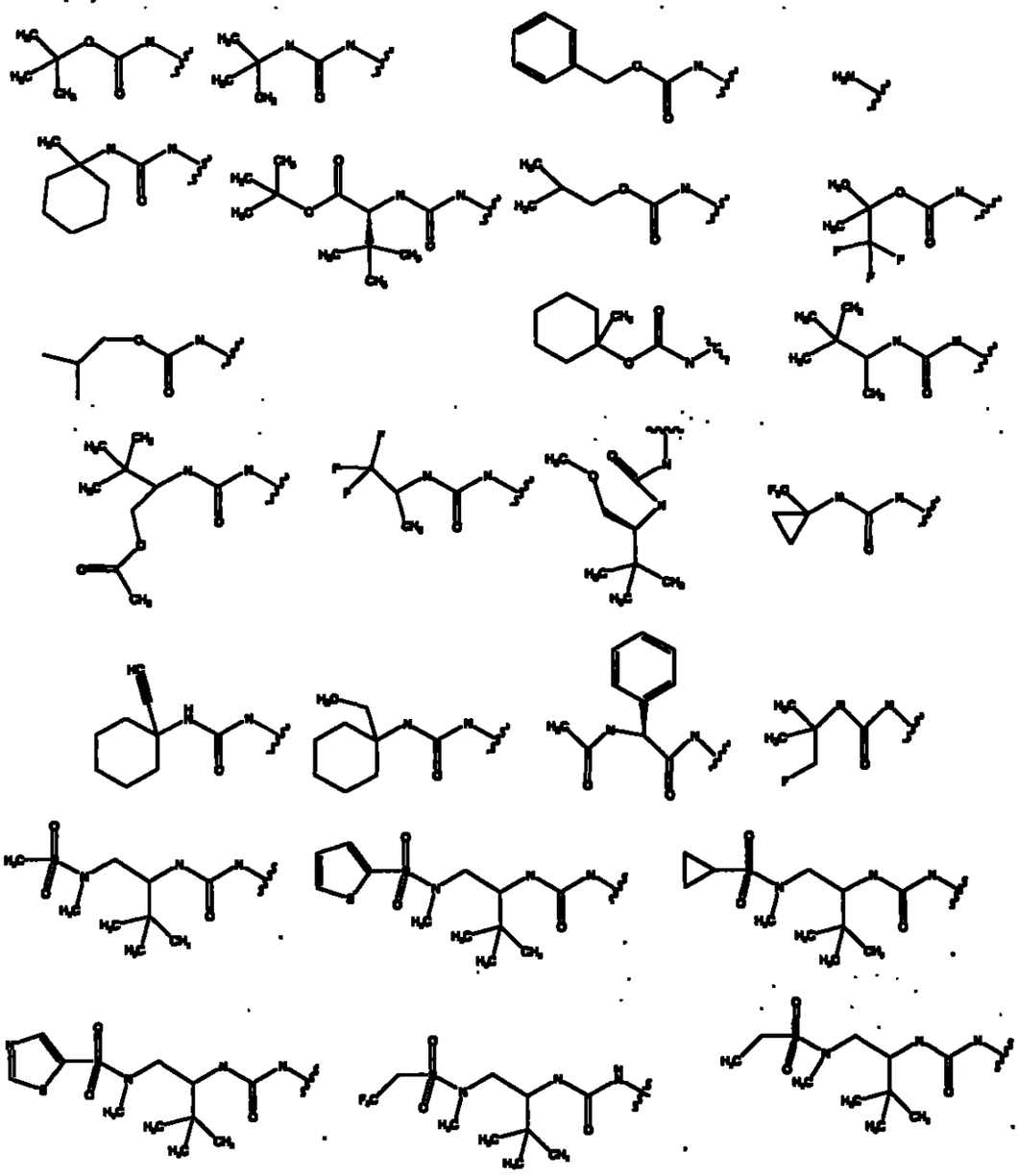
(iii)

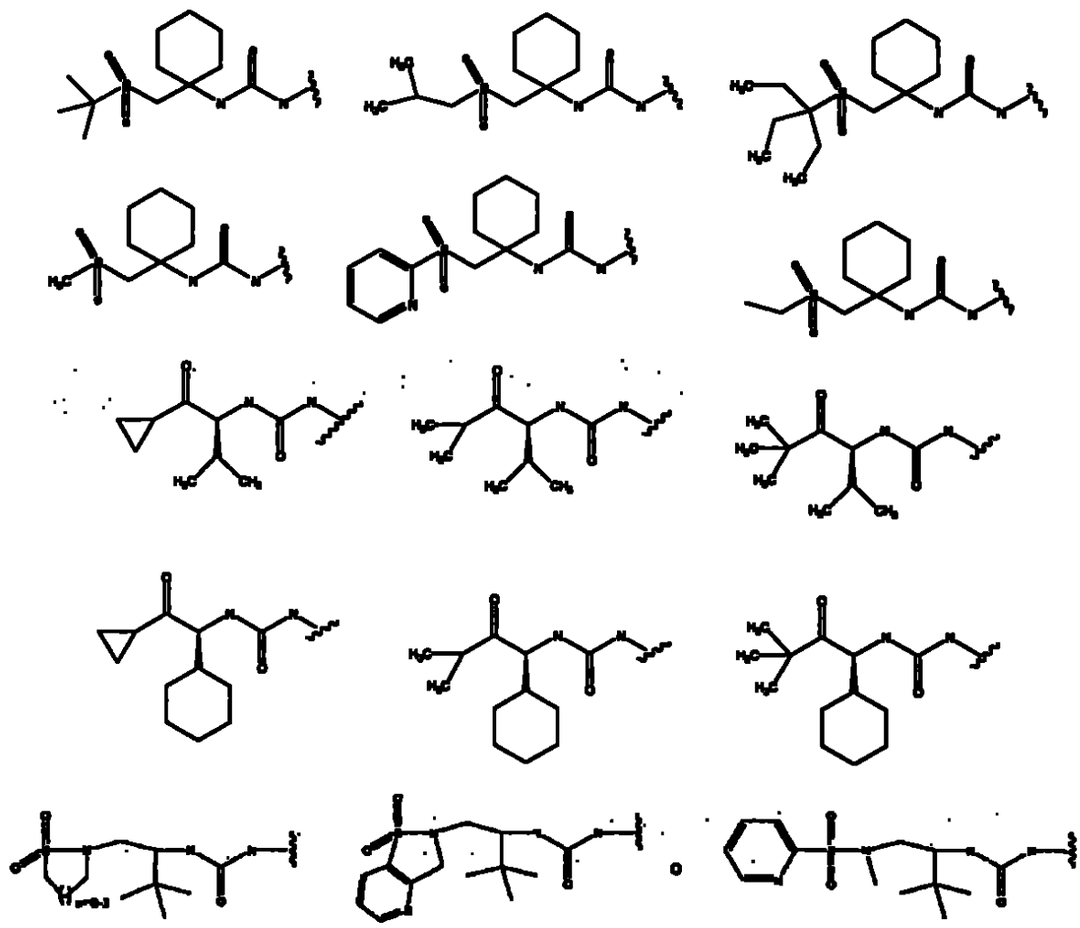


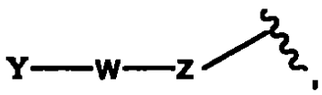
Fórmula C

en la cual el anillo de sulfona está sustituido opcionalmente con alquilo y cicloalquilo;

(iv) el resto:



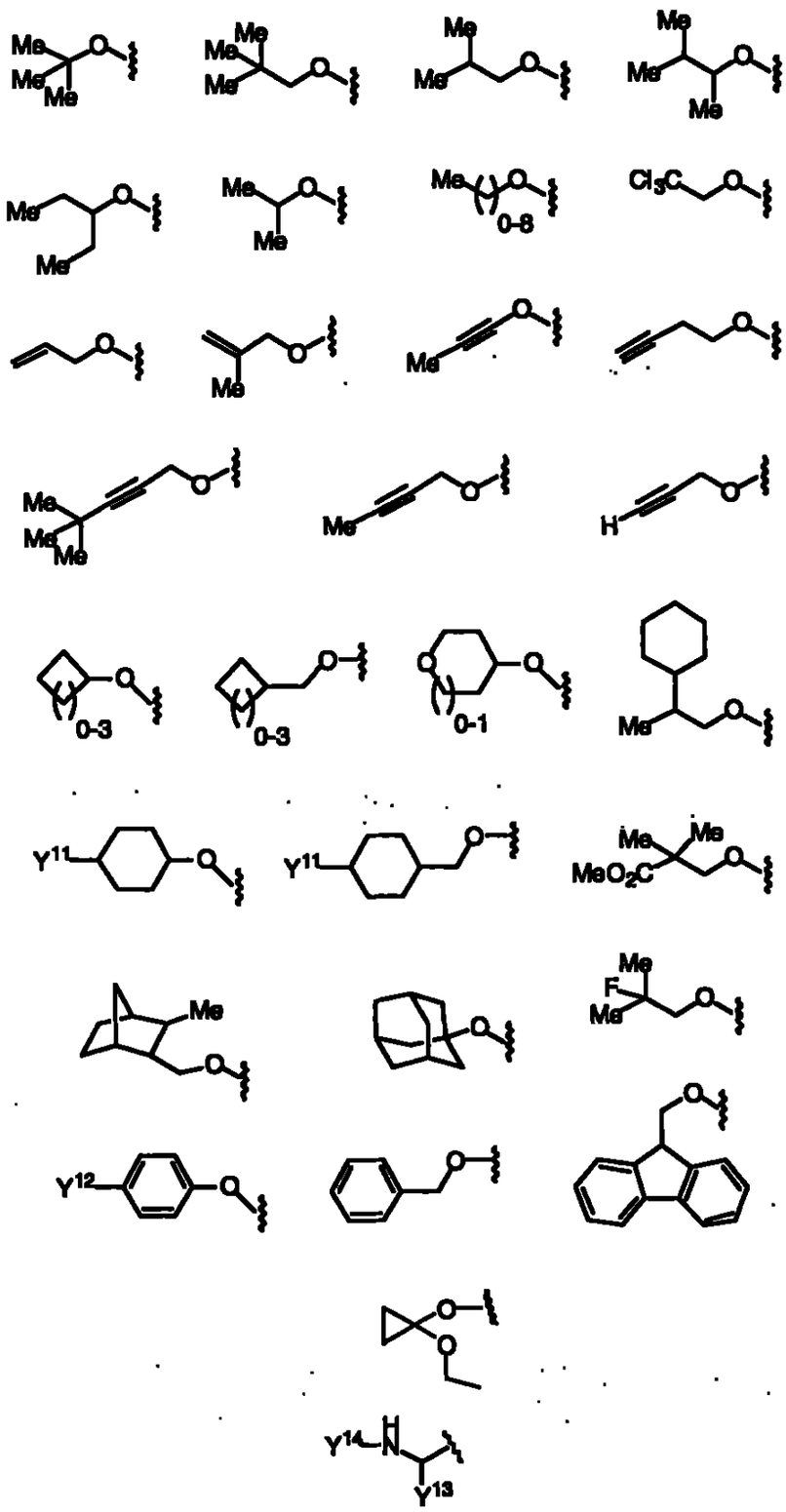


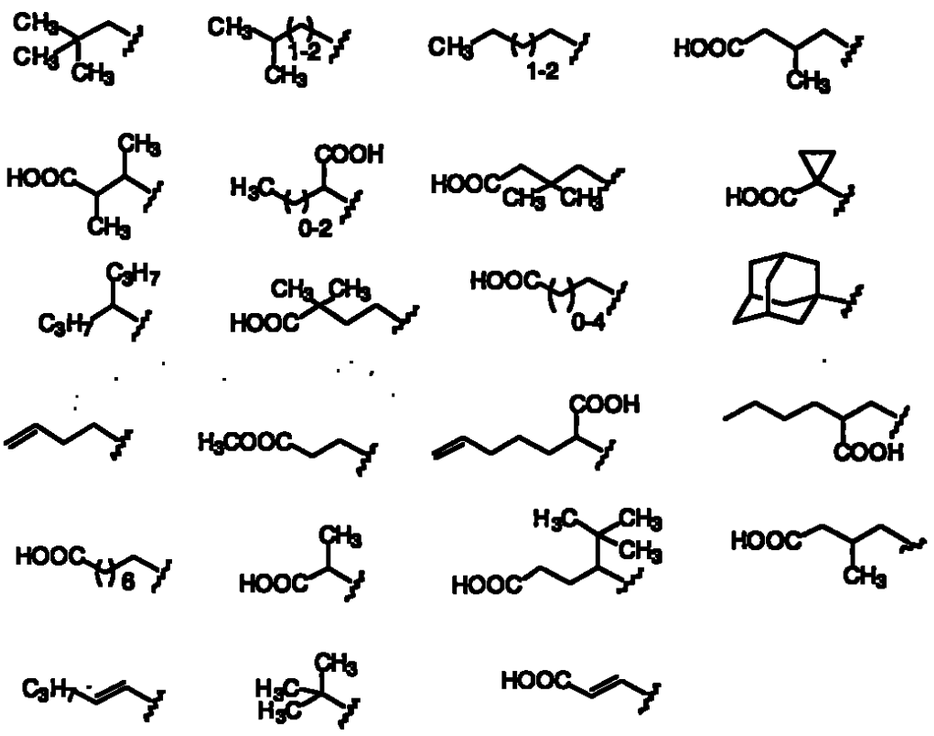
(v) el resto:  ,

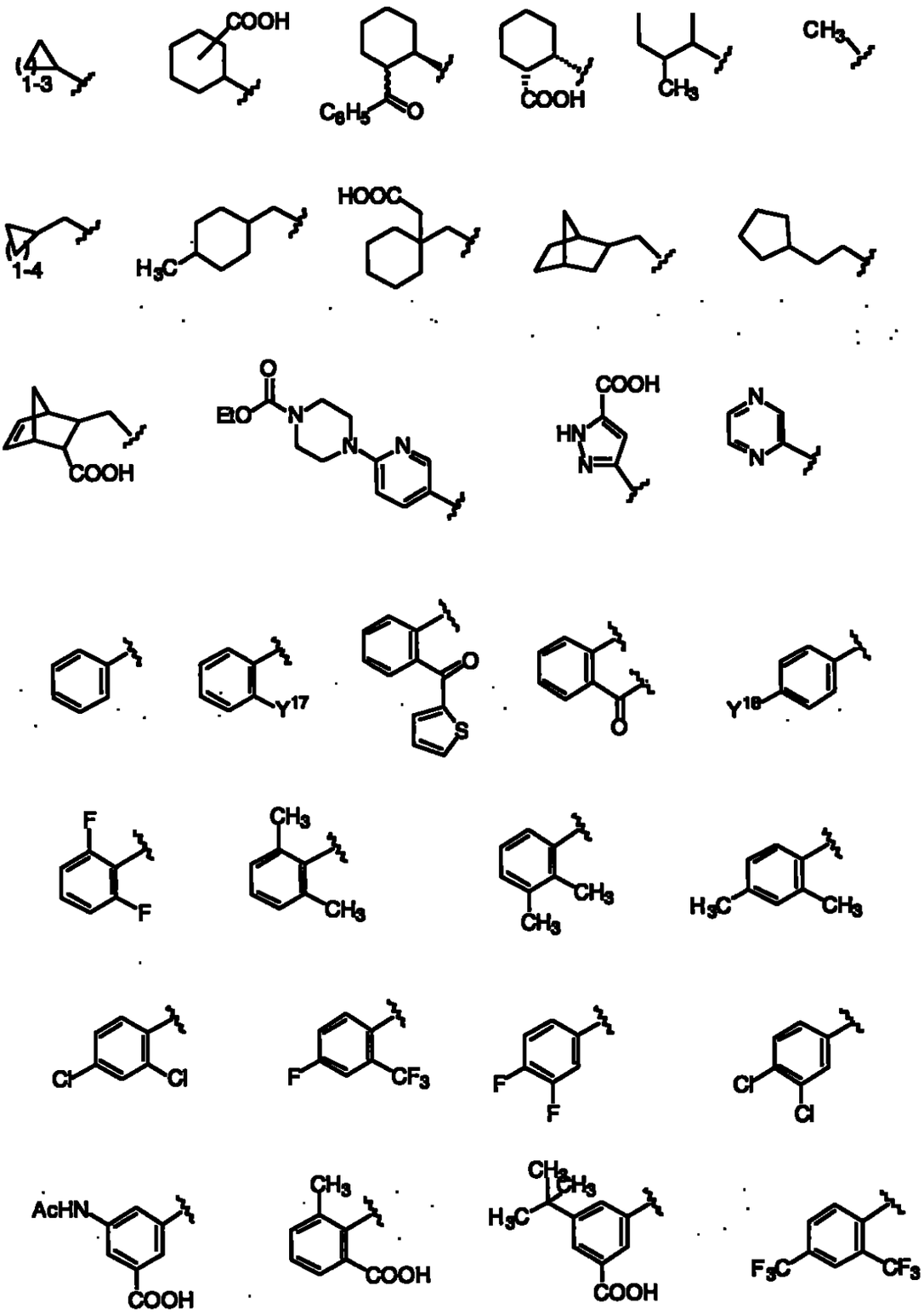
en el cual W es –C(=O)- o -S(O_2)- ;

Z es O o N;

e Y se selecciona del grupo conformado por:

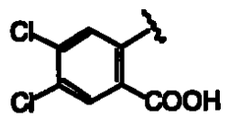

Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
0-8
Cl3C
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
H
0-3
0-3
0-1
Me
Y11
Y11
Me
Me
MeO2C
Me
Me
F
Me
Y12
O
Y14
N
Y13

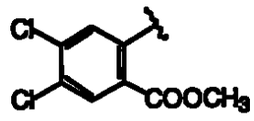

CH3
CH3
CH3
1-2
HOOC
COOH
0-2
C3H7
HOOC
0-4
H3COOC
6
OTHP
OH
Y15
Y16

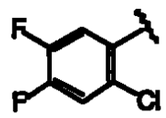

(4
1-3
COOH
C_6H_5
O
COOH
CH_3
CH_3
1-4
H_3C
HOOC
COOH
EtO
N
N
N
COOH
HN
N
N
N
Y^{17}
O
S
O
Y^{18}
F
F
CH_3
CH_3
CH_3
CH_3
H_3C
CH_3
Cl
Cl
F
CF_3
F
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CH_3
CH_3
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COOH
F_3C
CF_3

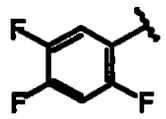
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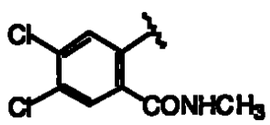
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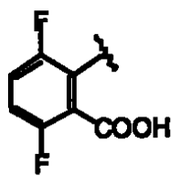

Cl
Cl
COOH

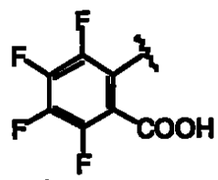

Cl
Cl
COOCH3

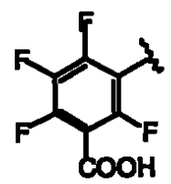

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F
Cl

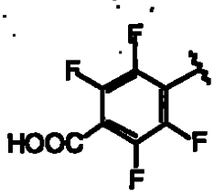

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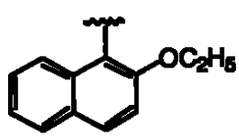

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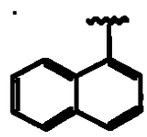

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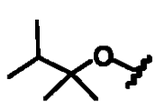

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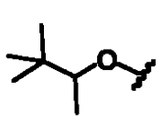

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COOH

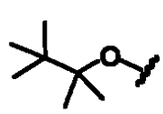

F
HOOC
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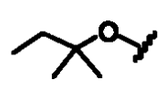

OC2H5

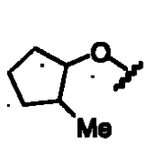


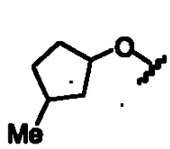

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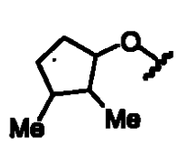

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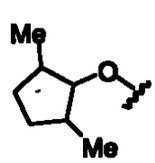

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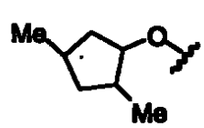

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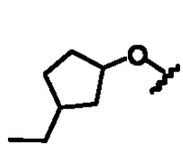

O
Me

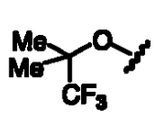

O
Me

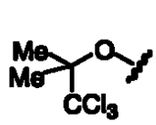

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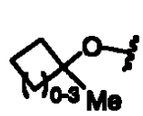

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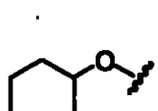

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Me

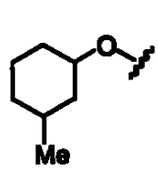

O

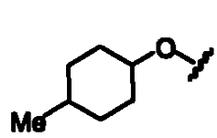

Me
Me
O
CF3

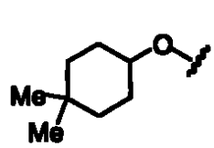

Me
Me
O
CCl3

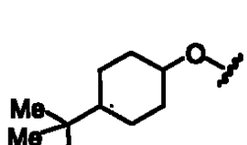

O
(CH2)0-3 Me

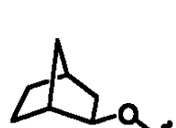

O
Me

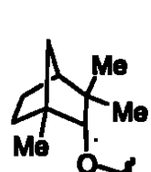

O
Me

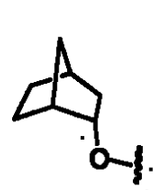

O
Me

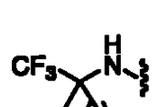

O
Me
Me

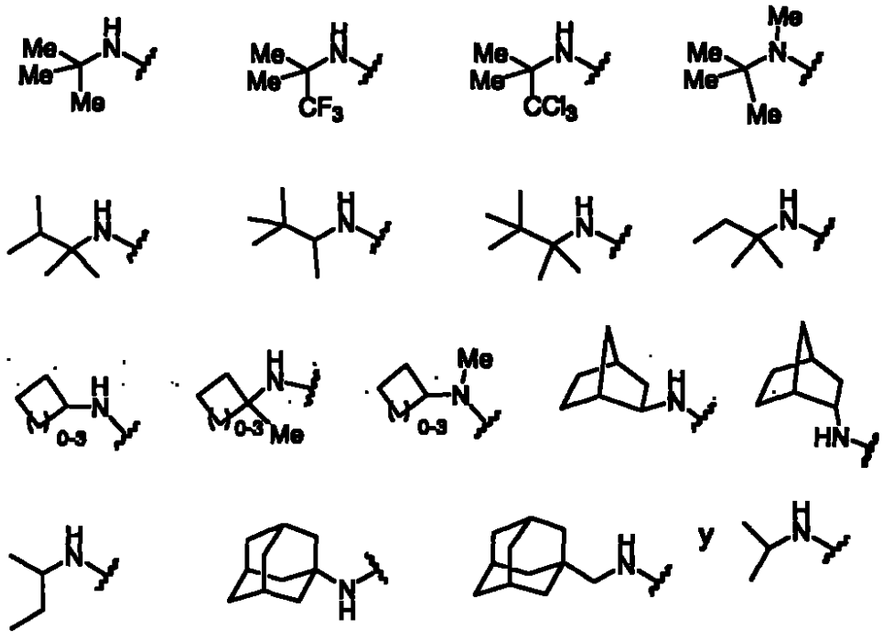

O
Me
Me
Me


O


Me
Me
Me
O


O


CF3
H
N
n=1-5

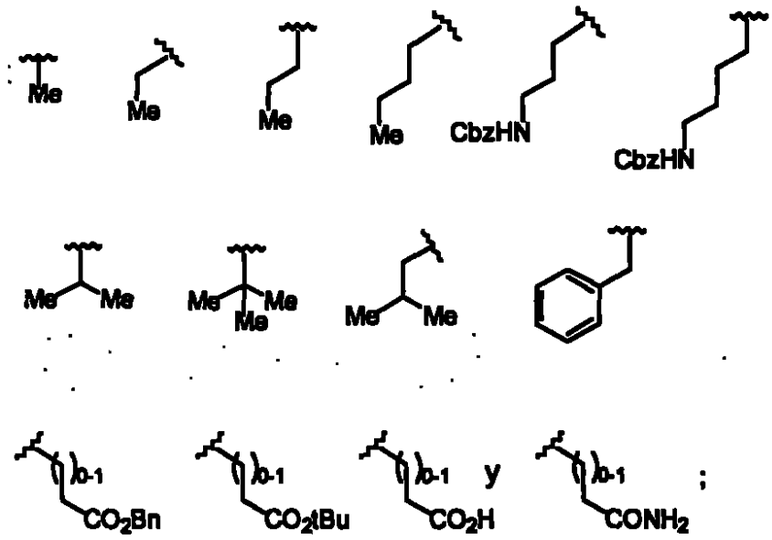


donde:

Y^{11} se selecciona del grupo conformado por: H, -C(O)OH, -C(O)OEt, -OMe, -Ph, -OPh, -NHMe, -NHAc, -NHPh, $-CH(Me)_2$, 1-triazolilo, 1-imidazolilo y $-NHCH_2COOH$;

Y^{12} se selecciona del grupo conformado por: H, -C(O)OH, -C(O)OMe, -OMe, F, Cl y Br;

Y^{13} se selecciona del grupo que consiste en los siguientes restos:



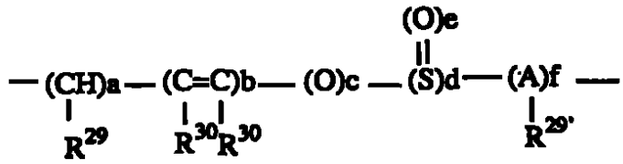
Y^{14} es $MeS(O_2)$-, -Ac, -Boc, -iBoc, -Cbz, o -Alloc;

Y^{15} e Y^{16} pueden ser iguales o diferentes y se seleccionan independientemente del grupo conformado por: alquilo, arilo, heteroalquilo y heteroarilo;

Y^{17} es $-CF_3$, $-NO_2$, $-C(O)NH_2$, -OH, $-C(O)OCH_3$, $-OCH_3$, $-OC_6H_5$, $-C_6H_5$, $-C(O)C_6H_5$, $-NH_2$ o $-C(O)OH$; e

Y^{18} es $-C(O)OCH_3$, $-NO_2$, $-N(CH_3)_2$, F, $-OCH_3$, $-C(H_2)C(O)OH$, $-C(O)OH$, $-S(O_2)NH_2$ o $-N(H)C(O)CH_3$;

(9) X está representado por la Fórmula estructural 4:



Fórmula 4

donde en la Fórmula 4, a es 2, 3, 4, 5, 6, 7, 8 o 9;

b, c, d, e y f pueden ser iguales o diferentes, siendo cada una independientemente 0, 1, 2, 3, 4 o 5;

A es C, N, S u O;

R^{29} y $R^{29'}$ se encuentran independientemente presentes o ausentes y si se encuentran presentes pueden ser iguales o diferentes, siendo cada uno, uno o dos sustituyentes seleccionados del grupo conformado por: H, halo, alquilo, arilo, cicloalquilo, cicloalquilamino, cicloalquilaminocarbonilo, ciano, hidroxi, alcoxi, alquiltio, amino, -NH(alquilo), -NH(cicloalquilo), $-N(alquilo)_2$, carboxilo, –C(O)O-alquilo, heteroarilo, aralquilo, alquilarilo, aralquenilo, heteroaralquilo, alquilheteroarilo, heteroaralquenilo, hidroxialquilo, ariloxi, aralcoxi, acilo, aroílo, nitro, arilоxicarbonilo, aralcoxicarbonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquilsulfinilo, arilsulfinilo, heteroarilsulfinilo, ariltio, heteroariltio, aralquiltio, heteroaralquiltio, cicloalquenilo, heterociclilo, heterociclenilo, Y_1Y_2N-alquilo-, $Y_1Y_2NC(O)$- e $Y_1Y_2NSO_2$-, en los cuales Y_1 e Y_2 pueden ser iguales o

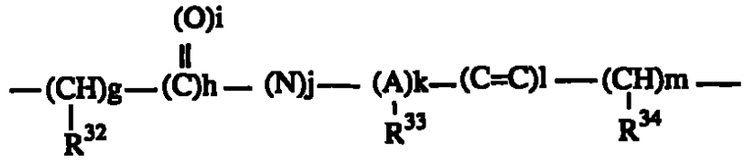
diferentes y se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, arilo y aralquilo;

o

R^{29} y $R^{29'}$ están unidos de manera que la combinación es una cadena alifática o heteroalifática de 0 a 6 carbonos;

R^{30} está presente o ausente y si se encuentra presente es uno o dos sustituyentes seleccionados independientemente del grupo conformado por: H, alquilo, arilo, heteroarilo y cicloalquilo;

(10) D en la Fórmula 1 está representado por la Fórmula estructural 5:



Fórmula 5

donde en la Fórmula 5, R^{32}, R^{33} y R^{34} se encuentran presentes o ausentes y si se encuentran presentes son uno o dos sustituyentes seleccionados independientemente del grupo conformado por: H, halo, alquilo, arilo, cicloalquilo, cicloalquilamino, espiroalquilo, cicloalquilaminocarbonilo, ciano, hidroxi, alcoxi, alquiltio, amino, -NH(alquilo), -NH(cicloalquilo), -N(alquilo)$_2$, carboxilo, –C(O)O-alquilo, heteroarilo, aralquilo, alquilarilo, aralquenilo, heteroaralquilo, alquilheteroarilo, heteroaralquenilo, hidroxialquilo, ariloxi, aralcoxi, acilo, aroílo, nitro, ariloxicarbonilo, aralcoxicarbonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquilsulfinilo, arilsulfinilo, heteroarilsulfinilo, ariltio, heteroariltio, aralquiltio, heteroaralquiltio, cicloalquenilo, heterociclilo, heterociclenilo, Y_1Y_2N-alquilo-, $Y_1Y_2NC(O)$- e $Y_1Y_2NSO_2$-, en los cuales Y_1 e Y_2 pueden ser iguales o diferentes y se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, arilo y aralquilo;

o

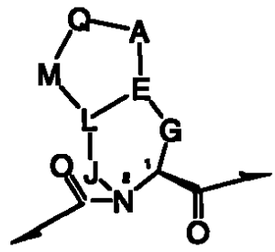
R^{32} y R^{34} están unidos de manera que la combinación forma una porción de un grupo cicloalquilo;

g es 1, 2, 3, 4, 5, 6, 7, 8 o 9;

h, I, J, k, l y m pueden ser iguales o diferentes, siendo cada uno independientemente 0, 1, 2, 3, 4 o 5; y

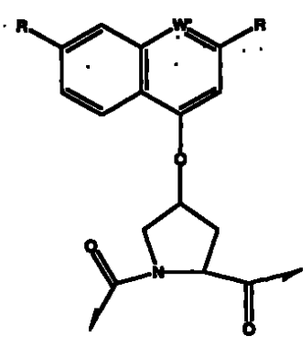
A es C, N, S u O,

(11) siempre que en la Fórmula 1 cuando la Fórmula estructural 2:



Fórmula 2

es



y

W' es CH o N, se aplican ambas exclusiones condicionales siguientes (i) y (ii):

exclusión condicional (i): Z' no es $-NH-R^{36}$, donde R^{36} es H, arilo C_6, arilo C_{10}, heteroarilo, $-C(O)-R^{37}$, $-C(O)-OR^{37}$ o $-C(O)-NHR^{37}$, donde R^{37} es alquilo C_{1-6} o cicloalquilo C_{3-6};

y

exclusión condicional (ii): R^1 no es $-C(O)OH$, una sal aceptable para uso farmacéutico de $-C(O)OH$, un éster de $-C(O)OH$ o $-C(O)NHR^{38}$, en el cual R^{38}

se selecciona del grupo que consiste en alquilo C_{1-8}, cicloalquilo C_{3-8}, arilo C_6, arilo C_{10}, o aralquilo C_{7-16}.

Otra característica de la invención es la de las composiciones farmacéuticas que contienen como componente activo al menos un compuesto de Fórmula I (o sus sales, ésteres, solvatos o isómeros) junto con un vehículo o excipiente aceptable para uso farmacéutico.

La invención también provee métodos para preparar compuestos de Fórmula I, al igual que métodos para el tratamiento de enfermedades tales como, por ejemplo, VHC, SIDA (Síndrome de Inmunodeficiencia Adquirida), y trastornos relacionados. Los métodos para llevar a cabo los tratamientos comprenden administrar a un paciente que padece una o más de las enfermedades anteriores o una o más enfermedades relacionadas una cantidad terapéuticamente efectiva de al menos un compuesto de Fórmula 1, o una composición farmacéutica que comprende al menos un compuesto de Fórmula 1.

También se revela el uso de al menos un compuesto de Fórmula 1 para la fabricación de un medicamento para el tratamiento de VHC, SIDA y trastornos relacionados.

También se revela un método para el tratamiento de un trastorno relacionado con el virus de la hepatitis C, que comprende administrar una cantidad efectiva de uno o más de los compuestos de la invención.

También se revela un método para modular la actividad de la proteasa del virus de la hepatitis C (VHC), que comprende poner en contacto la proteasa del VHC con uno o más compuestos de la invención, al igual que métodos para tratar o prevenir el VHC, o para aliviar uno o más síntomas de la hepatitis C, que comprende administrar una cantidad efectiva de uno o más de los compuestos de la invención. Dicha modulación, tratamiento, prevención o alivio también se puede llevar a cabo con las composiciones o formulaciones farmacéuticas de la

invención. Sin pretender que la teoría sea limitativa, se considera que la proteasa del VHC puede ser la proteasa NS3 o NS4. Los compuestos de la invención pueden inhibir dicha proteasa. También pueden modular el procesamiento del polipéptido del virus de la hepatitis C (VHC).

Descripción de la Invención

Según se empleó anteriormente, y a lo largo de la presente revelación, se entenderá que los siguientes términos, salvo que se indique de otra manera, poseen los siguientes significados:

"Paciente" incluye tanto seres humanos como animales.

"Mamífero" significa seres humanos y otros animales mamíferos.

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

"Alquinilo" significa un grupo alifático hidrocarbonado que contiene al menos un enlace triple carbono-carbono y que puede ser recto o ramificado y que

comprende alrededor de 2 a alrededor de 15 átomos de carbono en la cadena. Los grupos alquinilo preferidos poseen alrededor de 2 a alrededor de 12 átomos de carbono en la cadena; y con mayor preferencia alrededor de 2 a alrededor de 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 la cadena lineal de alquinilo. "Alquinilo inferior" significa alrededor de 2 a alrededor de 6 átomos de carbono en la cadena que puede ser recta o ramificada. 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 estar sustituido con uno o más sustituyentes que pueden ser iguales o diferentes, seleccionándose cada sustituyente independientemente del grupo que consiste en alquilo, arilo y cicloalquilo.

"Alifático" significa e incluye cadenas rectas o ramificadas de átomos de carbono parafínicos, olefínicos o acetilénicos. El grupo alifático puede estar sustituido opcionalmente con uno o más sustituyentes que pueden ser iguales o diferentes, seleccionándose cada sustituyente independientemente del grupo que consiste en H, halo, halógeno, alquilo, arilo, cicloalquilo, cicloalquilamino, alquenilo, heterocíclico, alquinilo, cicloalquilaminocarbonilo, hidroxilo, tio, ciano, hidroxi, alcoxi, alquiltio, amino, -NH(alquilo), -NH(cicloalquilo), -N(alquilo)$_2$, carboxilo, –C(O)O-alquilo, heteroarilo, aralquilo, alquilarilo, aralquenilo, heteroaralquilo, alquilheteroarilo, heteroaralquenilo, heteroalquilo, carbonilo, hidroxialquilo, ariloxi, aralcoxi, acilo, aroílo, nitro, amino, amido, éster, ácido carboxílico, ariloxicarbonilo, aralcoxicarbonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquilsulfinilo, arilsulfinilo, heteroarilsulfinilo, alquiltio, ariltio, heteroariltio, aralquiltio, heteroaralquiltio, cicloalquenilo, heterociclilo, heterociclenilo, carbamato, urea, cetona, aldehído, ciano, sulfonamida, sulfóxido, sulfona, sulfonilurea, sulfonilo, hidrazida, hidroxamato, S(alquil)Y_1Y_2N-alquilo-,

Y_1Y_2N-alquilo-, $Y_1Y_2NC(O)$- y $Y_1Y_2NSO_2$-, en los cuales Y_1 e Y_2 pueden ser iguales o diferentes y se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, arilo y aralquilo.

"Heteroalifático" significa un grupo de todas maneras alifático que contiene al menos un heteroátomo (tal como oxígeno, nitrógeno o azufre). El término heteroalifático incluye heteroalifático sustituido.

"Arilo" significa un sistema anular aromático monocíclico o multicíclico que comprende de alrededor de 6 a alrededor de 14 átomos de carbono, con preferencia de alrededor de 6 a alrededor de 10 átomos de carbono. El grupo arilo se puede sustituir opcionalmente con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son según se definió en la presente. Ejemplos no limitativos de grupos arilo adecuados incluyen fenilo y naftilo.

"Heteroalquilo" significa un alquilo según se definió anteriormente, en el cual uno o más átomos de hidrógeno están sustituidos con un heteroátomo seleccionado de N, S u O.

"Heteroarilo" significa un sistema anular aromático monocíclico o multicíclico que comprende alrededor de 5 a alrededor de 14 átomos en el anillo, con preferencia de alrededor de 5 a alrededor de 10 átomos en el anillo, en el cual uno o más de los átomos del anillo es un elemento que no es carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o en combinación. Los heteroarilos preferidos contienen de alrededor de 5 a alrededor de 6 átomos en el anillo. El "heteroarilo" puede estar sustituido opcionalmente con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son según se definió en la presente. El prefijo aza, oxa o tia antes de la denominación de la raíz del heteroarilo significa que al menos un átomo de nitrógeno, oxígeno o azufre respectivamente, se encuentra presente como un átomo del anillo. Un átomo de

nitrógeno de un heteroarilo puede estar opcionalmente oxidado al N-óxido correspondiente. Ejemplos no limitativos de heteroarilos adecuados incluyen piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, piridona (incluyendo piridonas N-sustituidas), isoxazolilo, isotiazolilo, oxazolilo, tiazolilo, pirazolilo, furazanilo, pirrolilo, pirazolilo, triazolilo, 1,2,4-tiadiazolilo, pirazinilo, piridazinilo, quinoxalinilo, ftalazinilo, oxindolilo, imidazo[1,2-a]piridinilo, imidazo[2,1-b]tiazolilo, benzofurazanilo, indolilo, azaindolilo, benzoimidazolilo, benzotienilo, quinilinilo, imidazolilo, tienopiridilo, quinazolinilo, tienopirimidilo, pirrolopiridilo, imidazopiridilo, isoquinilinilo, benzoazaindolilo, 1,2,4-triazinilo, benzotiazolilo y similares. El término "heteroarilo" también se refiere a restos heteroarilo parcialmente saturados, por ejemplo, tetrahidroisoquinolilo, tetrahidroquinolilo y similares.

"Aralquilo" o "arilalquilo" significa un grupo aril-alquilo- en el cual el arilo y el alquilo son según se describieron anteriormente. Los aralquilos preferidos comprenden un grupo alquilo inferior. Ejemplos no limitativos de grupos aralquilo adecuados incluyen bencilo, 2-fenetilo y naftalenilmetilo. El enlace al resto progenitor es a través del alquilo.

"Alquilarilo" significa un grupo alquil-arilo- en el cual el alquilo y arilo son según se describió anteriormente. Los alquilarilos preferidos comprenden un grupo alquilo inferior. Ejemplo no limitativo de un grupo alquilarilo adecuado es tolilo. El enlace al resto progenitor es a través del arilo.

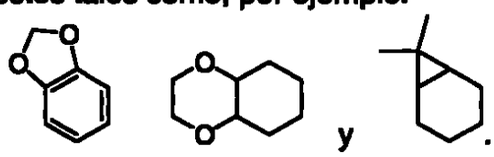
"Cicloalquilo" significa un sistema anular no aromático monocíclico o multicíclico que comprende de alrededor de 3 a alrededor de 10 átomos de carbono, con preferencia de alrededor de 5 a alrededor de 10 átomos de carbono. Los anillos cicloalquilo preferidos contienen de alrededor de 5 a alrededor de 7 átomos anulares. El cicloalquilo puede estar sustituido opcionalmente con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son según se definió anteriormente. Ejemplos no limitativos de cicloalquilos

357
389

monocíclicos adecuados incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo y similares. Ejemplos no limitativos de cicloalquilos multicíclicos adecuados incluyen 1-decalina, norbornilo, adamantilo y similares, al igual que especies saturadas tales como, por ejemplo, indanilo, tetrahidronaftilo y similares.

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

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



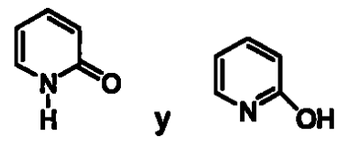
"Heterociclilo" o "heterocicloalquilo" o "heterocíclico" significa un sistema anular no aromático monocíclico o multicíclico saturado que comprende de alrededor de 3 a alrededor de 10 átomos en el anillo, con preferencia alrededor de 5 a alrededor de 10 átomos en el anillo, en el cual uno o más de los átomos del sistema anular es un elemento que no es carbono, por ejemplo nitrógeno, oxígeno, fósforo o azufre, solo o en combinación. No hay presentes átomos adyacentes de oxígeno y/o azufre en el sistema anular. Heterociclilos preferidos contienen alrededor de 5 a alrededor de 6 átomos en el anillo. El prefijo aza, oxa o tia antes del nombre de la raíz del heterociclilo significa que al menos un átomo de nitrógeno, oxígeno o azufre respectivamente se encuentra presente como un átomo del anillo. Cualquier –NH en un anillo heterociclilo puede existir protegido tal como, por ejemplo, un grupo -N(Boc), -N(CBz), -N(Tos) y similares; dichas protecciones también son consideradas parte de la presente invención. El heterociclilo se puede sustituir opcionalmente con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son según se definió en la presente. El átomo de nitrógeno o azufre del heterociclilo se puede oxidar opcionalmente al N-óxido, S-óxido o S,S-dióxido correspondientes. Ejemplos no limitativos de anillos monocíclicos heterociclilo incluyen piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,4-dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, lactama, lactona y similares.

Se debe observar que en sistemas anulares que contienen heteroátomos de la presente invención no hay grupos hidroxilo en los átomos de carbono adyacentes a N, O o S, al igual que no hay grupos N o S en el átomo de carbono adyacente a otro heteroátomo. Por lo tanto, por ejemplo, en el anillo:



no hay -OHs unidos directamente a los carbonos marcados 2 y 5.

También se debe observar que las formas tautoméricas tales como, por ejemplo, los restos:



se consideran equivalentes en ciertas realizaciones de la presente invención.

"Alquinilalquilo" significa un grupo alquinil-alquilo- en el cual el alquinilo y al alquilo son según se describió anteriormente. Los alquinilalquilos preferidos contienen un alquinilo inferior y un grupo alquilo inferior. El enlace al resto progenitor es a través del alquilo. Ejemplos no limitativos de grupos adecuados alquinilalquilo incluyen propargilmetilo.

"Heteroaralquilo" significa un grupo heteroaril-alquilo- en el cual el heteroarilo y alquilo son según se describieron anteriormente. Los heteroaralquilos preferidos contienen un grupo alquilo inferior. Ejemplos no limitativos de grupos aralquilo adecuados incluyen piridilmetilo, y quinolin-3-ilmetilo. El enlace al resto progenitor es a través del alquilo.

"Hidroxialquilo" significa un grupo HO-alquilo- en el cual el alquilo es según se definió anteriormente. Hidroxialquilos preferidos contienen alquilo inferior. 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 los cuales los diversos grupos son según se describieron anteriormente. El enlace al resto progenitor se realiza a través del carbonilo. Los acilos preferidos contienen un alquilo inferior. 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 se describió anteriormente. El enlace al resto progenitor es a través del carbonilo. Ejemplos no limitativos de grupos adecuados incluyen benzoílo y 1- y 2-naftoílo.

"Alcoxi" significa un grupo alquil-O- en el cual el grupo alquilo es según se describió anteriormente. Ejemplos no limitativos de grupos alcoxi adecuados incluyen metoxi, etoxi, n-propoxi, isopropoxi y n-butoxi. El enlace al resto progenitor es a través del oxígeno del éter.

"Ariloxi" significa un grupo aril-O- en el cual el grupo arilo es según se describió anteriormente. Ejemplos no limitativos de grupos ariloxi adecuados incluyen fenoxi y naftoxi. El enlace al resto progenitor es a través del oxígeno del éter.

"Aralquiloxi" significa un grupo aralquil-O- en el cual el grupo aralquilo es según se describió anteriormente. Ejemplos no limitativos de grupos aralquiloxi adecuados incluyen benciloxi y 1- o 2-naftalenmetoxi. El enlace al resto progenitor es a través de del oxígeno del éter.

"Alquiltio" significa un grupo alquil-S- en el cual el grupo alquilo es según se describió anteriormente. Ejemplos no limitativos de grupos alquiltio adecuados incluyen metiltio y etiltio. El enlace al resto progenitor es a través del azufre.

"Ariltio" significa un grupo aril-S- en el cual el grupo arilo es según se describió anteriormente. Ejemplos no limitativos de grupos ariltio adecuados incluyen feniltio y naftiltio. El enlace al resto progenitor es a través del azufre.

"Aralquiltio" significa un grupo aralquil-S- en el cual el grupo aralquilo es según se describió anteriormente. Un ejemplo no limitativo de un grupo aralquiltio adecuado es benciltio. El enlace al resto progenitor es a través del azufre.

"Alcoxicarbonilo" significa un grupo alquil-O-CO-. Ejemplos no limitativos de grupos alcoxicarbonilo adecuados incluyen metoxicarbonilo y etoxicarbonilo. El enlace al resto progenitor es a través del carbonilo.

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"Ariloxicarbonilo" significa un grupo aril-O-C(O)-. Ejemplos no limitativos de grupos ariloxicarbonilo adecuados incluyen fenoxicarbonilo y naftoxicarbonilo. El enlace al resto progenitor 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 al resto progenitor 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 al resto progenitor es a través del sulfonilo.

"Arilsulfonilo" significa un grupo aril-$S(O_2)$-. El enlace al resto progenitor es a través del sulfonilo.

El término "sustituido" significa que uno o más hidrógenos en el átomo indicado se reemplaza con una selección del grupo indicado, siempre que no se exceda la valencia normal del átomo designado bajo las circunstancias existentes, y que la sustitución genere un compuesto estable. Se permiten combinaciones de sustituyentes y/o variables solamente si dichas combinaciones producen compuestos estables. Se entiende por "compuesto estable" o "estructura estable" un compuesto que es lo suficientemente resistente como para sobrevivir el aislamiento a un grado útil de pureza de una mezcla de reacción, y formulación en un agente terapéutico eficaz.

El término "sustituido opcionalmente" significa una sustitución opcional con los grupos, radicales o ésteres especificados.

El término "aislado" o "forma aislada" para un compuesto se refiere al estado físico de dicho compuesto después de que se aísla de un proceso sintético o fuente natural o combinación de los mismos. El término "purificado" o "en forma purificada" para un compuesto se refiere al estado físico de dicho compuesto después de que se obtuvo de un proceso o procesos de purificación que se

describieron en la presente o conocidos para los expertos en la técnica, en una pureza suficiente para que puedan ser caracterizados mediante técnicas analíticas estándar descriptas en la presente o conocidas para los expertos.

También se debe observar que se asume que cualquier carbono, al igual, que heteroátomo con valencias no satisfechas en el texto, esquemas, ejemplos y Tablas en la presente posee la cantidad suficiente de átomos de hidrógeno para satisfacer las valencias.

Cuando un grupo funcional en un compuesto se denomina "protegido", esto significa que el grupo se encuentra en forma modificada para evitar las reacciones secundarias no deseadas en el sitio protegido cuando se somete el compuesto a una reacción. Aquellos de experiencia ordinaria en la técnica reconocerán los grupos protectores adecuados, al igual que mediante la referencia a libros de texto estándar, tales como por ejemplo, T. W. Greene *et al*, *Protective Groups in Organic Synthesis* (1991), Wiley, New York.

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

Según se emplea en la presente, el término "composición" pretende incluir un producto que comprende los componentes específicos en las cantidades específicas, al igual que cualquier producto que surja, directa o indirectamente, de la combinación de los componentes especificados en las cantidades especificadas.

También se consideran en la presente pro-fármacos, ésteres y solvatos de los compuestos de la invención. El término "pro-fármaco", según se emplea en la presente, denota un compuesto que es un precursor de fármaco que, al administrarlo a un sujeto, sufre una conversión química mediante procesos metabólicos o químicos para dar un compuesto de Fórmula I o una sal y/o solvato

del mismo. Se provee una discusión de pro-fármacos en T. Higuchi y V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) Volumen 14 de la A.C.S. Symposium Series, y en *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association y Pergamon Press, las cuales se incorporan, ambas, a la presente a modo de referencia.

"Solvato" significa una asociación física de la presente invención con una o más moléculas de solvente. Esta asociación física comprende grados variables de unión iónica y covalente, incluyendo la unión por puente de hidrógeno. En ciertas instancias, se podrá aislar el solvato, por ejemplo cuando una o más moléculas del solvente se incorporan en el reticulado del cristal del sólido cristalino. "Solvato" comprende tanto fase solución como solvatos aislables. Ejemplos no limitativos de solvatos adecuados incluyen etanolatos, metanolatos y similares. "Hidrato" es un solvato en el cual la molécula de solvente es H_2O.

"Cantidad efectiva" o "cantidad terapéuticamente efectiva" pretende describir una cantidad de compuesto o una composición de la presente invención efectiva para inhibir las enfermedades deseadas y así producir el efecto terapéutico, de alivio, inhibidor o preventivo deseado.

Los compuestos de Fórmula I pueden formar sales que también se encuentran dentro del alcance de la presente invención. Se entiende que la referencia a un compuesto de Fórmula I en la presente incluye la referencia a sus sales, salvo que se indique lo contrario. El término "sal(es)", según se emplea en la presente, denota sales de ácidos formadas con ácidos inorgánicos y/u orgánicos, al igual que sales de bases formadas con bases inorgánicas y/u orgánicas. Además, cuando un compuesto de Fórmula I contiene tanto un resto básico, tal como, pero sin limitación, piridina o imidazol, como un resto ácido, tal como, pero sin limitación, un ácido carboxílico, se pueden formar zwiteriones ("sales internas") y se incluyen dentro del término "sal(es)" según se emplea en la

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presente. Se prefieren las sales aceptables para uso farmacéutico (es decir, no tóxicas, aceptables fisiológicamente), aunque también sean útiles otras sales. Se pueden formar sales de los compuestos de Fórmula I, por ejemplo, haciendo reaccionar un compuesto de Fórmula I con una cantidad de ácido o base, tal como una cantidad equivalente, en un medio, tal como uno en el cual la sal se precipita o en un medio acuoso seguido de liofilización.

Sales de adición con ácidos que sirven de ejemplo incluyen acetatos, ascorbatos, benzoatos, bencensulfonatos, bisulfatos, boratos, butiratos, citratos, alcanforatos, alcanforsulfonatos, fumaratos, clorhidratos, bromhidratos, yodhidratos, lactatos, maleatos, metansulfonatos, naftalensulfonatos, nitratos, oxalatos, fosfatos, propionatos, salicilatos, succinatos, sulfatos, tartratos, tiocianatos, toluensulfonatos (también conocidos como tosilatos) y similares. Adicionalmente, se tratan ácidos que en general son considerados adecuados para la formación de sales útiles para uso farmacéutico de compuestos farmacéuticos básicos, por ejemplo, por P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; y en *The Orange Book* (Food & Drug Administration, Washington, D.C. en su sitio en Internet). Estas revelaciones se incorporan a modo de referencia a la misma.

Sales de bases que sirven de ejemplo incluyen sales de amonio, sales de metales alcalinos tales como sales de sodio, litio y de potasio, sales de metales alcalino-térreos tales como sales de calcio y magnesio, sales con bases orgánicas (por ejemplo, aminas orgánicas) tales como diciclohexilaminas, t-butil aminas, y sales con aminoácidos tales como arginina, lisina y similares. Grupos básicos que contienen nitrógeno se pueden cuaternizar con agentes tales como haluros de

alquilo inferior (por ej. cloruros, bromuros y yoduros de metilo, etilo, propilo y butilo), dialquil sulfatos (por ej. sulfatos de dimetilo, dietilo y dibutilo), haluros de cadena larga (por ej. cloruros, bromuros y yoduros de decilo, laurilo, miristilo y estearilo), haluros de aralquilo (por ej. bromuros de bencilo y fenetilo), y otros.

Todas las mencionadas sales de ácidos y sales de bases deben ser sales aceptables para uso farmacéutico dentro del alcance de la invención y todas las sales de ácidos y bases se consideran equivalentes a las formas libres de los compuestos correspondientes a los fines de la invención.

Uno o más compuestos de la invención también pueden existir como, o convertirse opcionalmente en, un solvato. La preparación de los solvatos es generalmente conocida. Así, por ejemplo, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe la preparación de los solvatos del antifúngico fluconazol en acetato de etilo, al igual que de agua. Preparaciones similares de solvatos, hemisolvatos, hidratos y similares son descriptas por E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), artículo 12 (2004); y A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). Un proceso típico, no limitativo, comprende disolver el compuesto de la invención en cantidades deseadas del solvente deseado (orgánicos o de agua o mezclas de los mismos) a una temperatura mayor que la ambiente, y enfriar la solución a una velocidad suficiente como para formar cristales que luego se aíslan por métodos estándar. Técnicas analíticas tales como, por ejemplo, espectroscopía I.R., muestran la presencia del solvente (o agua) en los cristales como un solvato (o hidrato).

Compuestos de Fórmula I, y sales, solvatos, ésteres y pro-fármacos de los mismos, pueden existir en su forma tautomérica (por ejemplo, como una amida o imino éter). En la presente, se consideran todas dichas formas tautoméricas como parte de la presente invención.

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Todos los estereoisómeros (por ejemplo isómeros geométricos, isómeros ópticos y similares) de los presentes compuestos (incluyendo aquellos de las sales, solvatos y pro-fármacos de los compuestos, al igual que las sales y solvatos de los pro-fármacos), tales como aquellos que pueden existir debido a los carbonos asimétricos en varios sustituyentes, incluyendo formas enantioméricas (que pueden existir aún en ausencia de carbonos asimétricos), formas rotaméricas, atropoisómeros y formas diastereoméricas, se consideran dentro del alcance de la presente invención, como lo son los isómeros de posición (tales como, por ejemplo, 4-piridilo y 3-piridilo). Los esteroisómeros individuales de los compuestos de la invención pueden, por ejemplo, no poseer en esencia otros isómeros, o pueden estar combinados, por ejemplo, como racematos con todos los demás, u otros estereoisómeros seleccionados. Los centros quirales de la presente invención pueden poseer la configuración S o R, según lo definido por las Recomendaciones de *IUPAC* 1974. Se pretende que el uso de los términos "sal", "solvato" "pro-fármaco" y similares, se aplique igualmente a la sal, solvato y pro-fármaco de enantiómeros, estereoisómeros, rotámeros, tautómeros, isómeros de posición, racematos o pro-fármacos de los compuestos de la invención.

Se pretende incluir las formas polimórficas de los compuestos de Fórmula 1 y de las sales, solvatos y pro-fármacos de los compuestos de Fórmula 1 en la presente invención.

En general, las flechas  y  de las Fórmulas estructurales de la presente solicitud se refieren a los respectivos puntos de conexión de la Fórmula relacionada con los puntos que se muestran en la estructura de su Fórmula progenitora.

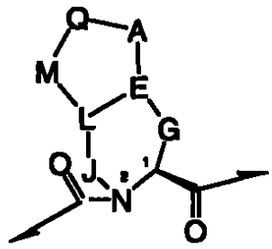
En una realización, la presente invención revela compuestos de Fórmula 1 como inhibidores de proteasa de VHC, en especial la serina proteasa NS3/NS4a

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de VHC, o un derivado aceptable para uso farmacéutico del mismo, donde las diversas definiciones se dieron anteriormente.

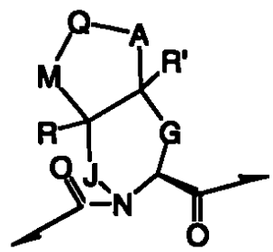
En otra realización, R^1 es cetoamida, ácido, cetoácido, cetoéster, cetoaldehído, dicetona, ácido borónico o trifluorocetona.

En otra realización, la presente invención revela compuestos de Fórmula 1 en los cuales la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2:



Fórmula 2

es



;

donde las flechas ⟶ y ⟵ se refieren a puntos de conexión de la Fórmula 2 con los puntos que se muestran en la Fórmula 1, y

G y J pueden o no encontrarse presentes inmediatamente y si se encuentran presentes pueden ser iguales o diferentes y se seleccionan independientemente del grupo que consiste en $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$ y $(CRR')_p$;

A y M pueden o no encontrarse presentes inmediatamente y si se encuentran presentes pueden ser iguales o diferentes y se seleccionan independientemente del grupo que consiste en O, S, $S(O_2)$, N(R), $(CH_2)_p$, $(CHR)_p$,

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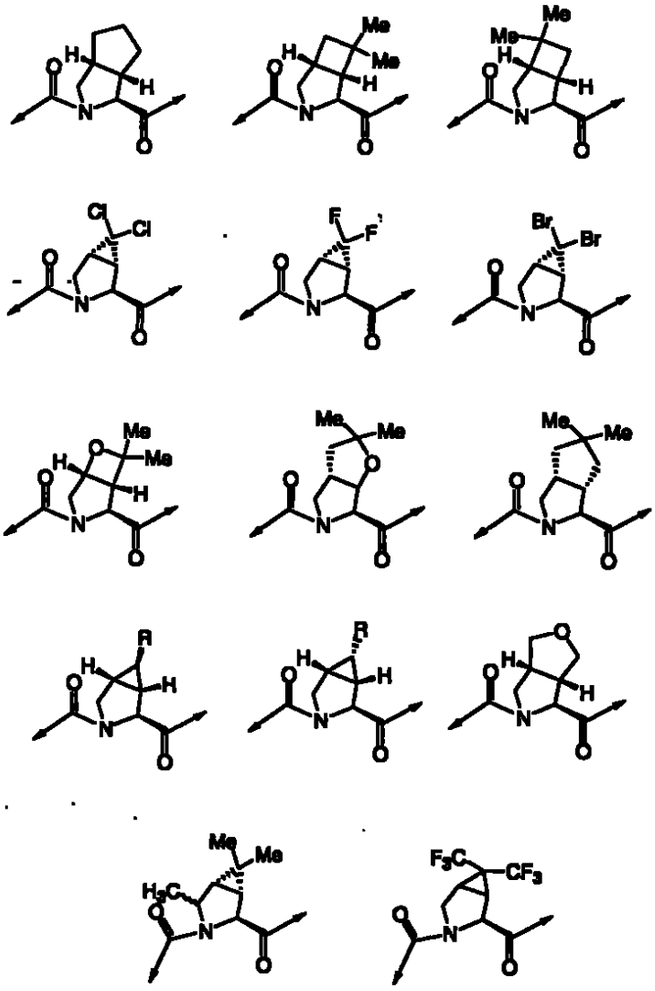
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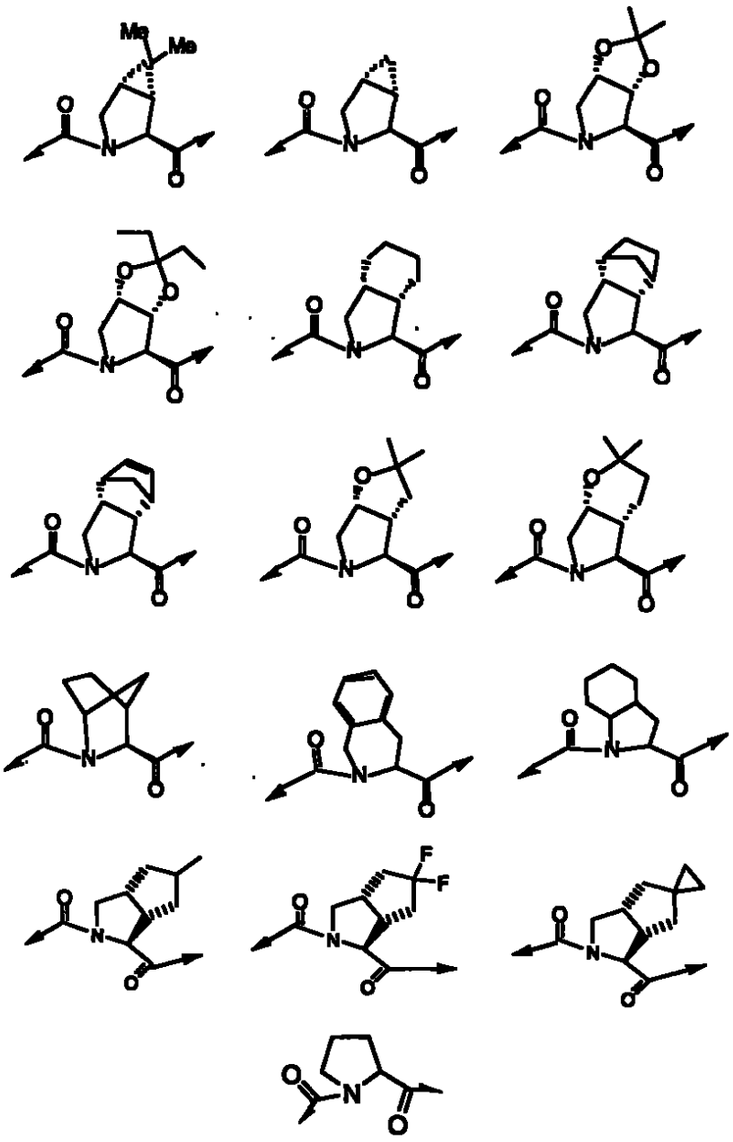
$(CHR\text{-}CHR')_p$, y $(CRR')_p$; o A y M están unidos para formar un puente cicloalquilo o heterocíclico; y

Q puede o no encontrarse presente y si se encuentra presente es $(CH_2)_p$, N(R), O, S, $S(O_2)$, $(CHR)_p$ o $(CRR')_p$.

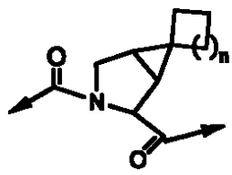
Cuando Q se encuentra ausente, y cualquiera de M o A se encuentra ausente, el A o M restante (presente) puede formar opcionalmente una estructura de cicloalquilo o heterociclilo con el carbono C(R) o C(R') de la Fórmula I. Algunos ejemplos representativos se muestran en algunas de las siguientes estructuras.

En una realización de la presente invención, la porción representada por la Fórmula estructural 2 se selecciona de las siguientes estructuras:





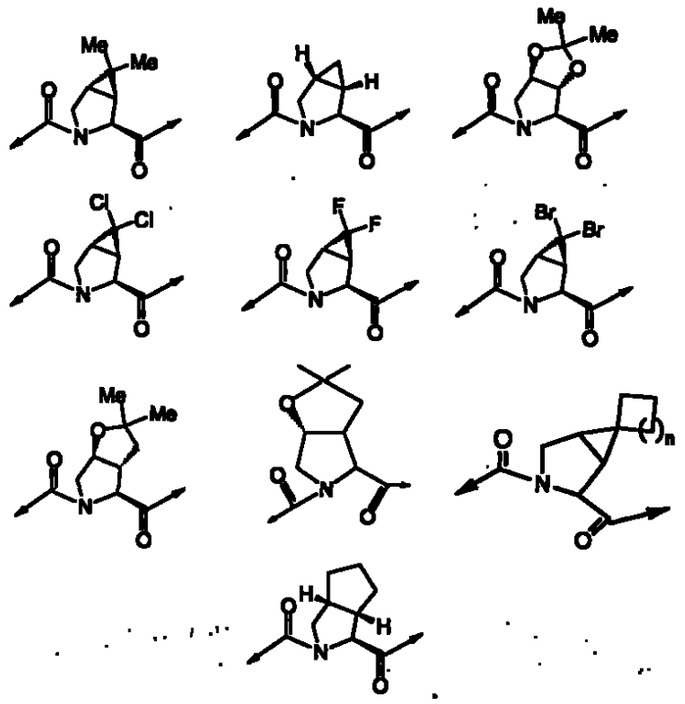
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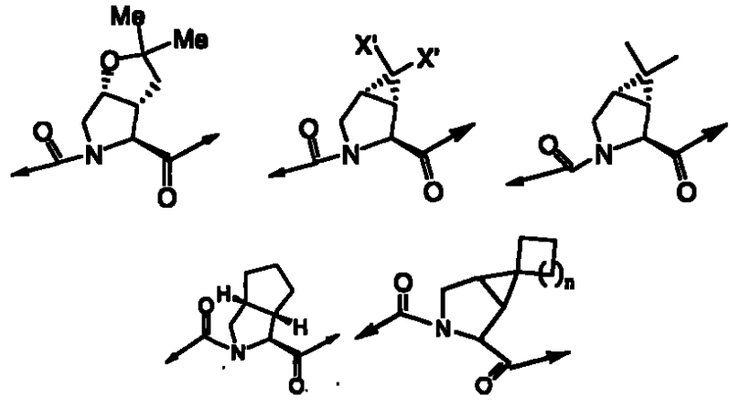
en las cuales n= 0-4.

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En otra realización de la presente invención, la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2 se selecciona de las siguientes estructuras:

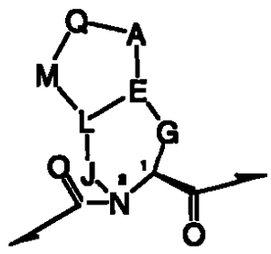


En otra realización de la presente invención, la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2 se selecciona de las siguientes estructuras:



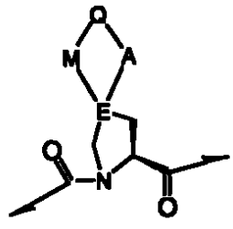
en las cuales X' es H, F, Cl o Br.

En aún otra realización de la presente invención, la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2:



es

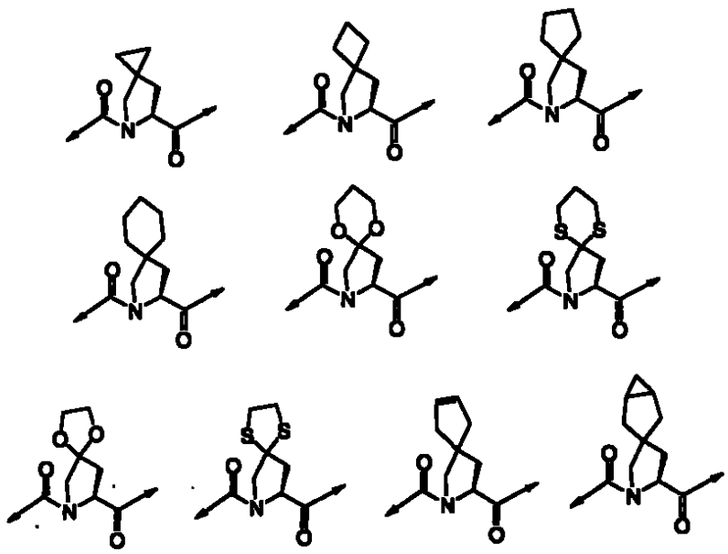
Fórmula 2



; y

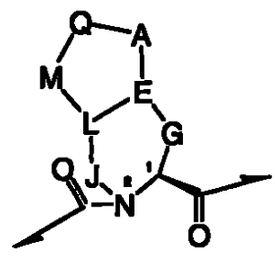
Q puede estar presente o ausente, y si Q se encuentra ausente, M está unida directamente a A.

En aún otra realización de la presente invención, la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2 se selecciona de las siguientes estructuras:



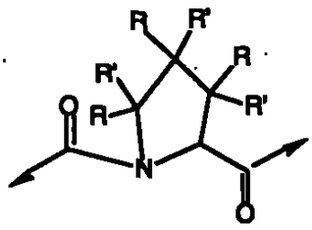
En otro aspecto de la presente invención, la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2:

402
399

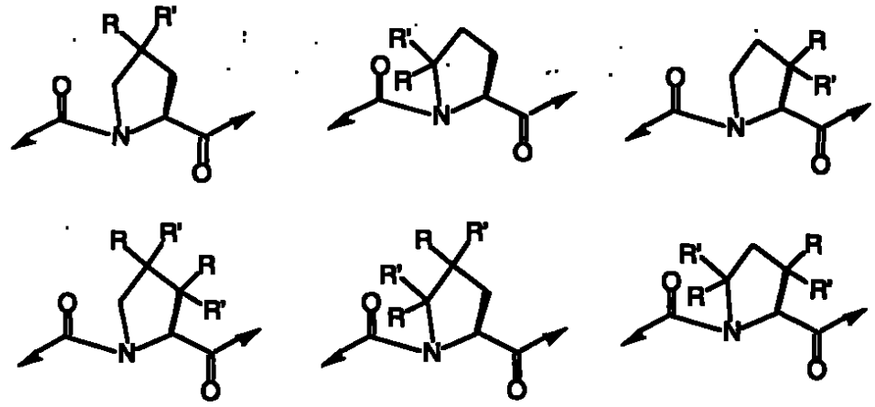


es

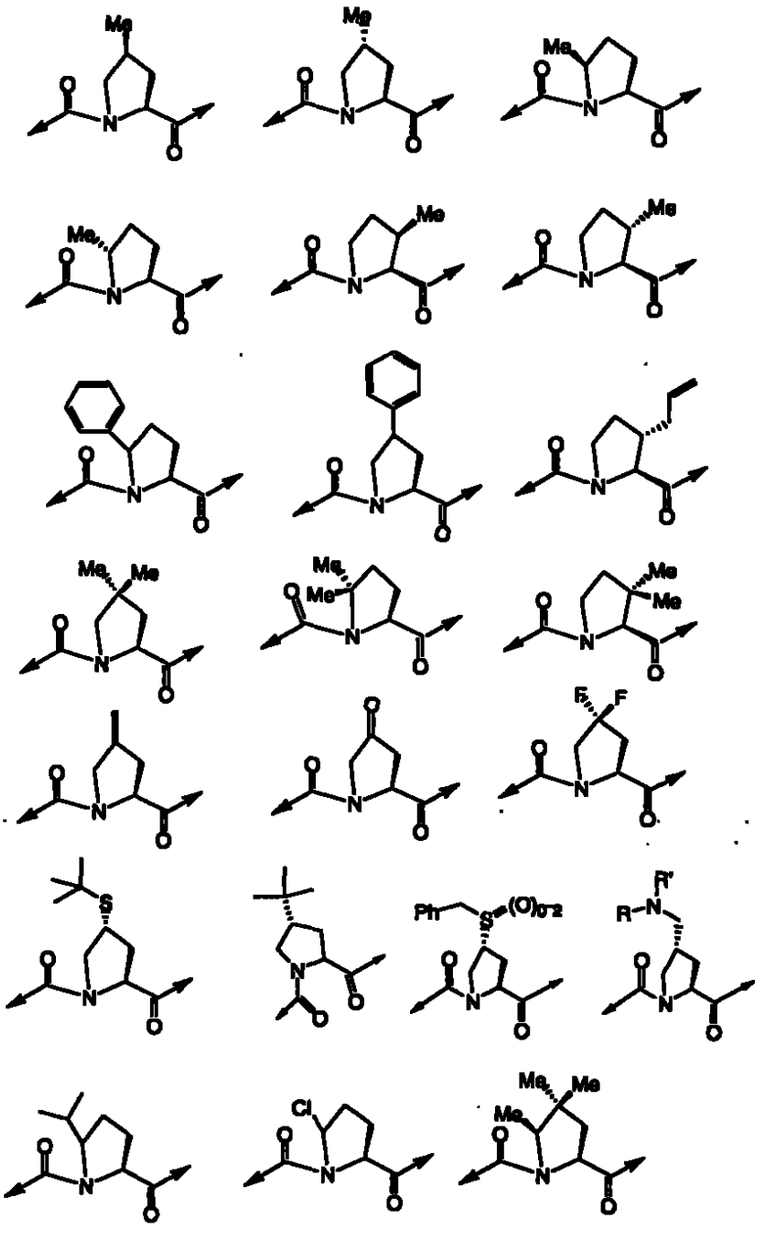
Fórmula 2



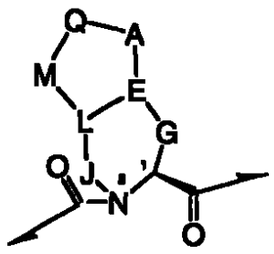
En aún otro aspecto de la presente invención, la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2 se selecciona de las siguientes estructuras:



En otro aspecto más de la presente invención, la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2 se selecciona de las siguientes estructuras:

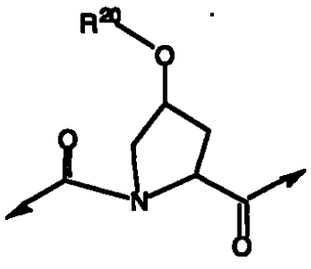


En aún otro aspecto de la presente invención, la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2:



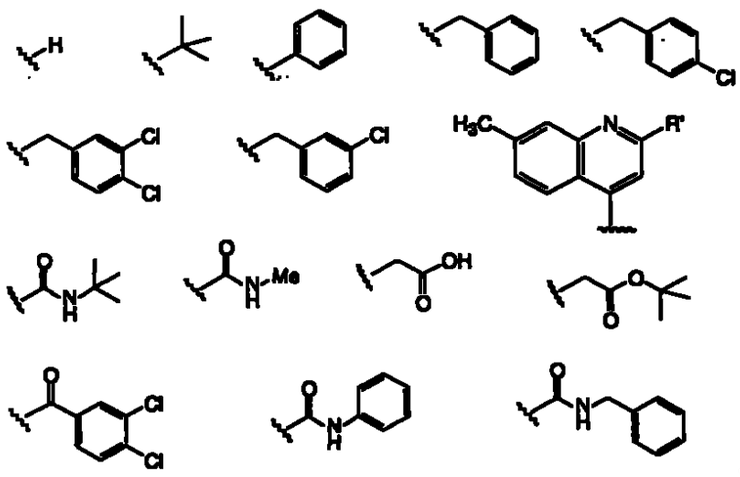
Formula 2

es

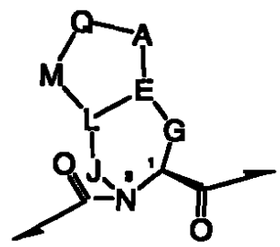


; y

R^{20} se selecciona de las siguientes estructuras:

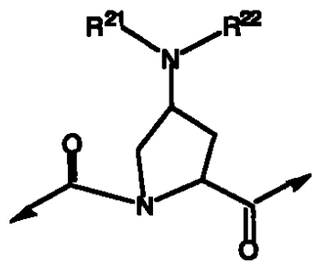


En otro aspecto de la presente invención, la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2:



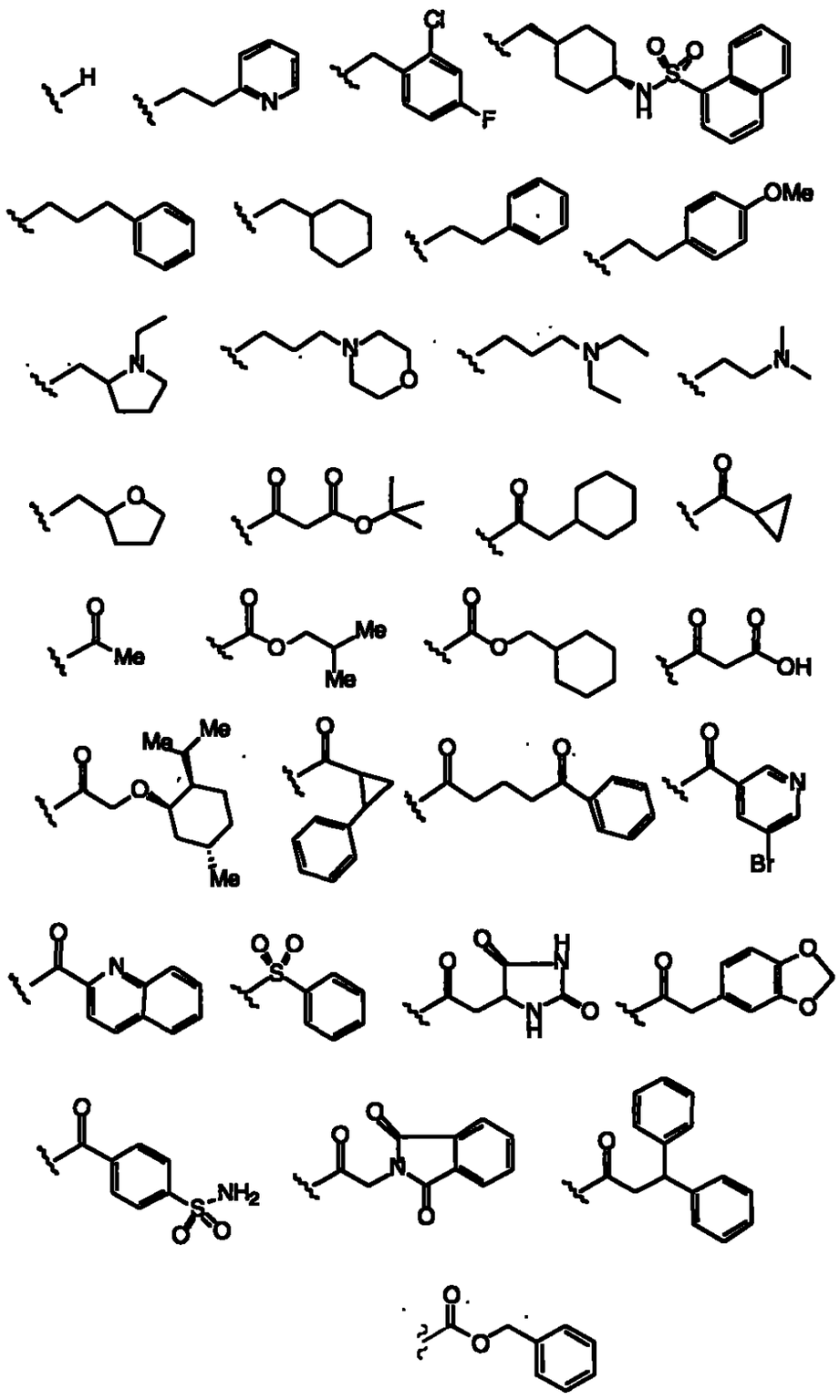
Fórmula 2

es



; y

R^{21} y R^{22} pueden ser iguales o diferentes y se seleccionan independientemente del grupo que consiste en las siguientes estructuras:



En otro aspecto de la presente invención, L y M se encuentran ausentes, y J está unido directamente a E.

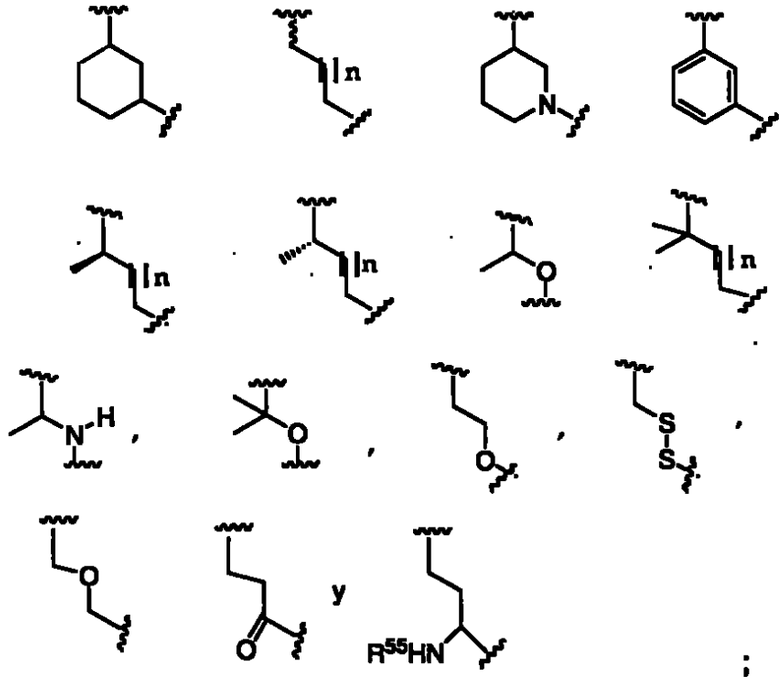
En otro aspecto de la presente invención, L, J y M se encuentran ausentes y E está unido directamente a N.

En otro aspecto de la presente invención, G y M se encuentran ausentes.

En aún otro aspecto de la presente invención, M' es

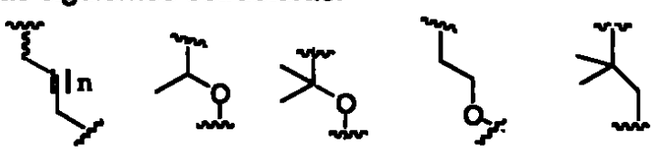


En aún otro aspecto de la presente invención, X se selecciona del grupo que consiste en las siguientes estructuras:



y R^{55} es alquilo, cicloalquilo, carbamato o urea; y n= 0-5.

En aún otro aspecto de la presente invención, X se selecciona del grupo que consiste en las siguientes estructuras:



405

En aún otro aspecto de la presente invención, R^1 es una cetoamida, cetoaldehído, dicetona, cetoácido o cetoéster.

En otra realización de la presente invención, R^1 es $-C(O)C(O)NR^9R^{10}$;

R^9 es H; y

R^{10} es H, $-R^{14}$,

$-[CH(R^{1'})]_pC(O)OR^{11}$,

$-[CH(R^{1'})]_pC(O)NR^{12}R^{13}$,

$-[CH(R^{1'})]_pS(O_2)R^{11}$,

$-[CH(R^{1'})]_pS(O_2)NR^{12}R^{13}$,

$-[CH(R^{1'})]_pC(O)R^{11}$,

$-CH(R^{1'})C(O)N(H)C(H)(R^{2'})C(O)OR^{11}$,

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

$-CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$.

En otra realización de la presente invención, R^{10} es H, $-R^{14}$,

$-CH(R^{1'})C(O)OR^{11}$,

$-CH(R^{1'})CH(R^{1'})C(O)OR^{11}$,

$-CH(R^{1'})C(O)NR^{12}R^{13}$,

$-CH(R^{1'})CH(R^{1'})C(O)NR^{12}R^{13}$,

$-CH(R^{1'})CH(R^{1'})S(O_2)R^{11}$,

$-CH(R^{1'})CH(R^{1'})S(O_2)NR^{12}R^{13}$,

$-CH(R^{1'})CH(R^{1'})C(O)R^{11}$,

$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$,

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

$-CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$;

$R^{1'}$ es H o alquilo; y

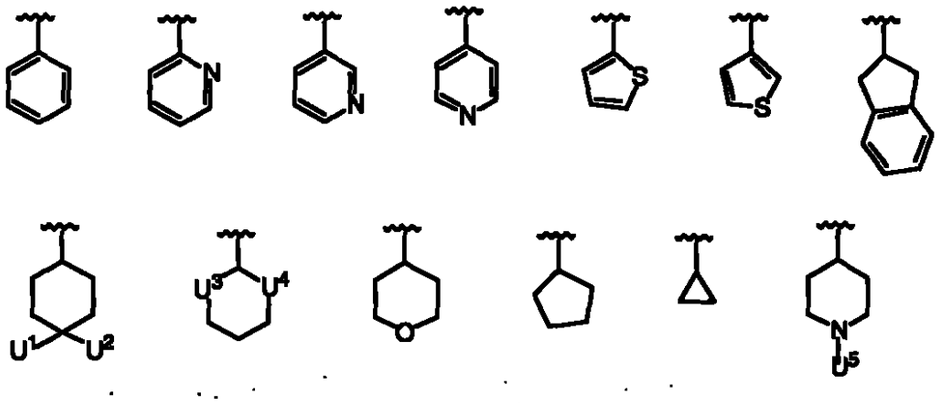
$R^{2'}$ es fenilo, fenilo sustituido, fenilo sustituido con heteroátomos, cicloalquilo, heterocicloalquilo, piperidilo o piridilo.

En otra realización de la presente invención, $R^{1'}$ es H.

En aún otra realización de la presente invención, R^{11} es H, metilo, etilo, alilo, *ter*-butilo, bencilo, α-metilbencilo, α,α-dimetilbencilo, 1-metilciclopropilo o 1-metilciclopentilo;

$R^{'}$ es hidroximetilo o $-CH_2C(O)NR^{12}R^{13}$;

$R^{2'}$ se selecciona independientemente del grupo que consiste en las siguientes estructuras:

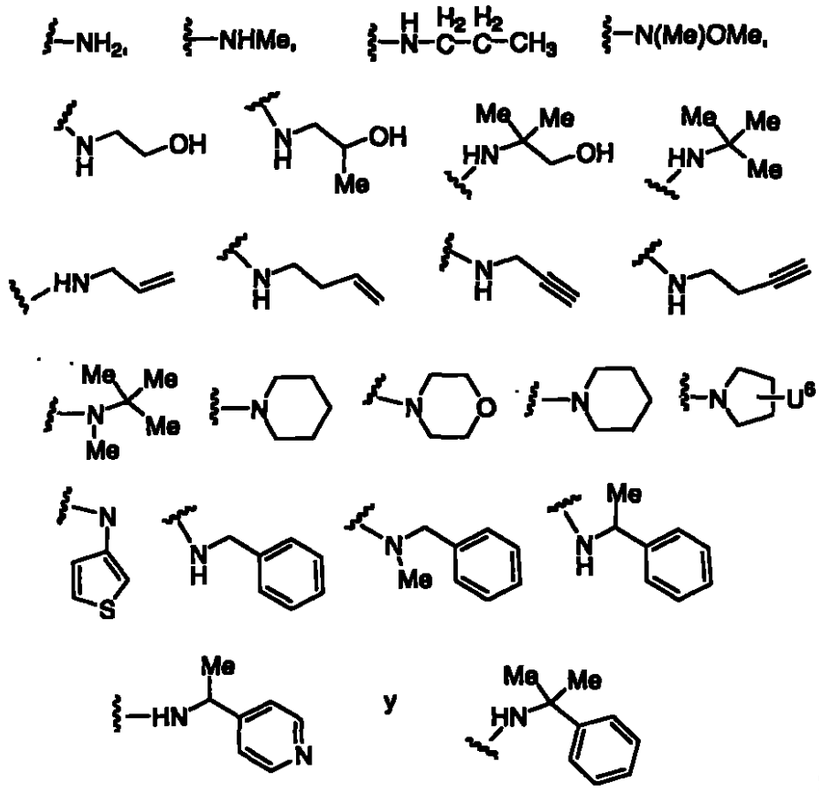


en las cuales U^1 y U^2 pueden ser iguales o diferentes y se seleccionan independientemente del grupo conformado por: H, F, $-CH_2C(O)OH$, $-CH_2C(O)OMe$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, $-CH_2C(O)NMe_2$, azido, amino, hidroxilo, amino sustituido e hidroxilo sustituido;

U^3 y U^4 son iguales o diferentes y son independientemente O o S;

U^5 es alquil sulfonilo, aril sulfonilo, heteroalquil sulfonilo, heteroaril sulfonilo, alquil carbonilo, aril carbonilo, heteroalquil carbonilo, heteroaril carbonilo, alcoxicarbonilo, ariloxicarbonilo, heteroariloxicarbonilo, alquilaminocarbonilo, arilaminocarbonilo, o heteroarilaminocarbonilo o una combinación de los mismos;

$NR^{12}R^{13}$ se selecciona del grupo conformado por:

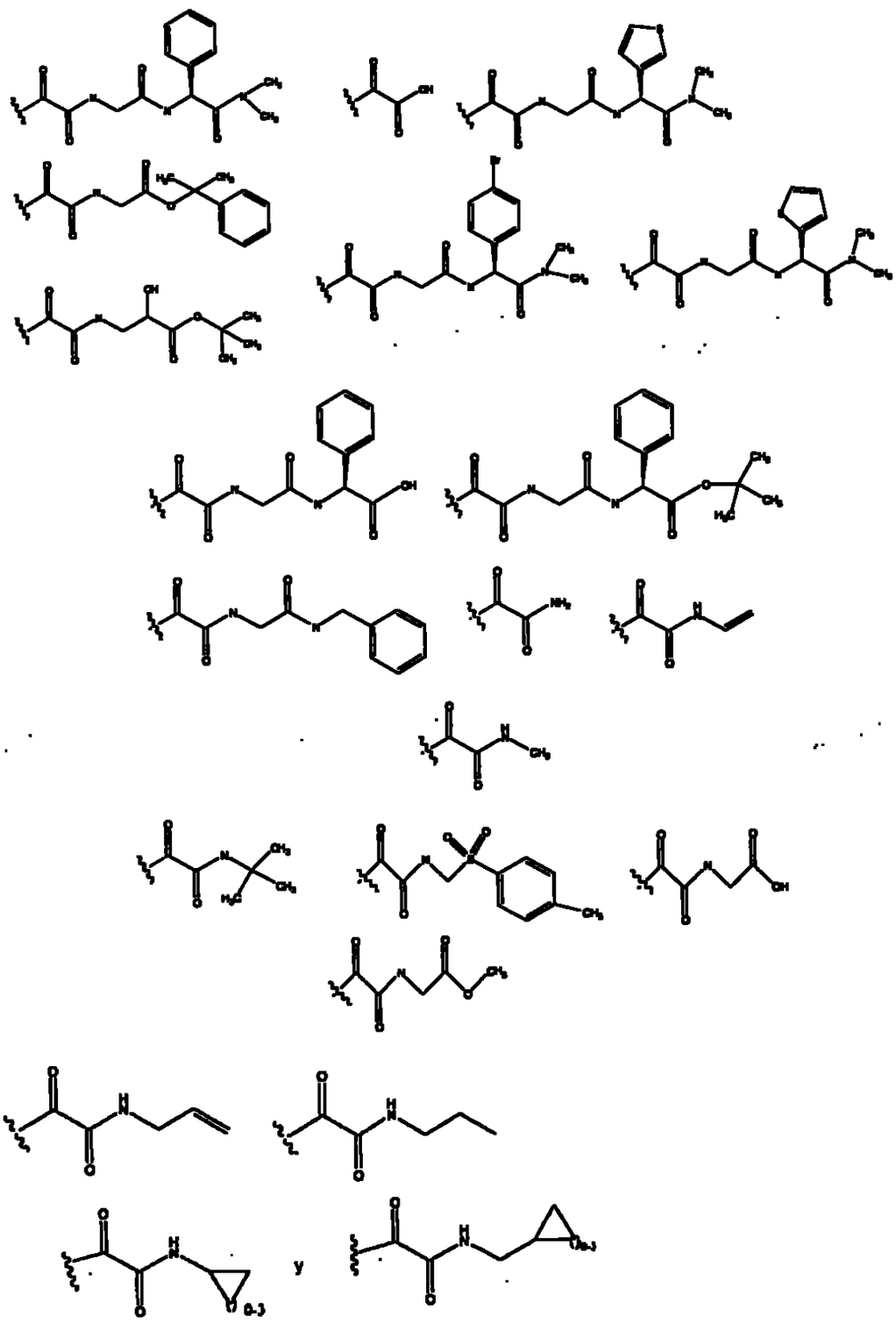


y

U^6 es H, OH, o CH_2OH, y

R^{14} se selecciona del grupo conformado por: H, $-CH_3$, Et, *n*-propilo, metoxi, ciclopropilo, *n*-butilo, 1-but-3-inilo, bencilo, α-metilbencilo, fenetilo, alilo, 1-but-3-enilo, $-OCH_3$ y ciclopropilmetilo.

En aún otra realización de la presente invención, R^1 se selecciona de las siguientes estructuras:



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409

En otro aspecto de la presente invención, D y X tomados juntos forman una cadena conectora parafínica no ramificada C7-C12 divalente que forma una porción de un macrocicio de 14-19 miembros.

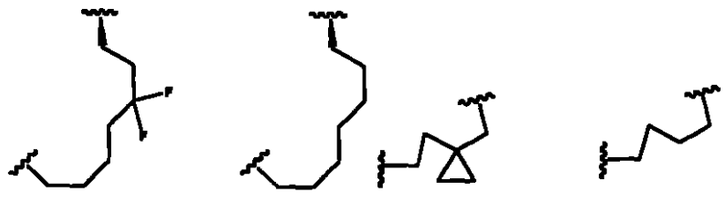
En otro aspecto de la presente invención, D y X tomados juntos forman una cadena conectora parafínica no ramificada de C8 o C9 que forma una porción de un heterociclo de 15 o 16 miembros.

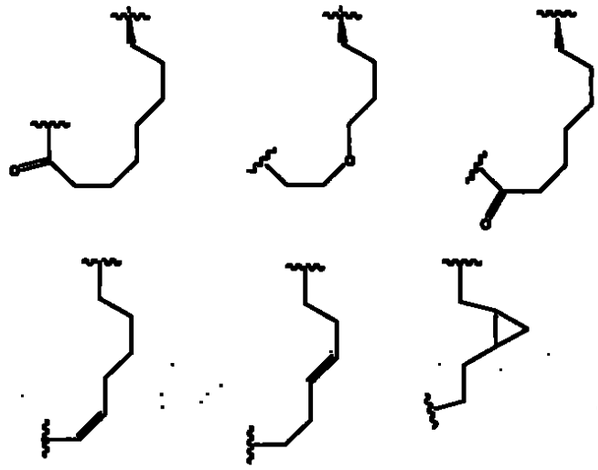
En otro aspecto de la presente invención, D y X tomados juntos forman una cadena conectora olefínica no ramificada de C7-C12 divalente que forma una porción de un macrocicio de 14-19 miembros que posee un grado simple de insaturación.

En otro aspecto de la presente invención, D y X tomados juntos forman una cadena conectora olefínica de C8 o C9 no ramificada que forma una porción de un heterociclo de 15 o 16 miembros que posee un grado simple de insaturación.

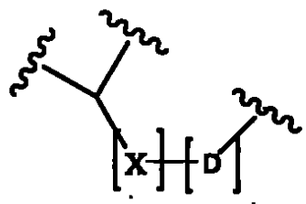
En otro aspecto de la presente invención, D y X tomados juntos forman una cadena alifática no ramificada C2–C12 divalente que forma una porción de un heterociclo de 9-19 miembros.

En otro aspecto de la presente invención, D se selecciona de las siguientes estructuras:

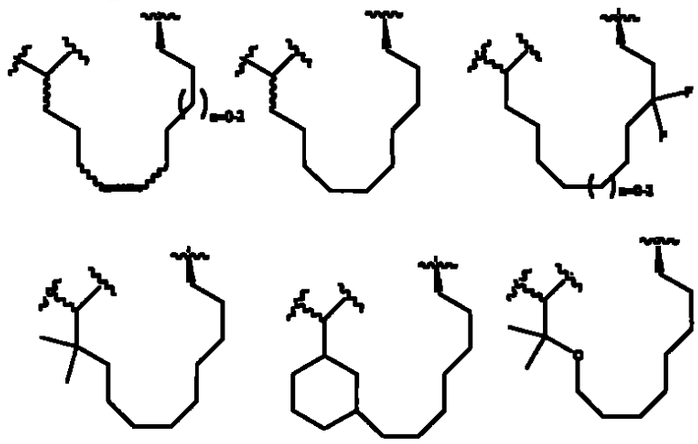




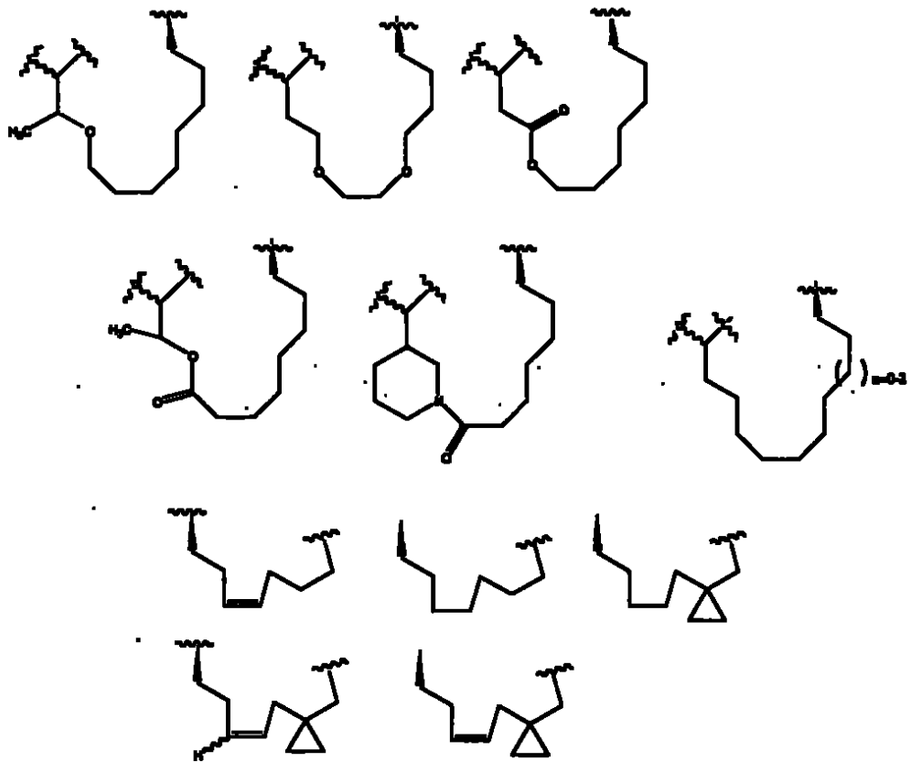
En aún otro aspecto de la presente invención, la porción de la Fórmula 1 representada por



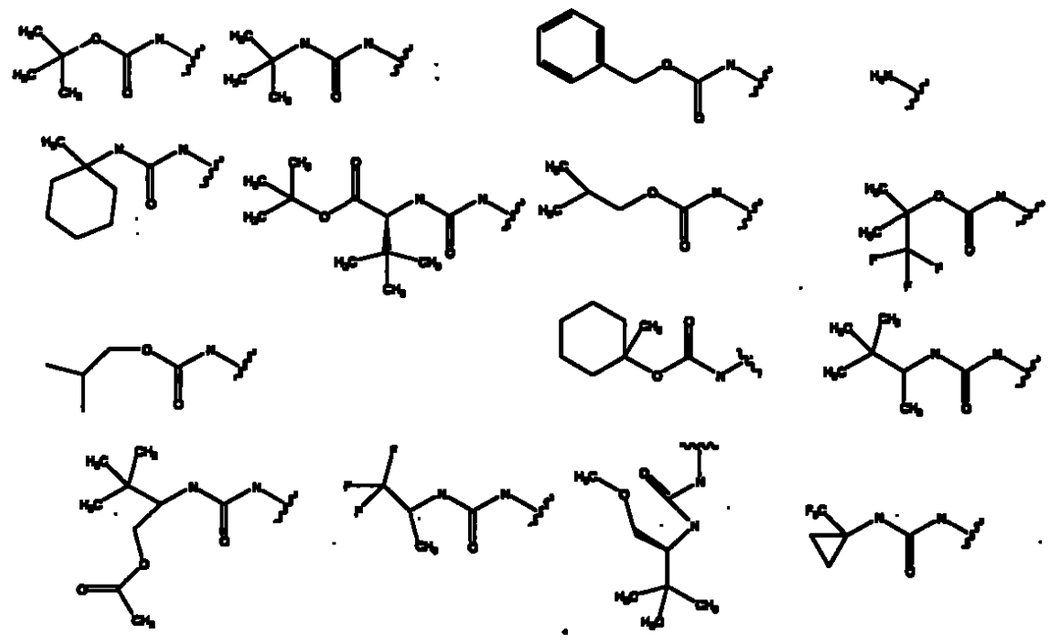
se selecciona de las siguientes estructuras:



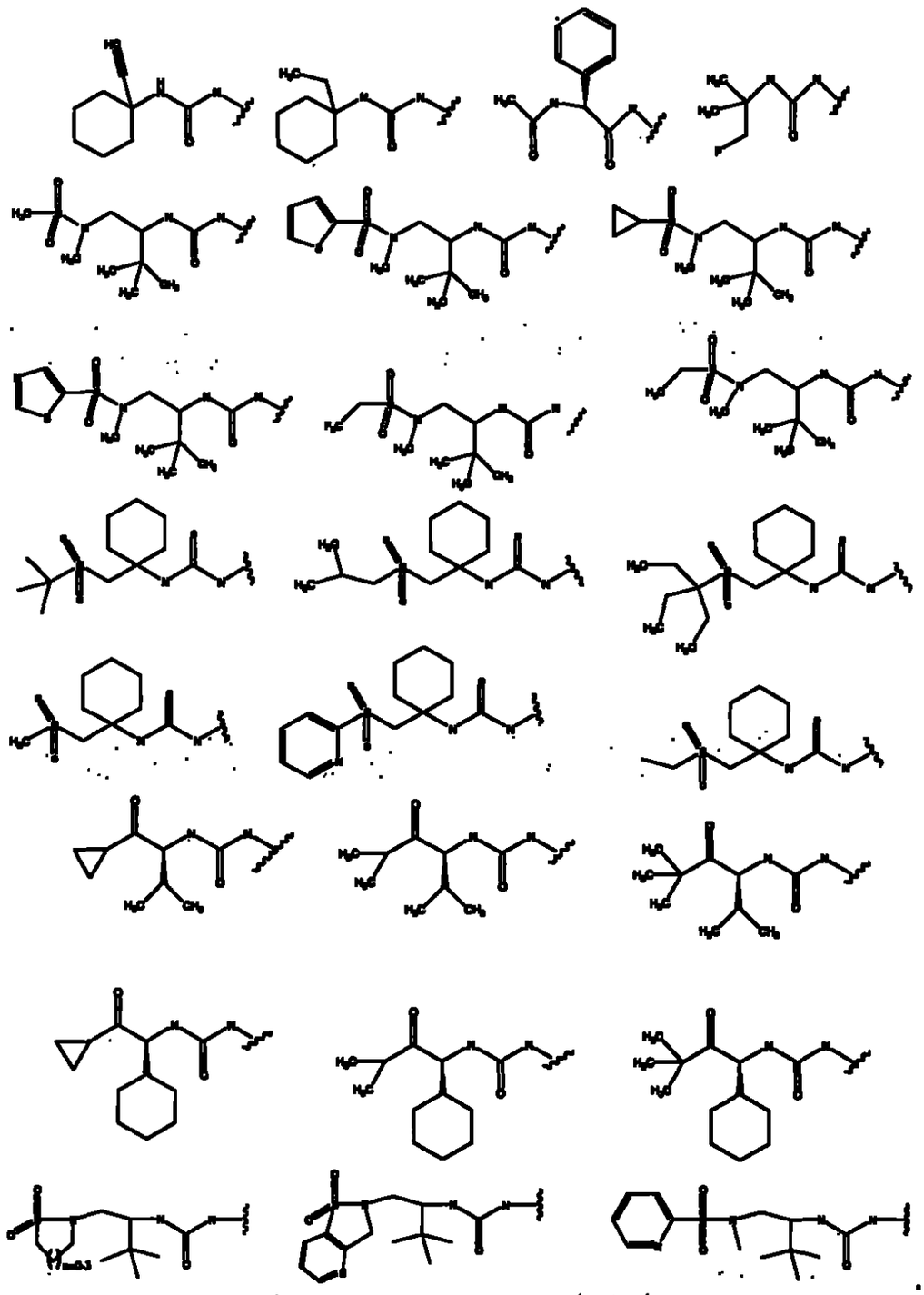
411



En otra realización de la presente invención, Z' se selecciona del grupo conformado por:



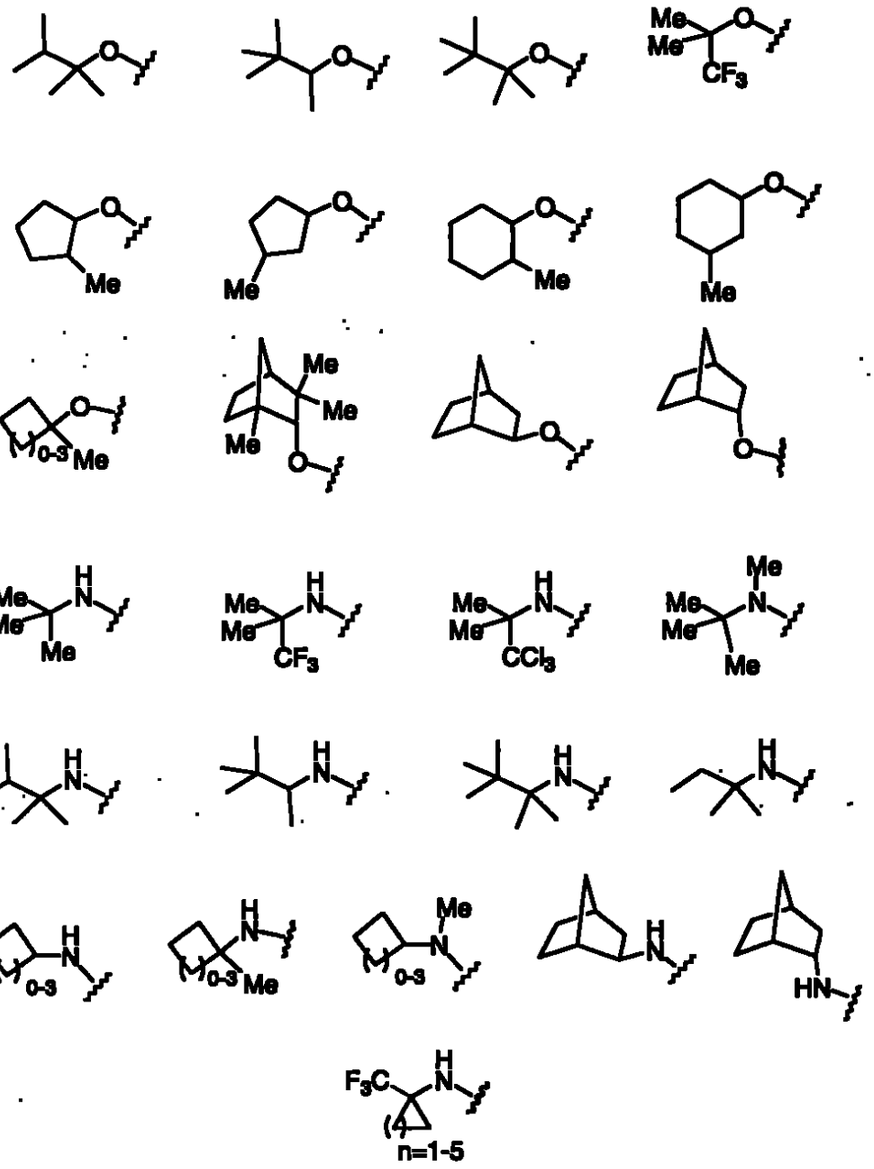
412 4/5



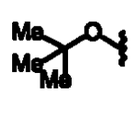
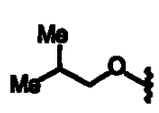
En otra realización de la presente invención, W es C=O.

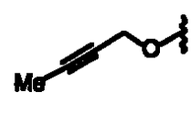
En otra realización de la presente invención, Z es N.

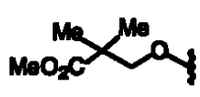
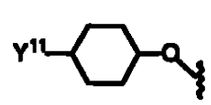
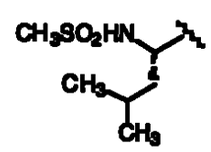
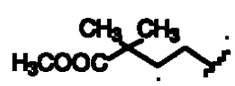
En otra realización de la presente invención, Y se selecciona de los siguientes restos:

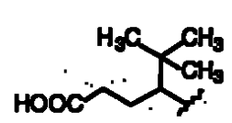

Me
Me
CF3
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CF3
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n=1-5

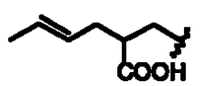
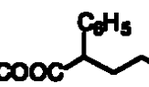
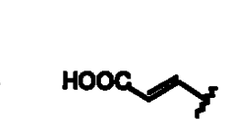
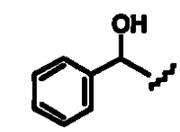
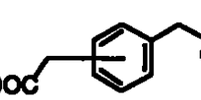
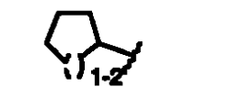
414

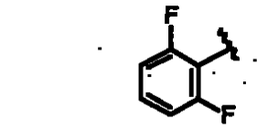
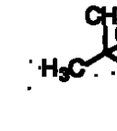



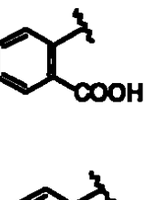
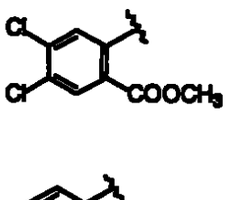
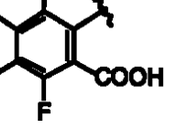
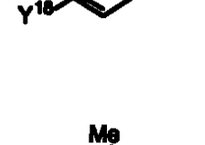
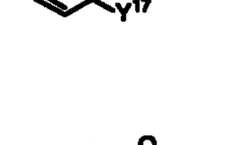
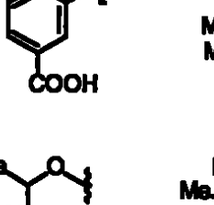
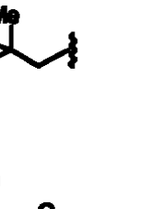
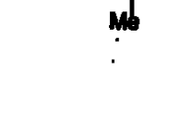




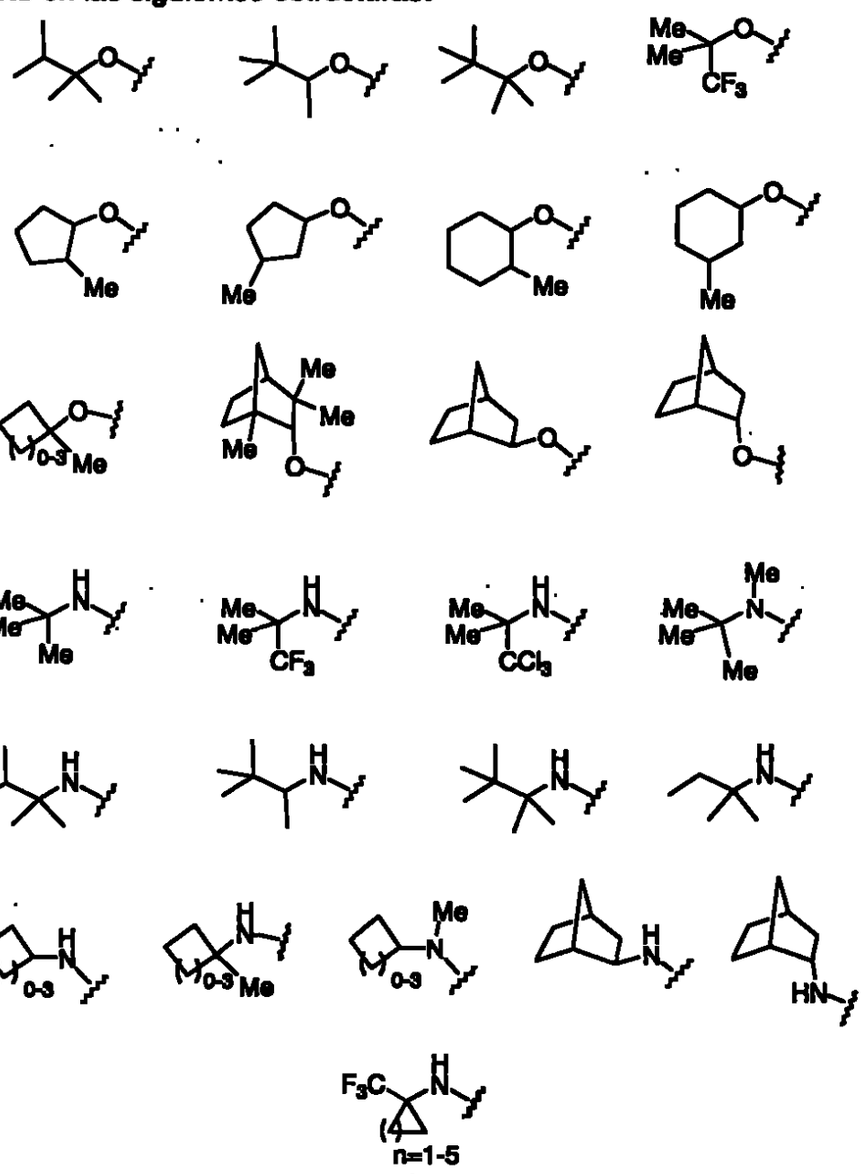










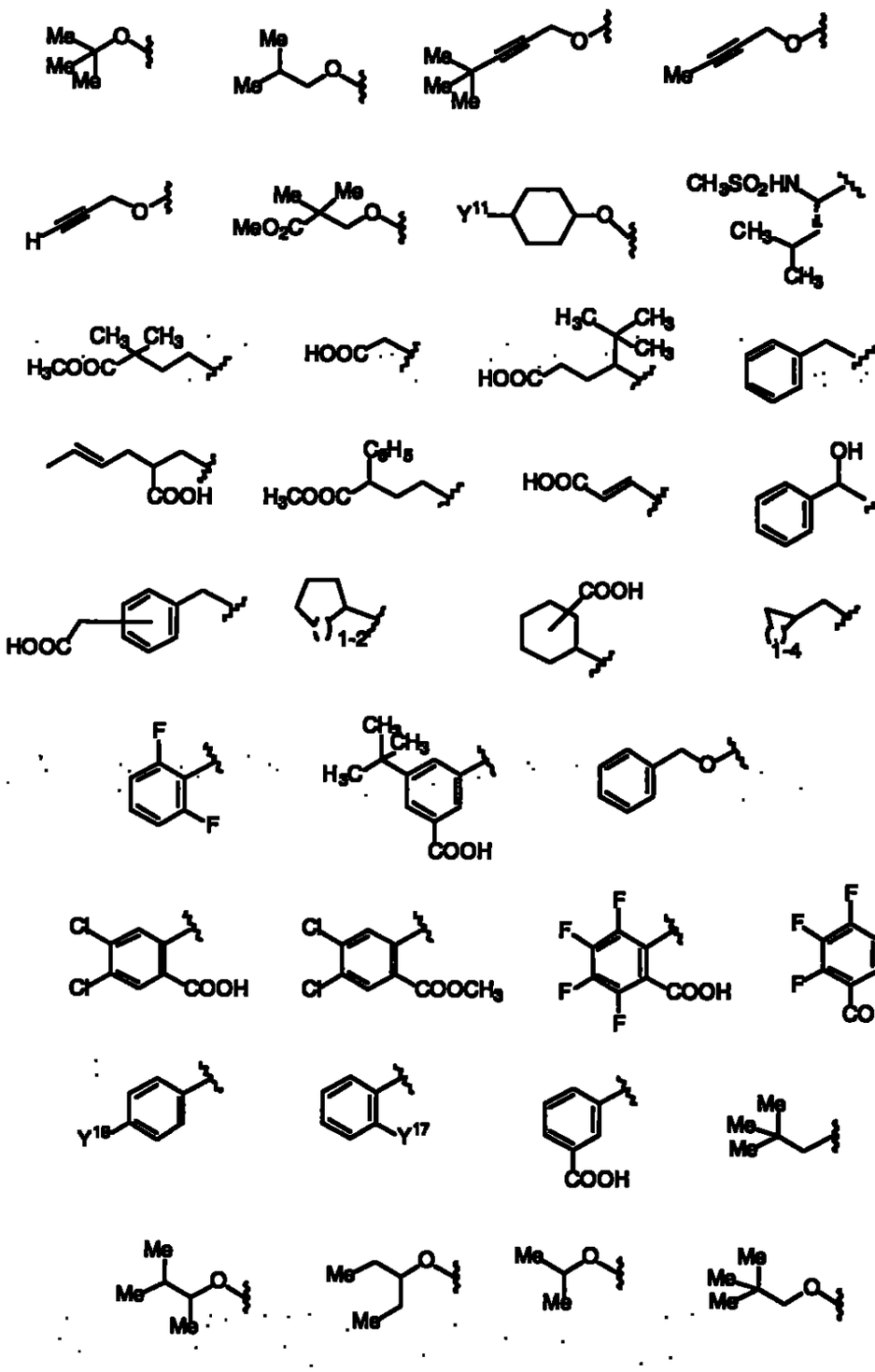

415

en los cuales Y^{17} es CF_3, NO_2, $C(O)NH_2$, OH, NH_2 o C(O)OH; e

Y^{18} es F o C(O)OH.

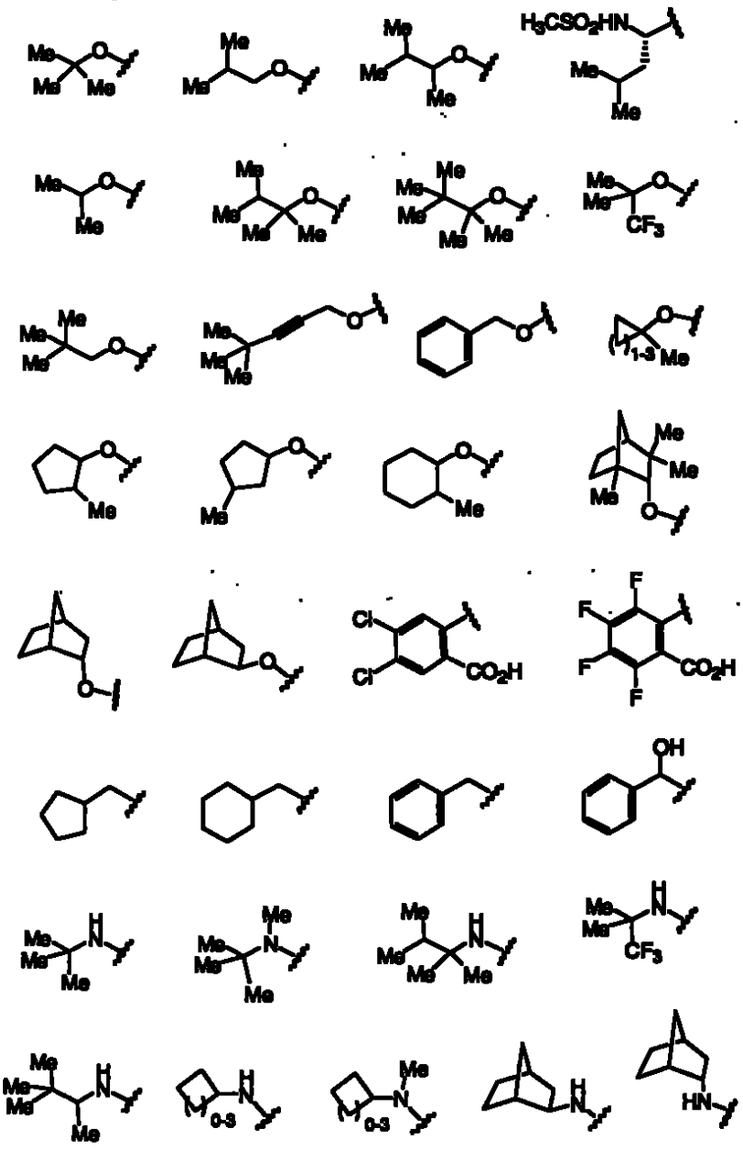
En aún otra realización de la presente invención, Y se selecciona del grupo que consiste en las siguientes estructuras:



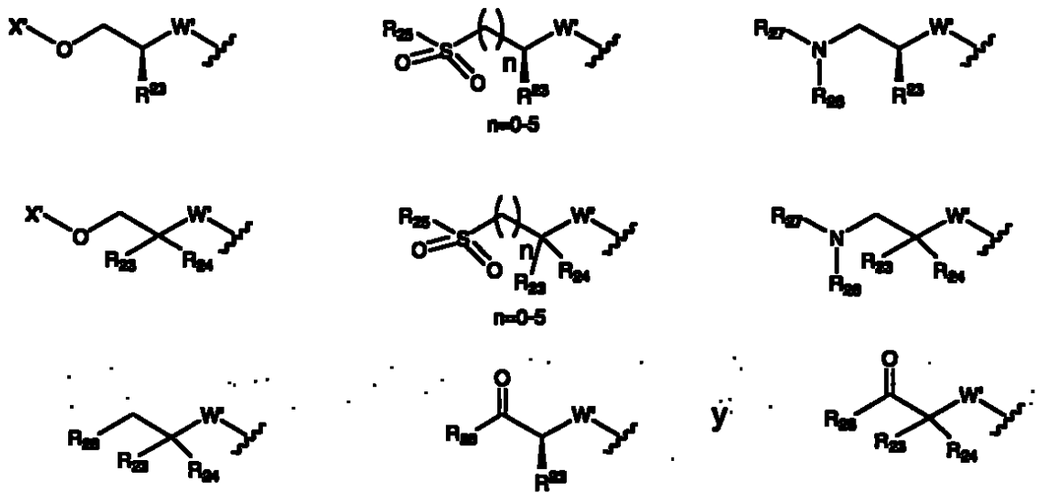

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HOOC
H3C
CH3
HOOC
COOH
C6H5
H3COOC
HOOC
OH
HOOC
1-2
COOH
1-4
F
F
CH3
CH3
H3C
COOH
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Cl
COOH
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Cl
COOCH3
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F
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COOH
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COOH
Y16
Y17
COOH
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O

en las cuales Y^{17} es CF_3, NO_2, $C(O)NH_2$, OH, NH_2 o C(O)OH; e Y^{18} es F o C(O)OH.

En aún otra realización de la presente invención, Y se selecciona del grupo que consiste en las siguientes estructuras:



En aún otra realización de la presente invención, Y se selecciona del grupo que consiste en las siguientes estructuras:



W' es N o O;

R^{23} es H, alquilo, arilo, heteroarilo, cicloalquilo o heterocicloalquilo, donde cada uno de dichos arilo, heteroarilo, cicloalquilo, heterocicloalquilo puede estar sustituido con un resto alquilo;

R^{24} es H, alquilo, arilo, heteroarilo, cicloalquilo o heterocicloalquilo, donde cada uno de dichos arilo, heteroarilo, cicloalquilo, heterocicloalquilo puede estar sustituido con un resto alquilo;

o R^{23} y R^{24} tomados juntos forman un anillo cíclico que contiene un carbociclo o heterociclo;

R^{25} es H, alquilo, heteroalquilo, arilo, heteroarilo, alquilamino, arilamino, heteroalquilamino o cicloalquilo,

R^{26} se selecciona del grupo conformado por: H, carbamato, sulfonamidas, alquilcarbonilo, alquilsulfonilo, arilsulfonilo, heteroarilo, sulfonilo, heteroalquilsulfonilo, ariloxicarbonilo, heteroalcoxicarbonilo, heteroariloxicarbonilo, alquilaminocarbonilo, arilaminocarbonilo y urea;

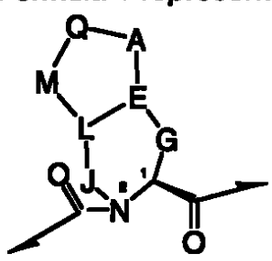
R^{27} es H, alquilo, cicloalquilo, arilo o heteroarilo;

R^{28} es H, alquilo, heteroalquilo, arilo o heteroarilo; y

X'-O- es un éter, éster o carbamato.

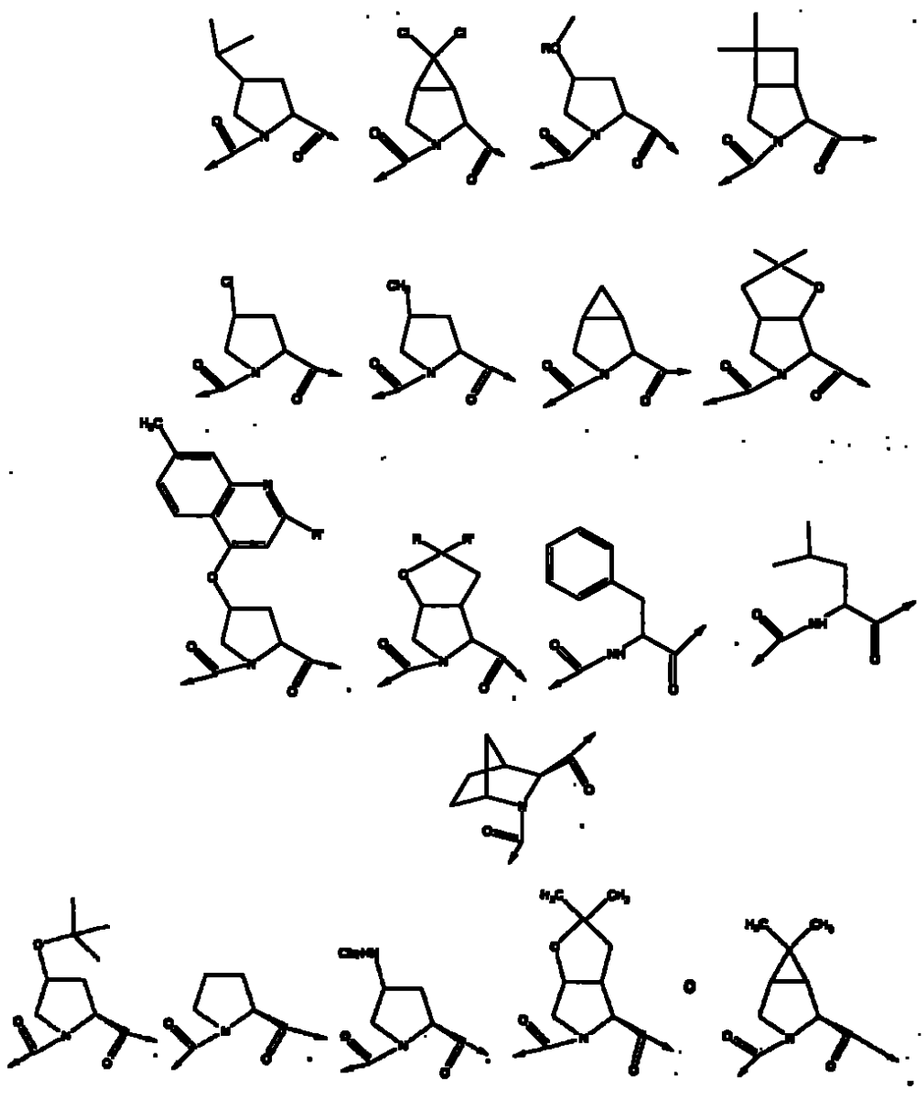
En aún otra realización de la presente invención:

(a) la porción de la Fórmula 1 representada por la Fórmula estructural 2:

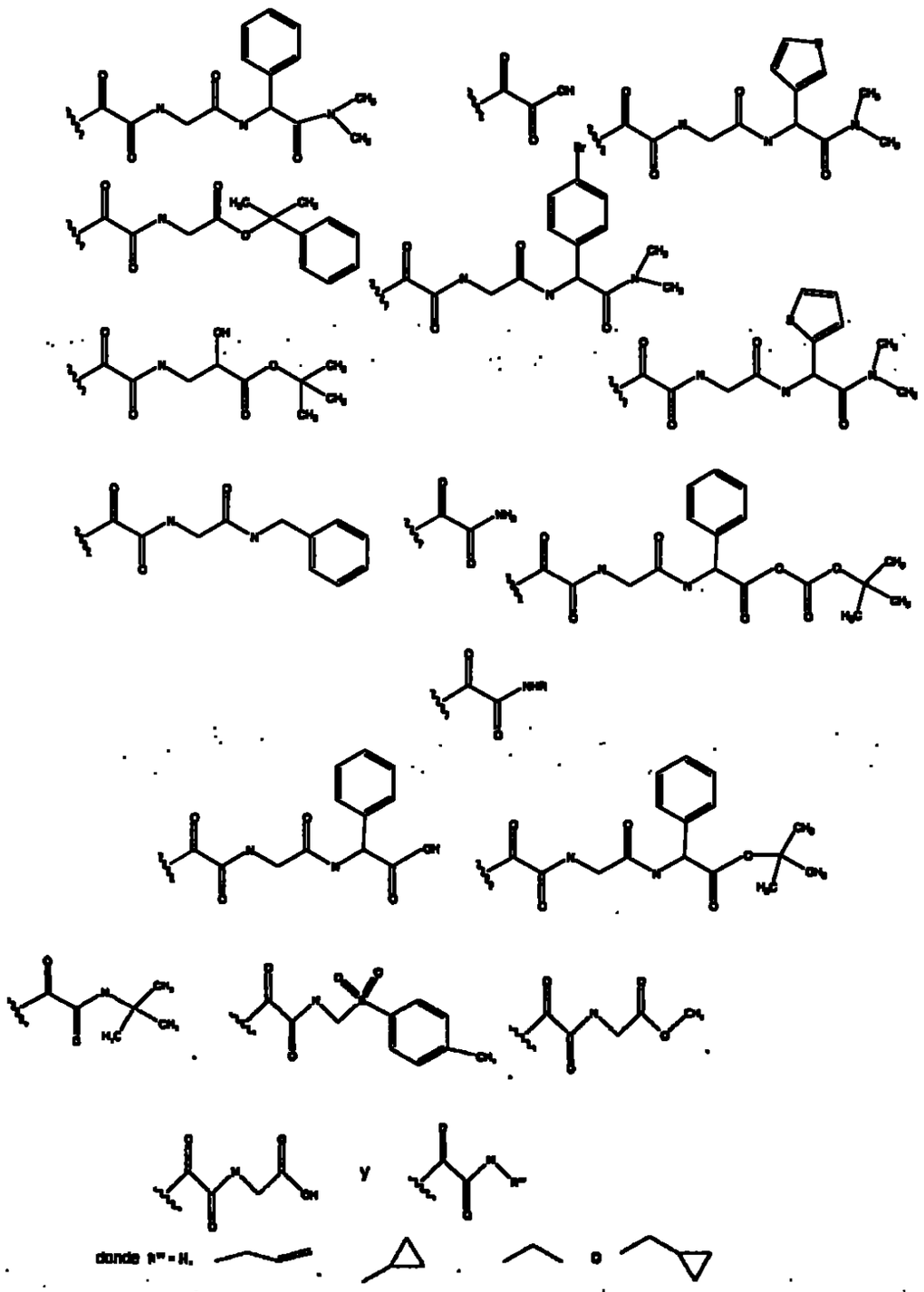


es

Fórmula 2



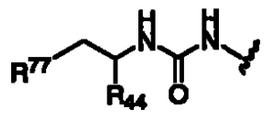
(b) R^1 se selecciona de las siguientes estructuras:



(c) Z' está representado por cualquiera de (i), (ii) o (iii) que se muestran a continuación:

(i)

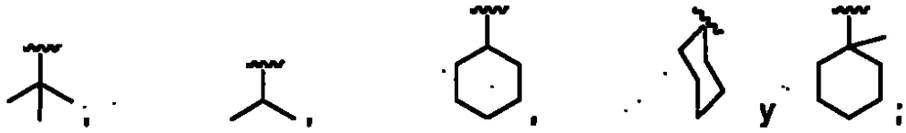
924
421



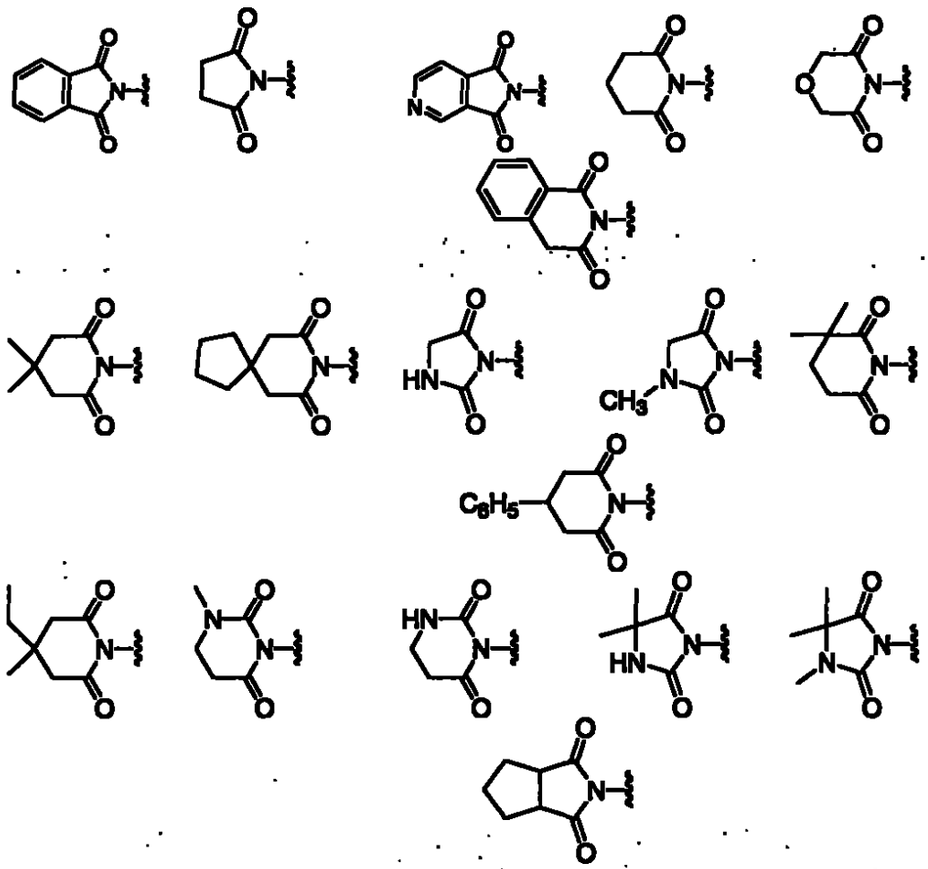
Fórmula A

en la cual:

R^{44} se selecciona del grupo conformado por:

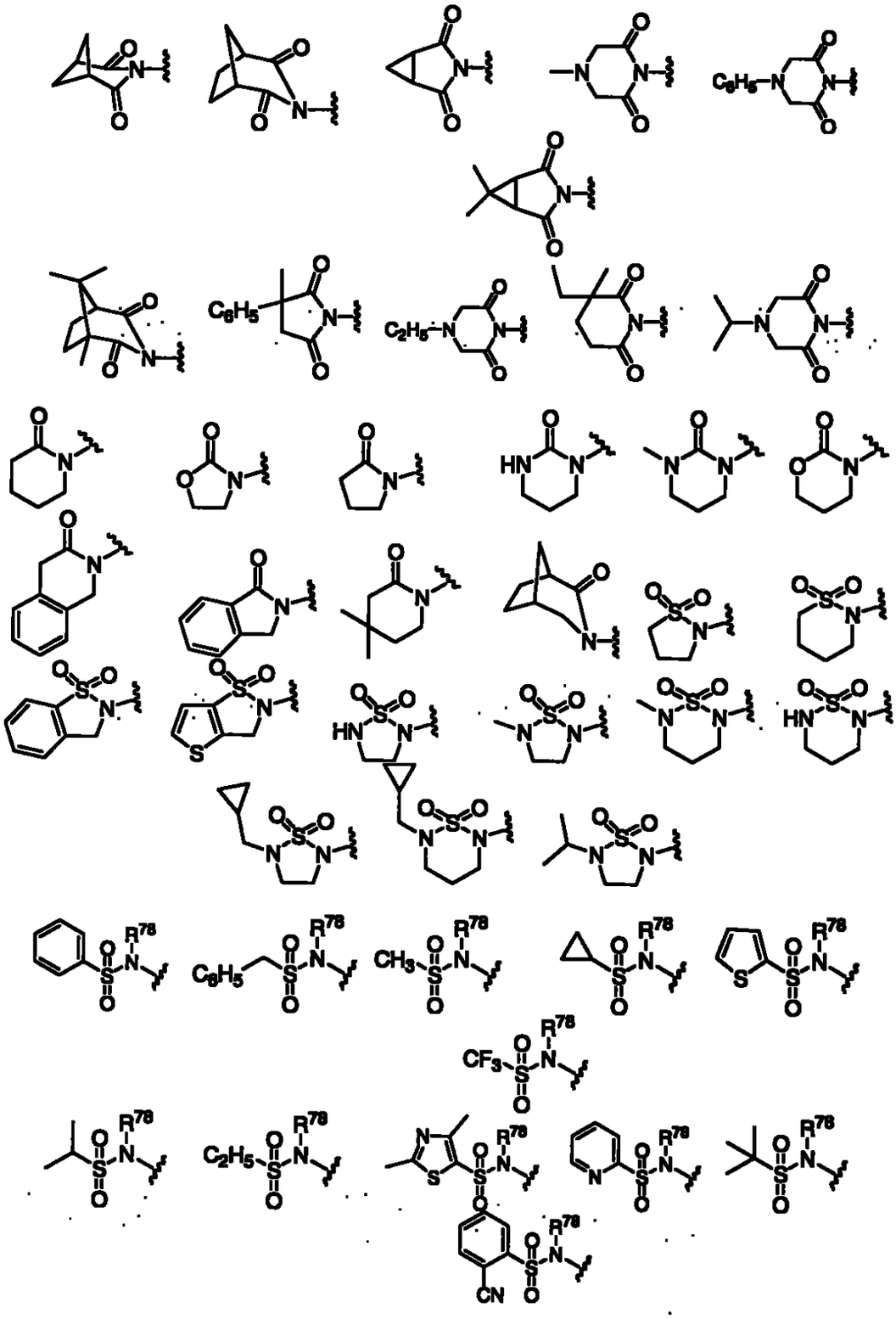


y R^{77} se selecciona del grupo conformado por:

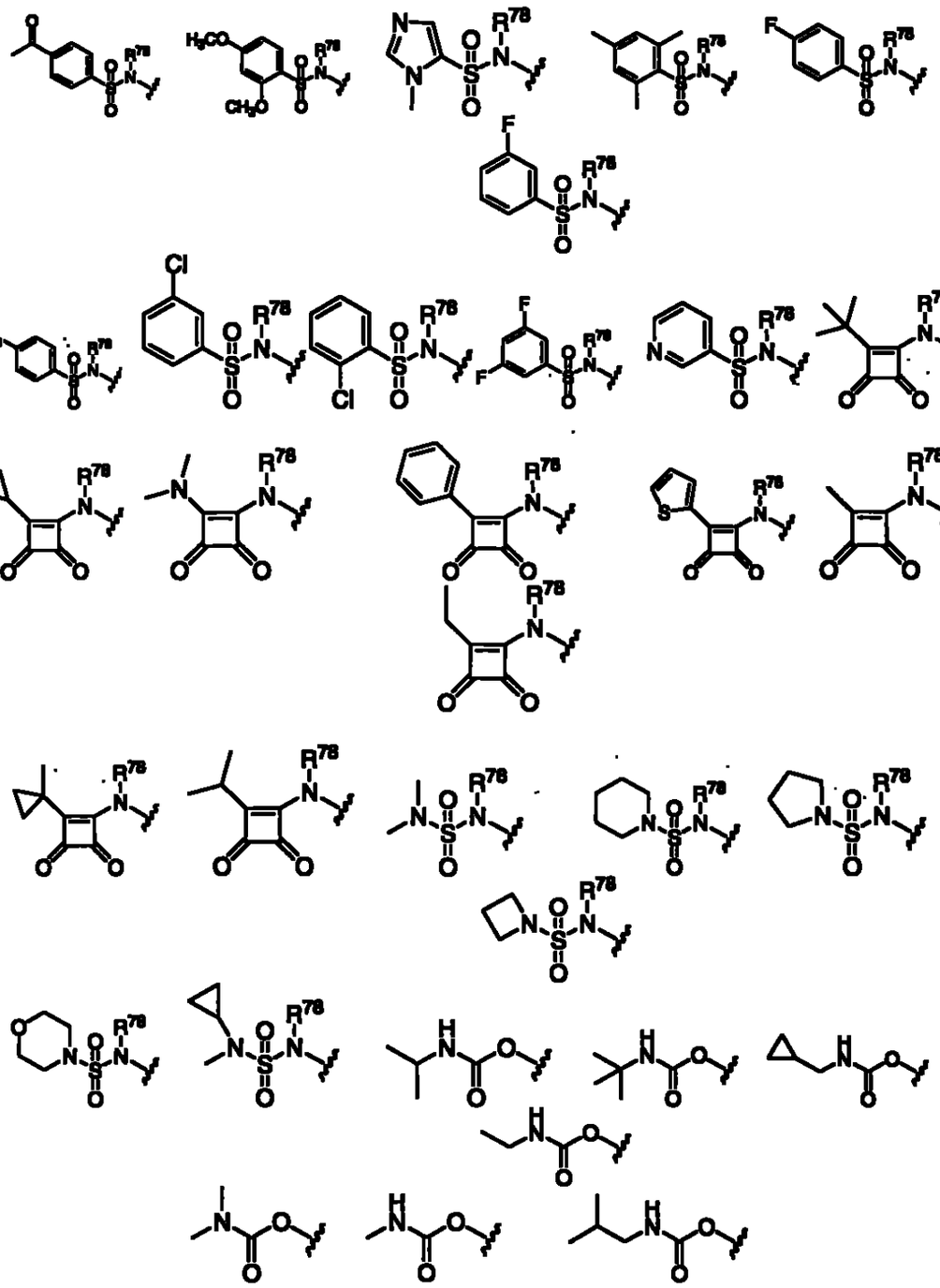


425

422

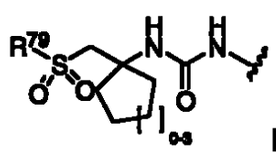


426
423



donde R^{78} se selecciona de metilo, etilo, isopropilo, ter-butilo y fenilo;

(il)

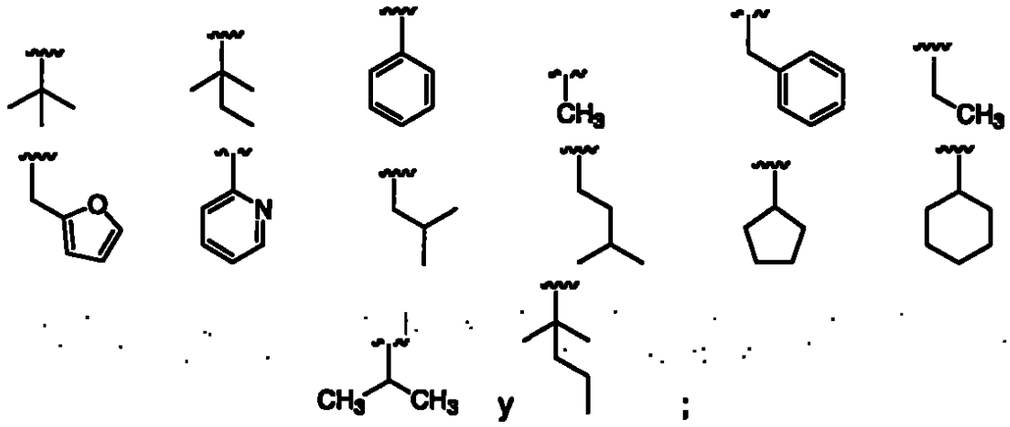


Fórmula B

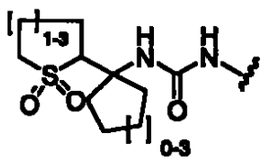
427

424

donde R^{79} se selecciona del grupo conformado por:



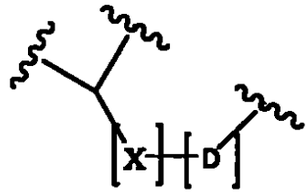
(iii)



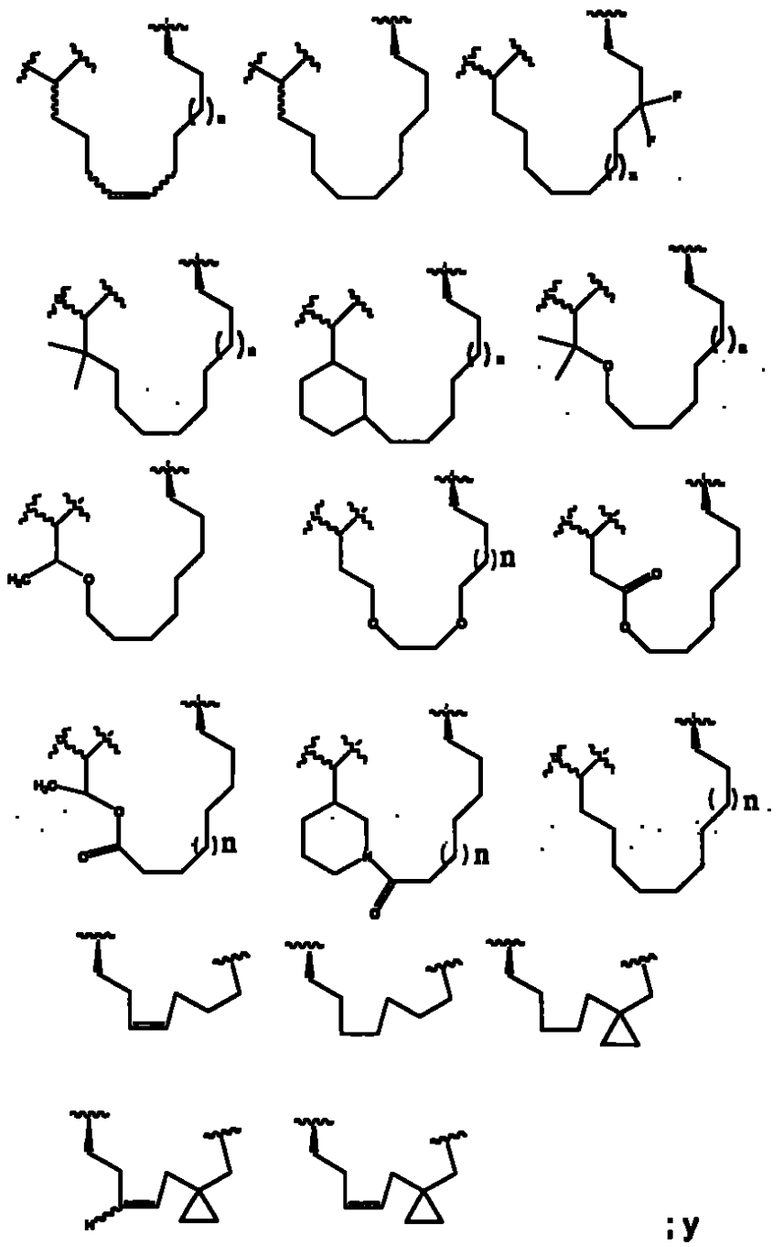
Fórmula C

en la cual el anillo sulfona está sustituido opcionalmente con alquilo y cicloalquilo; y

(d) la porción de la Fórmula 1 representada por



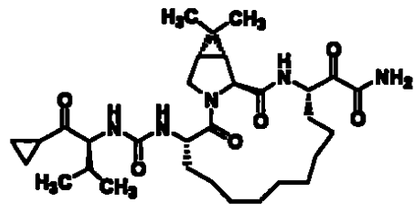
se selecciona de las siguientes estructuras:

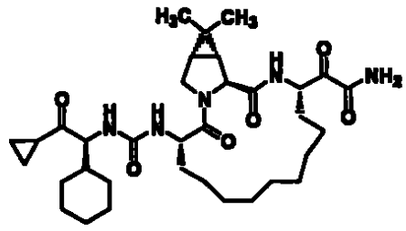


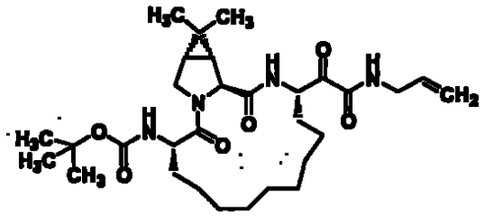
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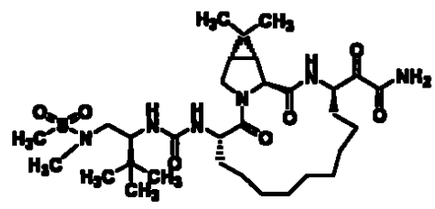
n= 0 a 3.

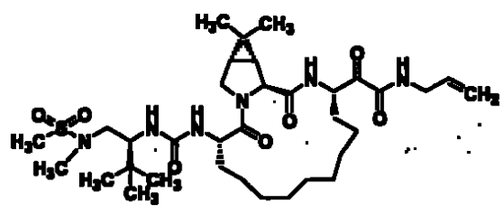
Además, los siguientes compuestos son representativos no limitativos de realizaciones de la presente invención:

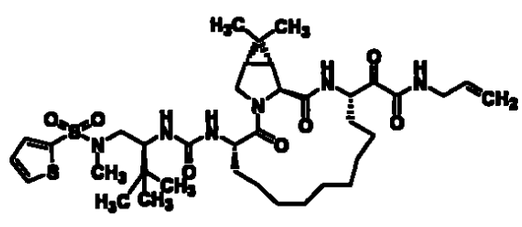


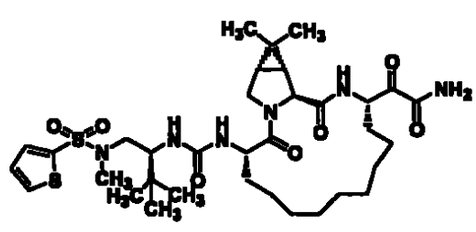


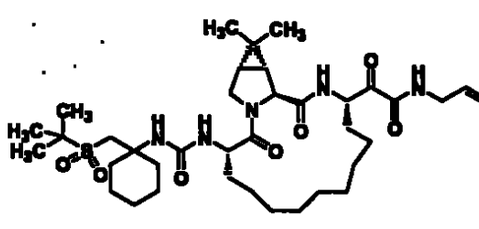






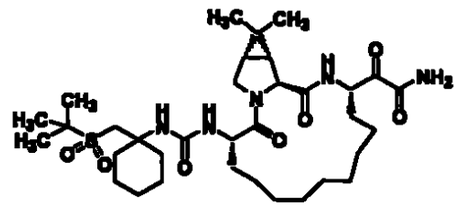


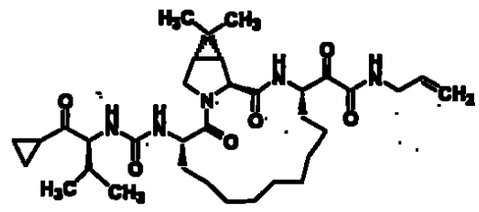


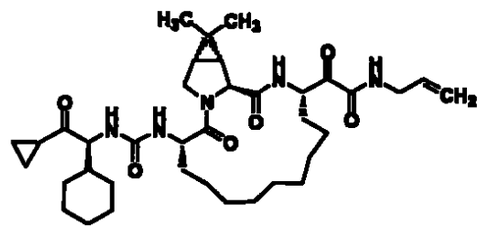


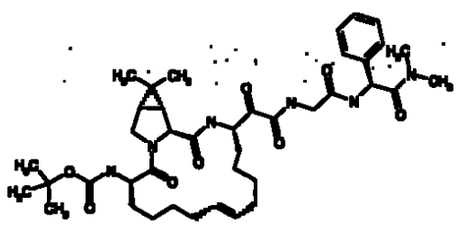
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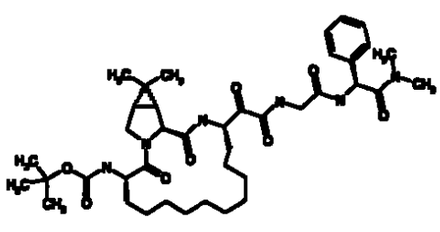
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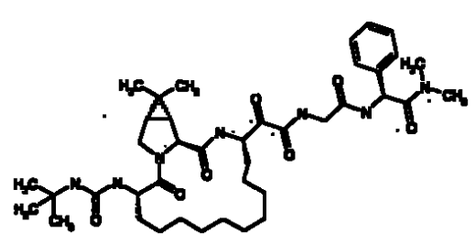


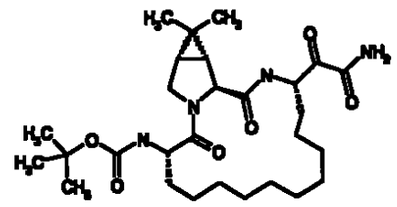


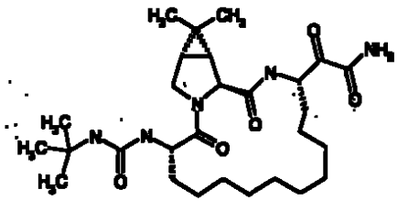


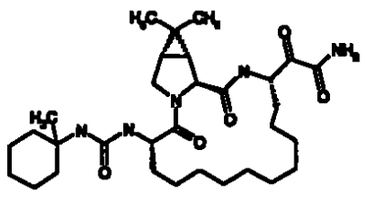


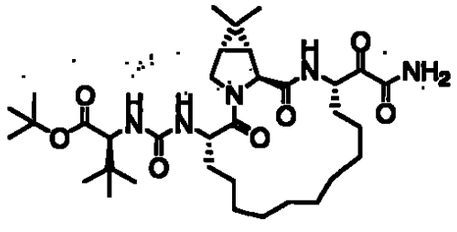


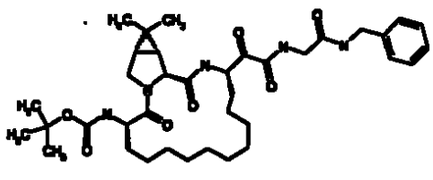


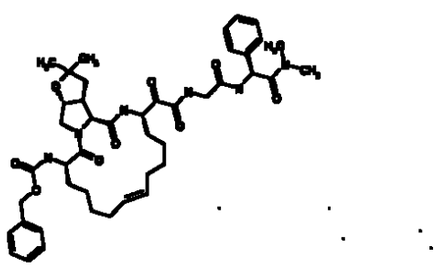






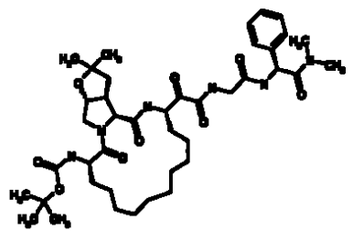


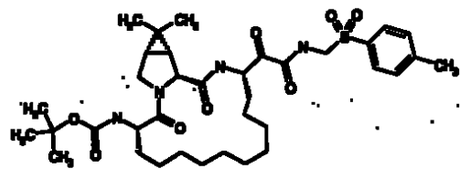


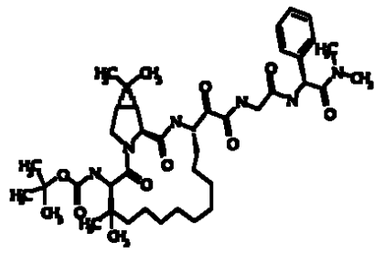


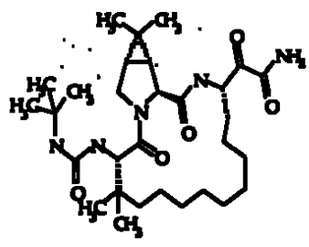
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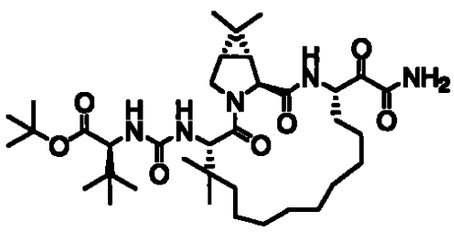
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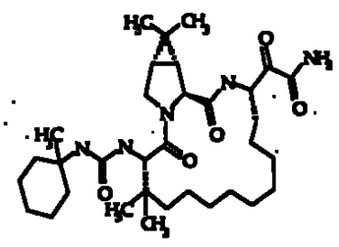






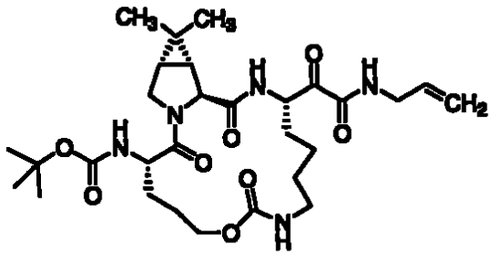


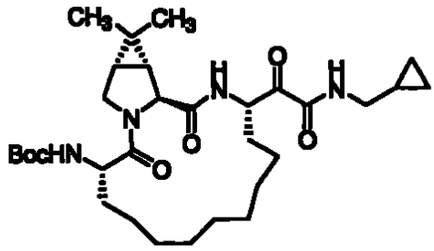


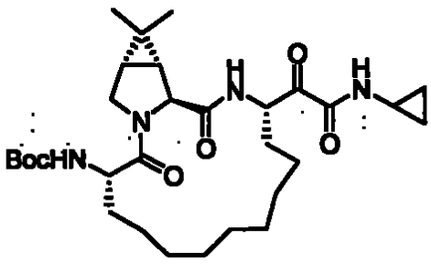


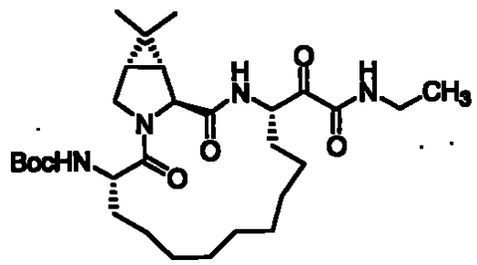
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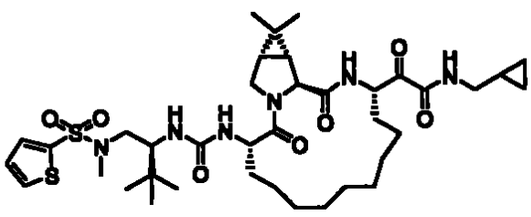
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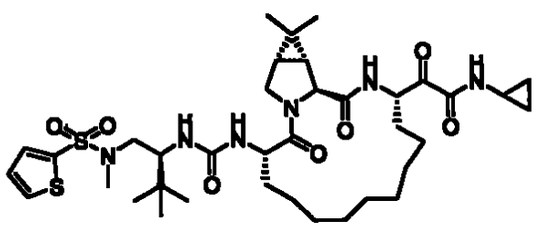


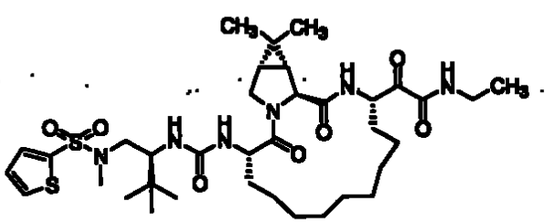


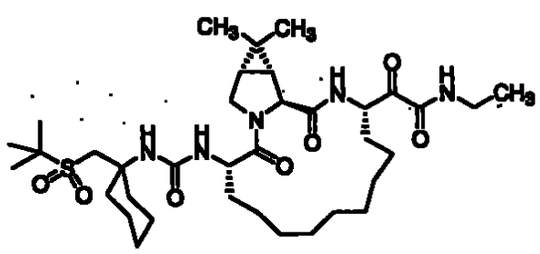


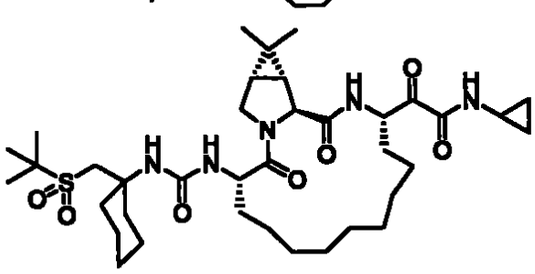


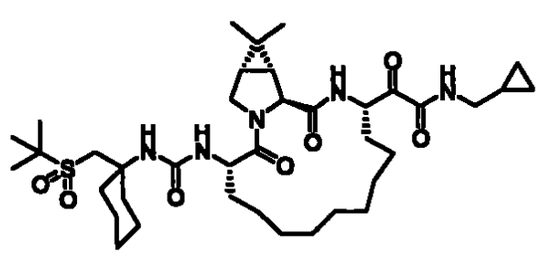


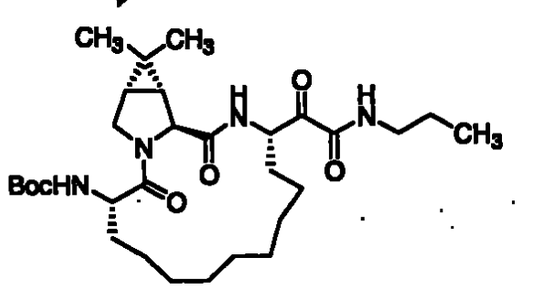


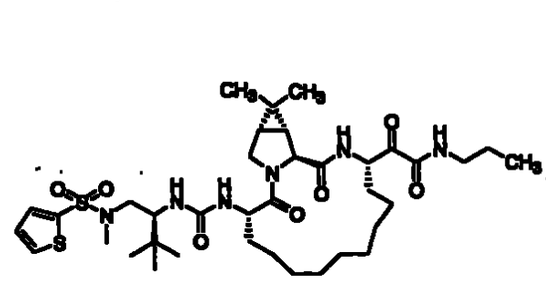


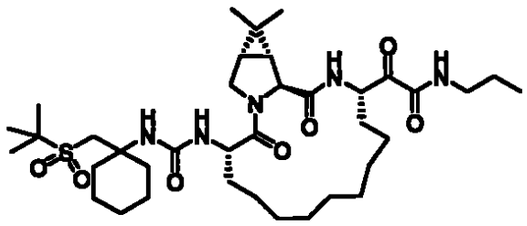


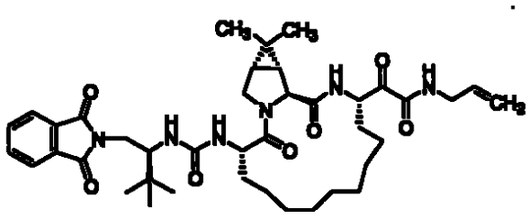


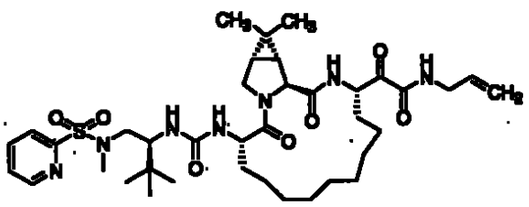


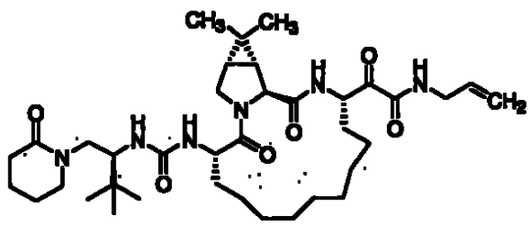


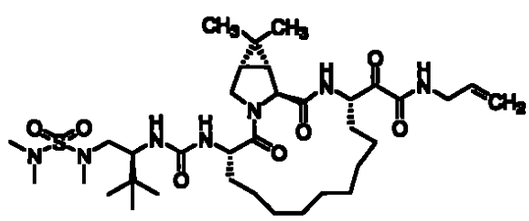


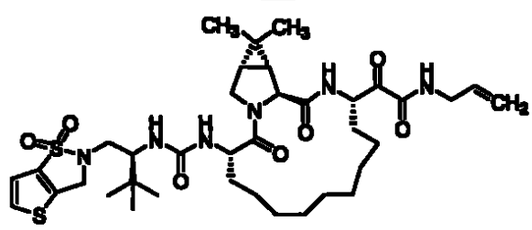


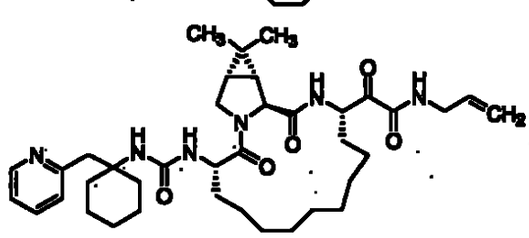


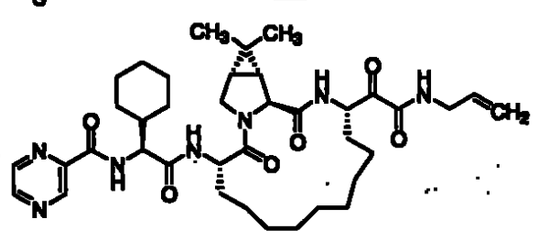


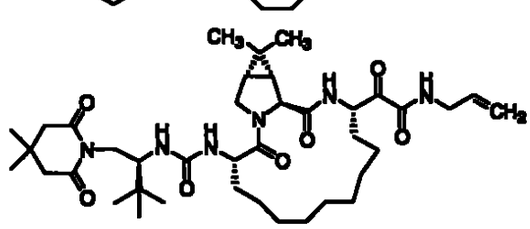


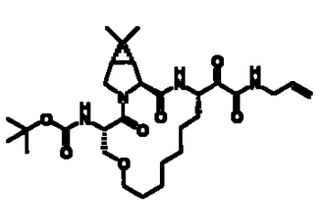


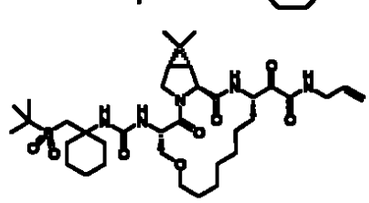






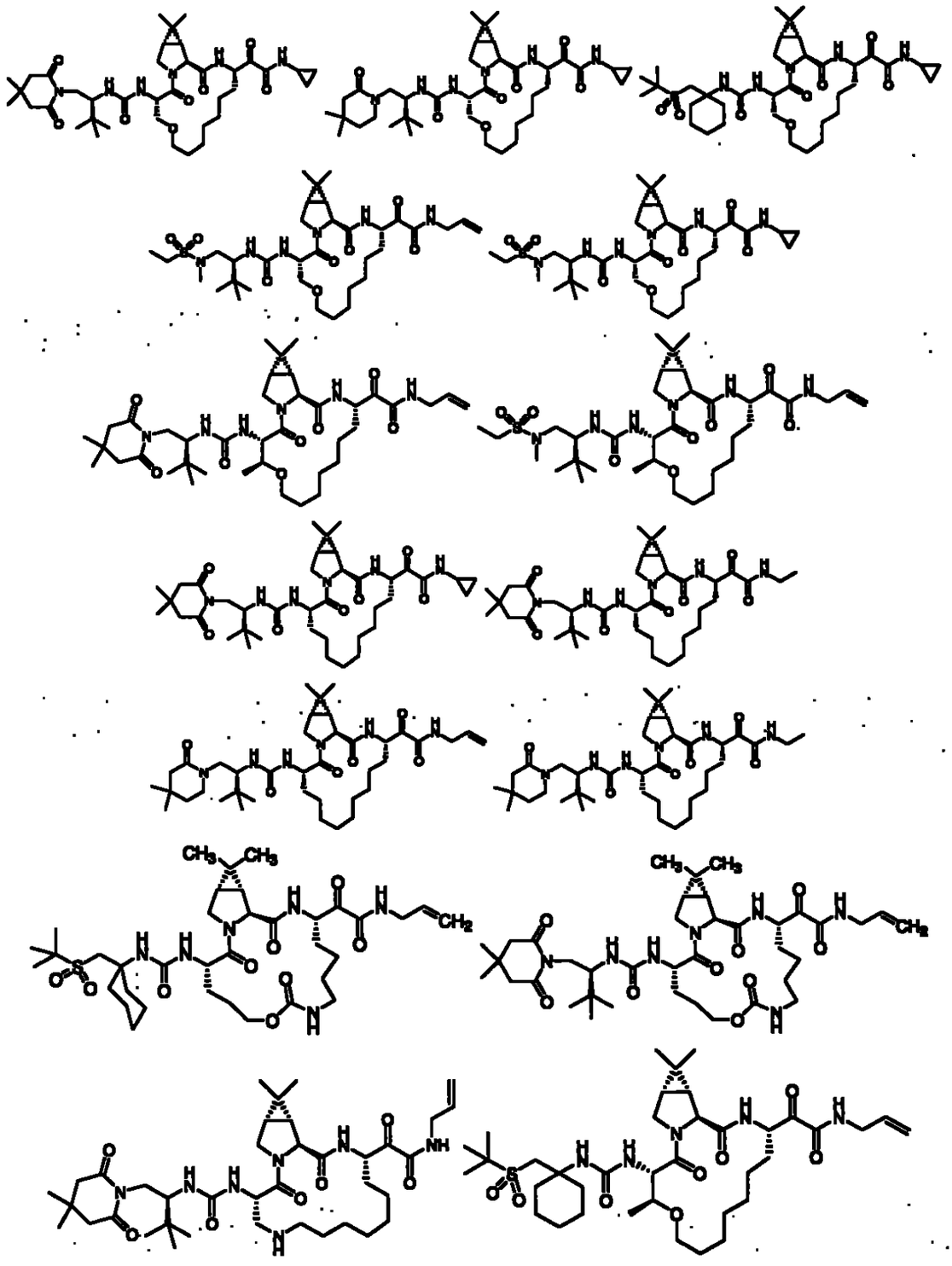


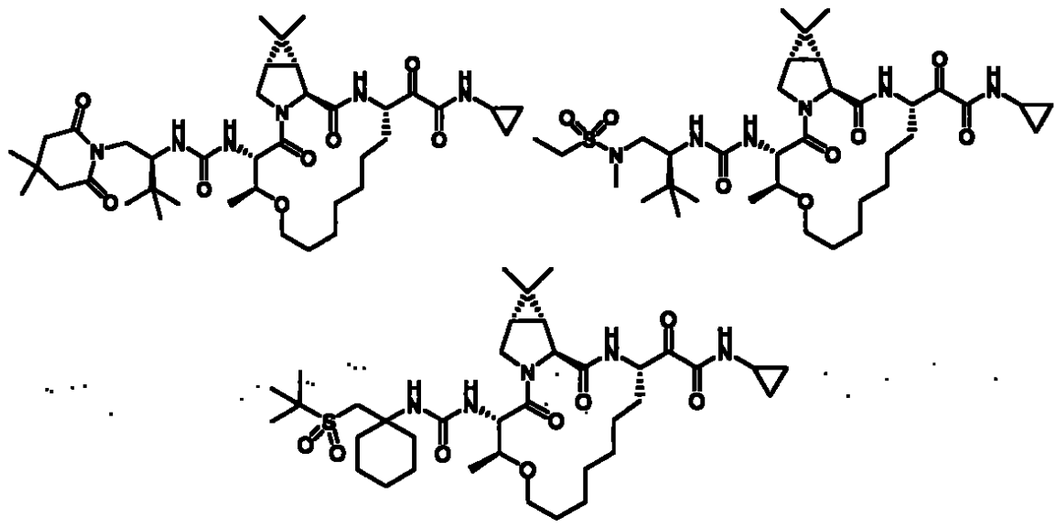




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En aún otro aspecto más de la invención, se provee una composición farmacéutica que comprende como componente activo un compuesto de Fórmula 1 que es para emplear en el tratamiento de trastornos asociados con el VHC. La composición en general incluiría un vehículo aceptable para uso farmacéutico. La composición puede contener uno o más agentes adicionales, tales como por ejemplo, un agente anti-viral, un interferón o un interferón pegilado y similares. Un agente anti-viral preferido es ribavirin y un interferón preferido es α-interferón.

Un método para tratar trastornos relacionados con la proteasa del VHC comprende administrar a un paciente que necesita dicho tratamiento cantidades terapéuticamente efectivas de un compuesto de Fórmula 1, o una composición farmacéutica que comprende cantidades terapéuticamente efectivas de un compuesto de Fórmula 1. La administración puede ser oral o subcutánea.

Los compuestos de Fórmula 1 se pueden emplear para la fabricación de un medicamento para tratar trastornos asociados con la proteasa del VHC, comprendiendo el método, por ejemplo, poner en contacto íntimo un compuesto de Fórmula 1 con un vehículo aceptable para uso farmacéutico. Este y otros aspectos de la invención, se describen en mayor detalle a continuación.

En realizaciones descriptas anteriormente, la presente invención revela compuestos de Fórmula 1 como inhibidores de la proteasa del VHC, en especial

la serina proteasa NS3/NS4a del VHC, o un derivado aceptable para uso farmacéutico de la misma, donde las diversas definiciones se dieron anteriormente.

En otra realización, la presente invención provee composiciones farmacéuticas que comprenden péptidos de la invención como componente activo. Las composiciones farmacéuticas, en general, comprenden adicionalmente un diluyente del vehículo, excipiente o vehículo (denominado colectivamente en la presente como materiales vehículo). Debido a su actividad inhibidora del VHC, dichas composiciones farmacéuticas poseen utilidad en el tratamiento de la hepatitis C y trastornos relacionados. La actividad inhibidora del VHC también puede conducir al uso de los compuestos y/o composiciones de la invención para tratar enfermedades (por ej., SIDA, etc.) que están asociadas o conectadas con el HVC.

En aún otra realización, la presente invención revela métodos para preparar composiciones farmacéuticas que comprenden los compuestos de la invención como componente activo. En las composiciones farmacéuticas y métodos de la presente invención, los componentes activos se administrarán de manera típica en combinación con materiales vehículo adecuados seleccionados adecuadamente con relación a la forma en que se pretenden administrar, es decir comprimidos orales, cápsulas (ya sea rellenas con sólido, rellenas con semi-sólido o rellenas con líquido), polvos para reconstitución, geles orales, elíxires, gránulos dispersables, jarabes, suspensiones y similares y de manera consistente con las prácticas farmacéuticas convencionales. Por ejemplo, para la administración oral en forma de comprimidos o cápsulas, el componente fármaco activo se puede combinar con cualquier vehículo inerte no tóxico, oral, aceptable para uso farmacéutico, tal como lactosa, almidón, sacarosa, celulosa, estearato de magnesio, fosfato dicálcico, sulfato de calcio, talco, manitol, alcohol etílico (formas

líquidas) y similares. Además, también se puede incorporar en la mezcla aglutinantes, lubricantes, agentes desintegrantes y agentes colorantes adecuados, cuando se desee o sea necesario. Los polvos y comprimidos pueden estar compuestos por alrededor de 5 a alrededor de 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, se pueden mencionar para el uso en estas formas de dosificación, el ácido bórico, benzoato sódico, acetato de sodio, cloruro de sodio y similares. Los desintegrantes incluyen almidón, metilcelulosa, goma guar y similares.

También se pueden incluir agentes edulcorantes y saborizantes y conservantes, cuando sea adecuado. A continuación se tratan en mayor detalle algunos de los términos que se indicaron anteriormente, a saber desintegrantes, diluyentes, lubricantes, aglutinantes y similares.

Además, las composiciones de la presente invención se pueden formular en forma de liberación sostenida para proveer la velocidad de liberación controlada de cualquiera o más de los componentes o componentes 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 comprimidos en capas que contienen capas de velocidades variables de desintegración o matrices poliméricas de liberación controlada impregnadas con los componentes activos y en forma de comprimido o cápsulas que contienen dichas matrices poliméricas impregnadas o porosas encapsuladas.

Las preparaciones en forma líquida incluyen soluciones, suspensiones y emulsiones. Como ejemplo, se puede mencionar agua o soluciones de agua-propilenglicol para inyecciones parenterales o el agregado de edulcorantes y

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opacantes para soluciones, suspensiones y emulsiones orales. 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 polvo, que pueden estar combinados con un vehículo aceptable para uso farmacéutico tal como gas comprimido inerte, por ejemplo nitrógeno.

Para la preparación de supositorios, en primer lugar se funde una cera de bajo punto de fusión tal como una mezcla de glicéridos de ácidos grasos tales como manteca de cacao y se dispersa el componente activo de manera homogénea en la misma mediante agitación o mezclado similar. Luego, la mezcla homogénea fundida se vierte en moldes de tamaño conveniente, se deja enfriar y por consiguiente solidificar.

También se incluyen preparaciones en forma sólida destinadas a transformarse, poco antes del uso, en preparaciones en forma líquida, ya sea para administración oral o parenteral. Tales formas líquidas incluyen soluciones, suspensiones y emulsiones.

Los compuestos de la invención se pueden administrar de manera transdérmica. Las composiciones transdérmicas pueden adoptar la forma de cremas, lociones, aerosoles y/o emulsiones y se pueden incluir en un parche transdérmico de tipo matriz o reservorio, según es convencional en la técnica con estos fines.

Los compuestos de la invención también se pueden administrar por vía oral, intravenosa, intranasal o subcutánea.

Los compuestos de la invención también pueden comprender preparaciones que se encuentran en una forma de dosificación unitaria. En tal forma, la preparación se subdivide en dosis unitarias de tamaño adecuado que

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contiene cantidades adecuadas de los componentes activos, por ej. una cantidad efectiva para lograr el propósito deseado.

La cantidad de la composición activa de la invención en una dosis unitaria de preparación, en general, se puede variar o regular de alrededor de 1,0 miligramo a alrededor de 1.000 miligramos, con preferencia de alrededor de 1,0 a alrededor de 950 miligramos, con mayor preferencia de alrededor de 1,0 a alrededor de 500 miligramos, y típicamente de alrededor de 1 a alrededor de 250 miligramos, de acuerdo con la aplicación en particular. La dosis real empleada se puede variar dependiendo de la edad del paciente, sexo, peso y gravedad de la afección que se somete a tratamiento. Tales técnicas son conocidas para aquellos expertos en la técnica.

En general, la forma de dosificación oral de seres humanos que contiene los componentes activos se puede administrar 1 o 2 veces por día. La cantidad y frecuencia de administración se regulará de acuerdo con el criterio del médico que asiste. Un régimen de dosificación diario que se recomienda, en general, para administración oral puede oscilar de alrededor de 1,0 miligramo a alrededor de 1.000 miligramos por día, en dosis únicas o divididas.

A continuación, se describen algunos términos útiles:

Cápsula – se refiere a un envase especial o envoltura hecho de metilcelulosa, alcoholes polivinílicos o gelatinas o almidón desnaturalizados para retener o contener composiciones que comprenden los componentes activos. Las cápsulas de cobertura dura se preparan típicamente de mezclas de gelatinas de piel y hueso porcino con resistencia de gel relativamente alta. La cápsula misma puede contener pequeñas cantidades de colorantes, agentes opacantes, plastificantes y conservantes.

Comprimido - se refiere a una forma de dosificación sólida comprimida o moldeada que contiene componentes activos con diluyentes adecuados. El

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comprimido se puede preparar mediante la compresión de mezclas o granulaciones que se obtienen mediante granulación húmeda, granulación seca o mediante compactación.

Gel oral – se refiere a componentes activos dispersos o solubilizados en una matriz hidrofílica semi-sólida.

El polvo para reconstitución se refiere a mezclas de polvo que contienen los componentes activos y diluyentes adecuados que se pueden suspender en agua o jugos.

Diluyente – se refiere a sustancias que usualmente componen la mayor parte 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 miicrocristalina. La proporción de diluyente en la composición puede oscilar de alrededor de 10 a alrededor de 90% en peso de la composición total, con preferencia de alrededor de 25 a alrededor de 75%, con mayor preferencia de alrededor de 30 a alrededor de 60% en peso, aún con mayor preferencia de alrededor de 12 a alrededor de 60%.

Desintegrante – se refiere a materiales agregados a la composición para ayudar a separarla (desintegrarla) y liberar los medicamentos. Los desintegrantes adecuados incluyen almidones; almidones modificados "solubles en agua fría" tales como carboximetilalmidón sódico; gomas naturales y sintéticas tales como algarroba, karaya, guar, tragacanto y agar; derivados de celulosa tales como metilcelulosa y carboximetilcelulosa sódica; celulosas microcristalinas y celulosas entrecruzadas microcristalinas tales como croscarmelosa sódica; alginatos tales como ácido algínico y alginato sódico; arcillas tales como bentonitas; y mezclas efervescentes. La proporción de desintegrante en la composición puede variar de

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alrededor de 2 a alrededor de 15% en peso de la composición, con mayor preferencia de alrededor de 4 a alrededor de 10% en peso.

Aglutinante - se refiere a sustancias que aglutinan o "adhieren" polvos entre sí y los hacen cohesivos mediante la formación de gránulos, sirviendo por consiguiente como "adhesivo" de la formulación. Los aglutinantes agregan fuerza de cohesión que ya se encuentra disponible en el diluyente o el agente de relleno. Los aglutinantes adecuados incluyen azúcares tales como sacarosa; almidones derivados de trigo, arroz y papa; gomas naturales tales como acacia, gelatina y tragacanto; derivados de algas marinas tales como ácido algínico, alginato sódico y alginato de calcio y amonio; materiales celulósicos, tales como metilcelulosa y carboximetilcelulosa sódica e hidroxipropilmetilcelulosa; polivinilpirrolidona; e inorgánicos tales como silicato de magnesio y aluminio. La proporción de aglutinante en la composición puede variar de alrededor de 2 a alrededor de 20% en peso de la composición, con mayor preferencia de alrededor de 3 a alrededor de 10% en peso, aún más preferentemente de alrededor de 3 a alrededor de 6% en peso.

Lubricante – se refiere a una sustancia agregada a la forma de dosificación para permitir que el comprimido, gránulos, etc. después de comprimidos se liberen 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 punto de fusión elevado; y lubricantes solubles en agua tales como cloruro de sodio, benzoato de sodio, acetato de sodio, oleato de sodio, polietilenglicoles y d'l-leucina. En general, los lubricantes se agregan en el último paso antes de la compresión, ya que deben encontrarse presentes en las superficies de los gránulos y entre estos y las partes de la prensa de comprimidos. La proporción de lubricante en la composición puede oscilar de alrededor de 0,2 a alrededor de 5%

en peso de la composición, con preferencia de alrededor de 0,5 a alrededor de 2%, con mayor preferencia de alrededor de 0,3 a alrededor de 1,5% en peso.

Deslizante – material que previene la aglomeración y mejora las características de fluencia de las granulaciones, de manera que el flujo sea fluido y uniforme. Los deslizantes adecuados incluyen dióxido de silicio y talco. La proporción de deslizante en la composición puede variar de alrededor de 0,1% a alrededor de 5% en peso de la composición total, con preferencia de alrededor de 0,5 a alrededor de 2% en peso.

Agentes colorantes - excipientes que proveen coloración a la composición o a la forma de dosificación. Tales excipientes incluyen colorantes de grado alimenticio y colorantes de grado alimenticio absorbidos en un absorbente adecuado tales como arcilla u óxido de aluminio. La proporción de agente colorante puede variar de alrededor de 0,1 a alrededor de 5% en peso de la composición, con preferencia de alrededor de 0,1 a alrededor de 1%.

Biodisponibilidad – se refiere a la velocidad y medida en que el componente activo del fármaco o resto terapéutico es absorbido en la circulación sistémica a partir de una forma de dosificación administrada en comparación con un patrón o control.

Se conocen métodos convencionales para preparar comprimidos. Tales métodos incluyen métodos secos tales como compresión directa y compresión de granulación producida mediante compactación, o métodos húmedos u otros procedimientos especiales. También son conocidos métodos convencionales para preparar otras formas de administración tales como, por ejemplo, cápsulas, supositorios y similares.

Otra realización de la invención revela el uso de las composiciones farmacéuticas reveladas anteriormente para tratar enfermedades tales como, por ejemplo, hepatitis C y similares. El método comprende administrar una cantidad

terapéuticamente efectiva de la composición farmacéutica de la invención a un paciente que padece tal enfermedad o enfermedades y que necesita tal tratamiento.

En aún otra realización, los compuestos de la invención se pueden emplear para el tratamiento del VHC en seres humanos a modo de monoterapia o a modo de terapia combinada (por ejemplo combinación doble, combinación triple, etc.) tal como, por ejemplo, en combinación con agentes antivirales y/o inmuno-moduladores. Ejemplos de tales agentes antivirales y/o inmuno-moduladores incluyen Ribavirin (de Schering-Plough Corporation, Madison, New 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, Massachusetts), Thymosin™ (de SciClone Pharmaceuticals, San Mateo, California), Maxamine™ (Maxim Pharmaceuticals, San Diego, California), micofenolato mofetil (de Hoffman-LaRoche, Nutley, New Jersey), interferón (tales como, por ejemplo, interferón-alfa, conjugados PEG-interferón alfa) y similares. Los "conjugados PEG-interferón alfa" son moléculas de interferón alfa unidas covalentemente a una molécula de PEG. Conjugados ilustrativos PEG-interferón alfa incluyen el interferón alfa-2a (Roferon™, de Hoffman La-Roche, Nutley, New Jersey) en forma de interferón alfa-2a peglado (por ej., según se comercializa bajo la denominación comercial Pegasys™), interferón alfa-2b (Intron™, de Schering-Plough Corporation) en forma de interferón alfa-2b peglado (por ej., según se comercializa bajo la denominación comercial PEG-Intron™), interferón alfa-2c (Berofor Alfa™, de Boehringer Ingelheim, Ingelheim, Alemania) o interferón de consenso definido por determinación de una secuencia de consenso de interferones alfa naturales (Infergen™, de Amgen, Thousand Oaks, California).

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Según se expuso anteriormente, la invención incluye tautómeros, rotámeros, enantiómeros y también otros estereoisómeros de los compuestos de la invención. Por consiguiente, como podrá apreciar un experto en la técnica, algunos de los compuestos de la invención pueden existir en formas isoméricas adecuadas. Tales variaciones se consideran dentro del alcance de la invención.

Otra realización de la invención revela un método para preparar los compuestos que se revelan en la presente. Los compuestos se pueden preparar mediante varias técnicas conocidas en la técnica. Procedimientos ilustrativos que son representativos se destacan en los siguientes esquemas de reacción. La invención que se revela en la presente, se ejemplifica además mediante ejemplos preparativos y compuestos de ejemplo que no se deben considerar limitantes del alcance de la invención que se define en las reivindicaciones que se adjuntan. Serán evidentes rutas mecanísticas alternativas y estructuras análogas para aquellos expertos en la técnica.

Se debe entender que mientras que aunque los siguientes esquemas ilustrativos describen la preparación de unos pocos compuestos representativos de la invención, la sustitución adecuada de cualquiera de los aminoácidos naturales o no naturales dará lugar a la formación de los compuestos deseados basados en dicha sustitución. Tales variaciones se consideran dentro del alcance de la invención.

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

AcOH: ácido acético

ADDP: 1,1'-(azodicarbobil)dipiperidina

Boc significa t-butiloxi o ter-butiloxicarbonilo

^{t}Bu, TBu o Bu^t: *ter*-butilo

Cbz: Benciloxicarbonilo

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

Bn o Bzl: Bencilo

Bz: Benzoílo

Chg: Ciclohexilglicina

Cp: Ciclopentildienilo

DCM significa diclorometano;

DCC: 1,3-diciclohexilcarbodiimida

DEAD: Dietilazodicarboxilato

DMAP: 4-N,N-dimetilaminopiridina

DMF significa *N,N*-dimetilformamida;

DMSO significa dimetil sulfóxido;

EDCI: clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida;

Et: Etilo;

EtOAc significa acetato de etilo;

Et_2O: Dietiléter;

HATU significa O-(7-azabenzotriazol-1-ul)-1,1,3,3-tetrametiluronio;

HOOBt: 3-hidroxi-1,2,3-benzotriazin-4(3*H*)-ona;

HOBt: N-hidroxibenzotriazol;

iBoc: isobutoxicarbonilo;

iPr: isopropilo;

KHMDS significa hexametil disililamida de potasio;

LiHMDS significa hexametildisilazida;

Me: Metilo;

MS significa espectrometría de masa;

nBuLi significa n-butil litio;

NMM significa N-metil morfolina;

RMN significa resonancia magnética nuclear;

Phg: Fenilglicina;

Ph: Fenilo;

Pd/C significa catalizador de paladio sobre carbón mineral;

PyBrOP: hexafluorofosfato de bromo-*tris*-pirrolidinfosfonio;

TBuNCO significa t-butil isocianato;

TEMPO: 2,2,6,6-tetrametil-1-piperidiniloxi;

THF significa tetrahidrofurano;

THP significa tetrahidrofurano;

TMSI significa yoduro de trimetil sililo;

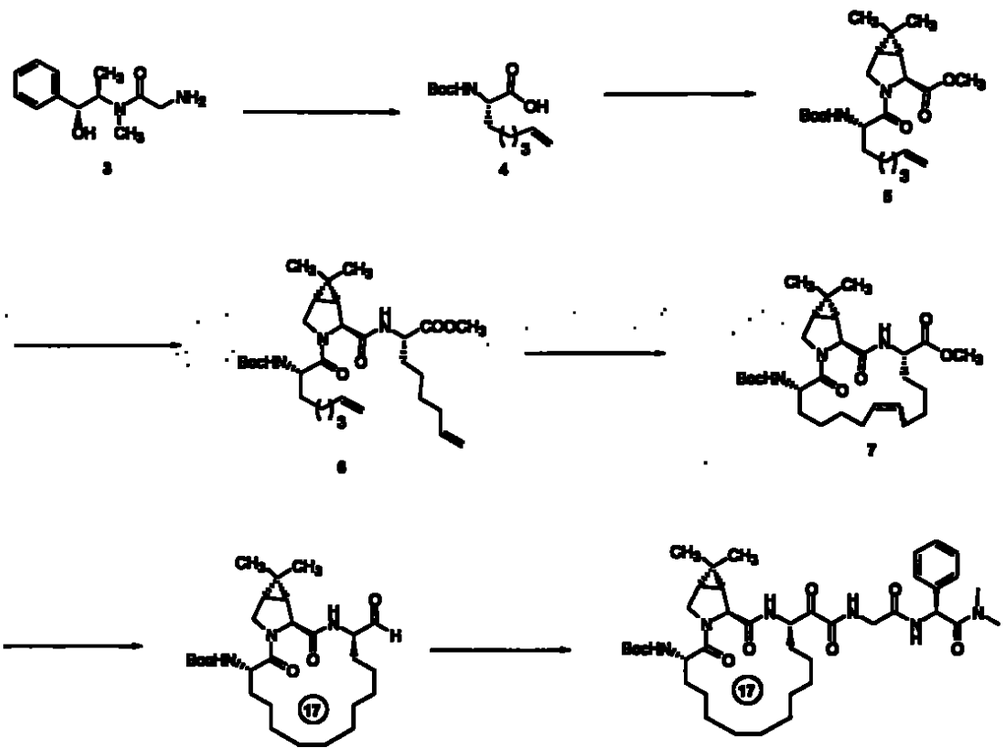
T_3N significa trietilamina;

Ts: p-toluensulfonilo.

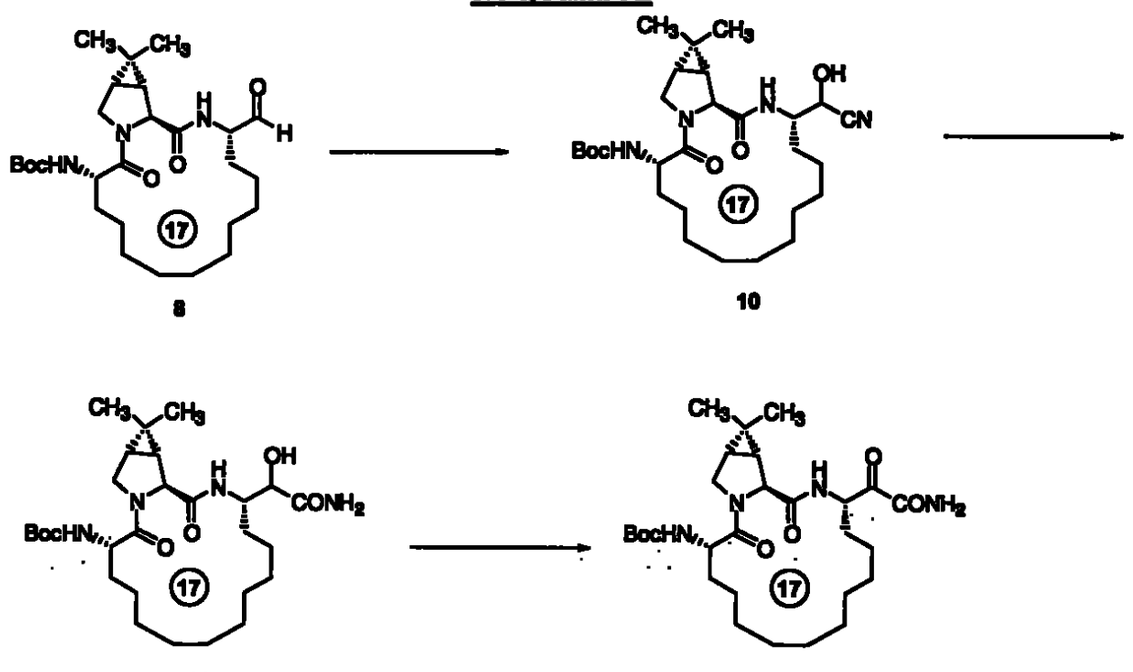
Muchos de los intermediarios y/o ejemplos preparativos empleados en los siguientes procedimientos sintéticos han sido revelados en WO 01/77113; WO 01/081325; WO 02/08198; WO 02/08256; WO 02/08187; WO 02/08244; WO 02/48172; WO 02/08251; y solicitud pendiente de patente estadounidense Acta No. 10/052.386, presentada el 18 de enero de 2002. Las revelaciones de aquellas solicitudes se incorporan en la presente a modo de referencia a las mismas.

Esquemas Preparativos Generales y Procedimientos para Ejemplos Preparativos

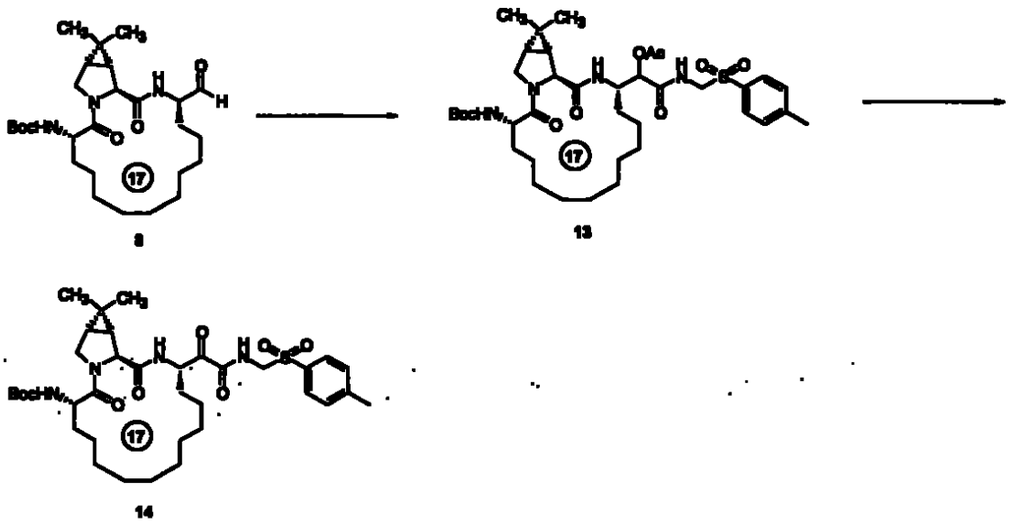
ESQUEMA 1



ESQUEMA 2



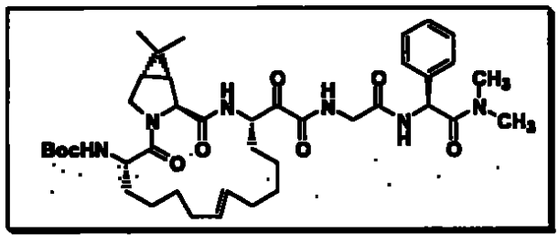
ESQUEMA 3



8 13 14

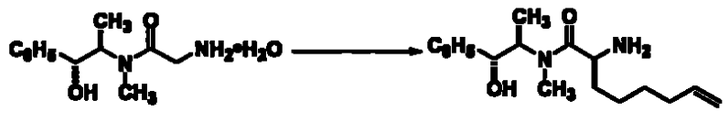
Procedimientos para Ejemplos Preparativos

Ejemplo Preparativo 1



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Paso A



1a 1b

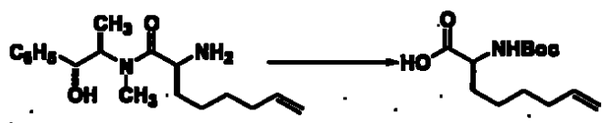
La síntesis de **1b** se puede lograr mediante el uso del procedimiento de (1) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W.; *J. Am. Chem. Soc* **1997**, *119*, 656; (2) Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W.; *J. Org. Chem.*, **1999**, 64, 3322; o (3) Myers, A. G.; Gleason, J. L.; *Org. Synth.* **1998**, *76*, 57,

Se trató una solución de amina **1a** (24 g, 120 mmol) en THF (300 ml) con LiCl anhidro (16,80 g, 400 mmol) durante 0,5 h y se agitó hasta que la mezcla de reacción se homogeneizó. La mezcla de reacción se enfrió a 0°C y se trató con

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una solución de THF de LIHMDS (66,80 g , 400 mmol en 300 ml de THF) durante 20 min. La mezcla de reacción se agitó a 0°C durante 0,5 h y se trató con 6-bromohexeno (19,44 g, 120 mmol) y se agitó a t.a. durante 24 h. La mezcla de reacción se disolvió en HCl 1 M acuoso y se concentró in *vacuo* para eliminar el THF. La mayor parte de la capa acuosa se diluyó también con HCl 3M acuoso (300 ml) y se extrajo con éter (2x200 ml). La capa acuosa se alcalinizó a un pH 14 usando NaOH acuoso (50%) y se extrajo con CH_2Cl_2 (3x 300 ml). Las capas orgánicas combinadas se secaron con $MgSO_4$ se filtraron y se concentraron in *vacuo* para dar **1b** bruto (15,1 g) que se empleó en el siguiente paso sin otra purificación.

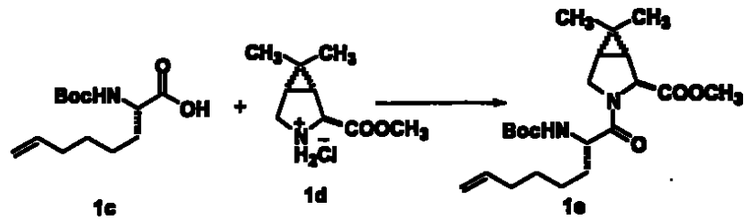
Paso B



1b **1c**

Una solución de **1b** (12,5 g, 41,2 mmol) se disolvió en NaOH acuoso (1 M, 88,0 ml, 88 mmol) y se calentó a reflujo durante 3 h. La mezcla de reacción se enfrió a ta. y se extrajo con CH_2Cl_2 (3x100 ml). La capa acuosa se trató con 100 ml de dioxano seguido por $NaHCO_3$ (8,00 g, 95,2 mmol) y di-terbutil dicarbonato (8,95 g, 41 mmol) y se agitó a t.a. durante 5 h. La mezcla de reacción se extrajo con éter (2x250 ml) y la capa acuosa se acidificó a un pH~2 con HCl acuoso y se extrajo con CH_2Cl_2 (2x200 ml). Las capas orgánicas combinadas se secaron con MgSO4, se filtraron, se concentraron in *vacuo* para dar el ácido **1c** (10,8 g) como un sólido incoloro.

Paso C



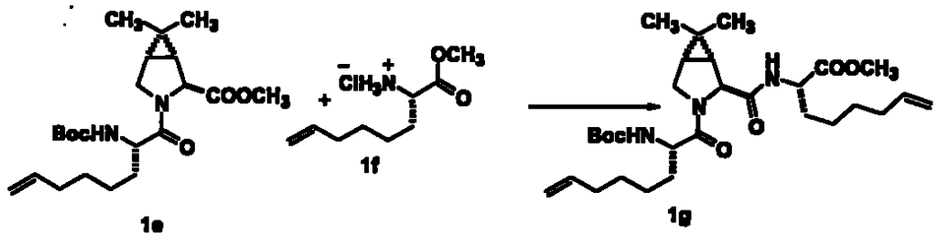
1c 1d 1e

Una solución de ácido **1c** (5g, 19,44 mmol) y amina **1d** (3,98 g, 19,44 mmol) en CH_2Cl_2 (30 ml), DMF (30 ml) a 0°C se trató con HATU (8,87 g, 23,31 mmol) y NMM (4,91 g, 5,33 ml) y se agitó hasta el día siguiente a 0°C. La mezcla de reacción se concentró in *vacuo* y se diluyó con 650 ml de CH_2Cl_2. La capa acuosa se lavó con HCl acuoso (1M, 2x300 ml), NaHCO3 acuoso (1M, 2x300 ml). Las capas orgánicas se secaron con $MgSO_4$, se filtraron y se concentraron in *vacuo* y se purificaron mediante cromatografía (SiO_2, Acetona/Hexanos 5:1) para dar **1e** como un aceite incoloro (5,5 g).

^{1}H RMN : (CD_3OD, 300 MHz) δ 5,87-5,76 (m, 1 H), 4,97-4,92 (dd, 2 H), 4,26 (bt, 1 H, J=7,8 Hz), 3,98 (d, 1 H, J= 10,2 Hz), 3,61 (dd, 2 H, J=5,1, 5,1 Hz), 3,73 (s, 3 H), 2,14-2,07 (m, 2 H), 1,74-1,42 (m, 9 H), 1,41 (s, 9 H), 1,12 (s, 3 H), 0,92 (s, 3 H).

^{13}C RMN : (CD_3OD, 75 MHz), δ 173,8, 173,2, 158,0, 139,8, 115,0, 80,4, 60,91, 53,42, 52,80, 34,7, 33,5, 32,3, 31,4, 29,8, 28,7, 26,4, 26,1, 20,6, 12,9.

Paso D



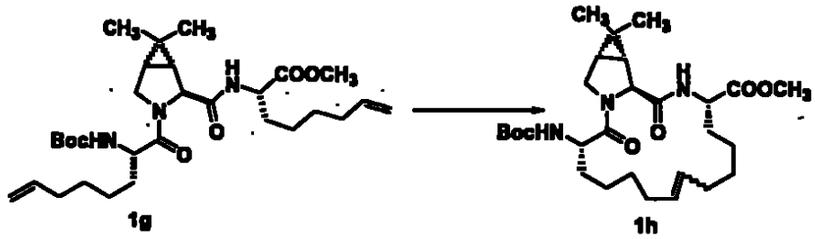
1e 1f 1g

Una solución del éster **1e** (4g, 9,79 mmol) en THF (20 ml), H_2O (20 ml) y MeOH (10 ml) se trató con $LiOH{\cdot}H_2O$ (575 mg, 14 mmol) y se agitó a t.a. durante 4h. La mezcla de reacción se concentró in *vacuo* para eliminar THF y MeOH. La capa preponderantemente acuosa se acidificó con HCl acuoso y se extrajo en

CH_2Cl_2 (3x100 ml). Las capas orgánicas combinadas se secaron con $MgSO_4$, se filtraron, se concentraron in *vacuo* y se utilizaron como se encontraban.

Una solución del ácido que se obtuvo de hidrólisis de **1e**, segmento de amina **1f** (2,02 g, 9,79 mmol) en DMF (40 ml), CH_2Cl_2 (40 ml) a 0°C se trató con HATU (4,46 g, 11,84 mmol) y NMM (3,5 g, 35 mmol) y se agitó a 0° C durante 24 h. La mezcla de reacción se concentró in *vacuo* y se diluyó con HCl acuoso (100 ml). La capa acuosa se extrajo con CH_2Cl_2 (3x75 ml). Las capas orgánicas combinadas se lavaron con $NaHCO_3$ acuoso saturado (3x100 ml), salmuera, se secaron con $MgSO_4$, se filtraron y se concentraron in *vacuo* y se purificaron mediante cromatografía de gel de sílice (EtOAc/Hex 1:3) para dar **1g** (4,5 g) como una espuma incolora.

Paso E

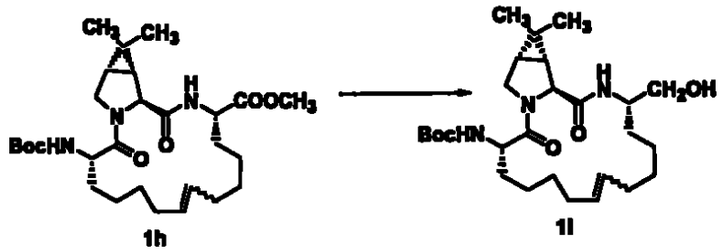


Una solución del dieno **1g** (1,1 g, 2,0 mmol) en CH_2Cl_2 seco (20 ml) se trató con catalizador de Grubbs $[(Cy)_3RuCl_2{=}CHC_6H_5$, 83,8 mg, 0,1 mmol) y se agitó a t.a. durante 24 h. La mezcla de reacción se concentró in *vacuo* y se purificó mediante cromatografía (SiO_2, EtOAc/Hex 1:3) para dar **1h** (501 mg) como un sólido incoloro y una mezcla de isómeros *E/Z*.

^{1}H RMN ($CDCl_3$, 300 MHz) δ, 7,38 (d, 1 H, J=8,1 Hz), 5,30-5,18 (m, 2 H), 4,55 (dt, 1 H, J= 2,4, 9,6 Hz), 3,92 (bs, 1 H), 3,77 (s, 3 H), 3,79-3,77 (bm, 1H), 2,06-2,1 (bm, 3 H). 1,95-1,81 (m, 2 H), 1,79-1,77 (m, 13 H), 1,31 (s, 9 H), 1,05 (s, 3 H), 0,85 (s, 3H).

MS (ESI), m/z, intensidad relativa 542 [$(M+Na)^+$ 45], 464 (20), 448 (25) 420 (100) .

Paso F



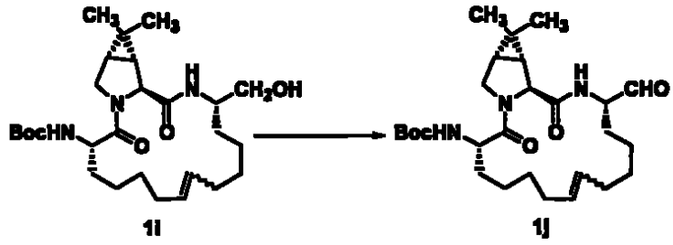
1h 1l

Una solución del éster **1h** (100 mg, 0,19 mmol) en THF seco (1 ml) se trató con $LiBH_4$ (2M de solución en THF, 0,2 ml) y se agitó a t.a. durante 16 h. La mezcla de reacción se desactivó con HCl acuoso (1M, 30 ml) y se extrajo con CH_2Cl_2 (3x30 ml). Las capas orgánicas combinadas se lavaron con $NaHCO_3$ acuoso (100 ml) salmuera, se secaron con $MgSO_4$ se filtraron y se concentraron in *vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 1:3) para dar **1l** (70 mg) como un sólido amorfo.

^{1}H RMN ($CDCl_3$, 300 MHz) δ 6,96 (d, 1 H, J=8,1 Hz), 5,32-5,21 (m, 2 H), 4,43-4,37 (m, 2 H) 4,01-3,93 (m, 1 H), 3,77 (dd, 1 H, J=5,7, 4,8 Hz), 3,65 (dd, 1 H, J= 3,9, 6,6 Hz), 3,53 (dd, 1 H, J= 6,0, 10,8 Hz), 2,11-1,77 (m, 6 H), 1,55-1,31 (m, 12 H), 1,45 (s, 9 H), 1,05 (s, 3 H), 0,87 (s, 3 H).

MS (ESI), m/z, Intensidad relativa 530 [$(M+K)^+$, 10], 514 [$(M+Na)^+$, 70], 492 [$(M+1)^+$, 20], 392 (100).

Paso H



1l 1j

Una solución del alcohol **1l** (70 mg, 0,15 mmol), en CH_2Cl_2 (3 ml) se trató con reactivo de Dess-Martin (85 mg, 0,2 mmol) y se agitó a t.a. durante 2 h. La mezcla de reacción se desactivó con solución de $Na_2S_2O_3$ (10%, 10 ml) y solución saturada de $NaHCO_3$ (10 ml) y se agitó a t.a. durante 0,5 h. La mezcla de reacción se extrajo con CH_2Cl_2 (50 ml). La capa orgánica se secó con $MgSO_4$, se filtró y se

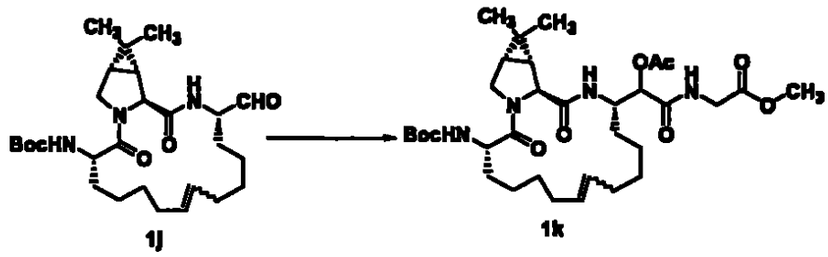
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concentró in *vacuo* y se purificó mediante cromatografía (SiO_2, acetona/hexanos 4:1) para dar **1j** (50 mg) como un sólido incoloro esponjoso.

^{1}H RMN ($CDCl_3$, 300 MHz) δ9,54 (s, 1 H), 7,43 (d, 1 H, J = 7,8 Hz), 5,30-5,19 (m, 2 H), 4,55-4,40 (m, 2 H), 3,93 (d, 1 H, J=10,2 Hz), 3,77 (dd, 1 H, J=5,4, 5,1 Hz), 2,04-1,78 (m, 4 H), 1,55-1,27 (m, 14), 1,31 (s, 9 H), 1,02 (s, 3 H), 0,95 (s, 3 H).

MS (ESI), m/z, intensidad relativa 512 [$(M+Na)^+$, 80], 490 [$(M+1)^+$, 10], 434 (20), 390 (100).

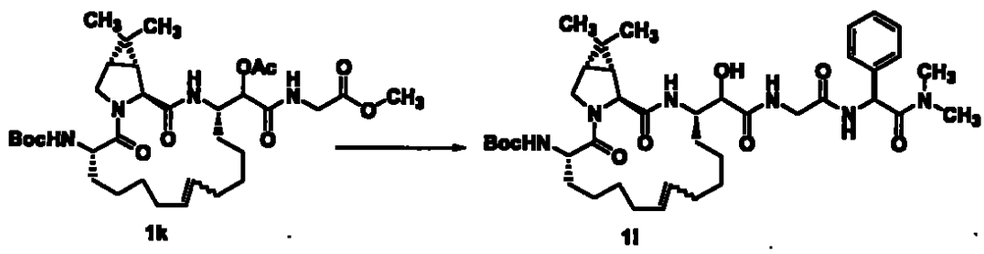
Paso I



Una solución del aldehído **1j** (50 mg, 0,11 mmol) en CH_2Cl_2 seco (2 ml) se trató con CH_3COOH (19 mg, 0,31 mmol) y metilisocianoacetato (31 mg, 0,31 mmol). La mezcla de reacción se agitó a ta. durante 48 h y se concentró in *vacuo*. El residuo se purificó mediante cromatografía (SiO_2, acetona/hexanos 1:2) para dar **1k** (50 mg) como una mezcla de diastereómeros.

MS (ESI), m/z, intensidad relativa 671 [$(M+Na)^+$, 45], 649 [$(M+1)^+$, 30], 549 (100).

Paso J



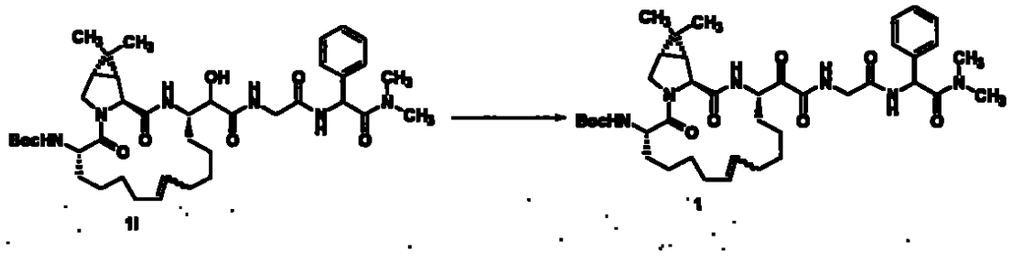
Una solución del metil éster **1k** (50 mg, 0,078 mmol) en THF (2 ml), H_2O (2 ml) y CH_3OH (2 ml) se trató con $LiOH·H_2O$ (20 mg, 0,5 mmol) y se agitó a t.a. durante 2 h. Después de completada, la reacción se acidificó con HCl acuoso (2

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452

ml) y se concentró in *vacuo*. El residuo se secó in *vacuo* y se usó como tal sin otra purificación.

El ácido se disolvió en CH_2Cl_2 (2 ml), DMF (2 ml) y se trató con H-Phg-$N(CH)_2$ ·HCl (26 mg, 0,12 mmol), NMM (32 mg, 0,32 mmol) HATU (45 mg, 0,12 mmol) y se agitó a 0°C durante 24 h. La solución de color amarillo se concentró in *vacuo* y se diluyó con CH_2Cl_2 (70 ml). Las capas orgánicas se lavaron con $NaHCO_3$ acuoso saturado, HCl acuoso y salmuera. La mezcla de reacción se secó ($MgSO_4$) se filtró, se concentró in *vacuo* y se usó tal cual en el siguiente paso (47 mg).

Paso K



11 1

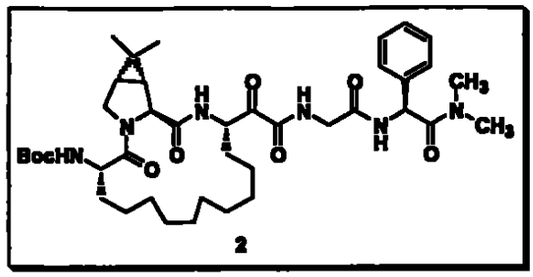
Una solución del alcohol 11 (50 mg, 0,066 mmol) en CH_2Cl_2 (2 ml) se trató con Reactivo de Dess-Martin (60 mg, 0,14 mmol) y se agitó a t.a. durante 2 h. La reacción se diluyó con solución acuosa de $Na_2S_2O_3$ y solución acuosa de $NaHCO_3$ (20 ml cada una) y se extrajo con CH_2Cl_2 (50 ml). La capa orgánica se lavó con $NaHCO_3$ saturado, salmuera, se secó con $MgSO_4$, se filtró, se concentró in *vacuo* y se purificó mediante cromatografía (acetona/hexanos 2:3) para dar 1 (22 mg) como un sólido incoloro.

MS (ESI), m/z, intensidad relativa 773 [$(M+Na)^+$, 80], 751 [$(M+1)^+$, 60], 651 (100).

Ejemplo Preparativo 2

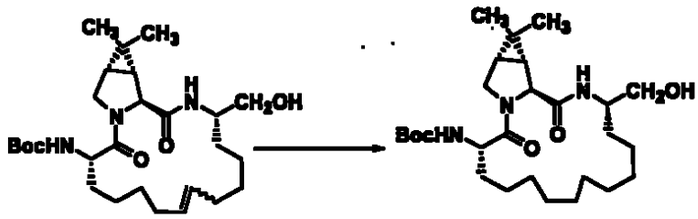
456

453



2

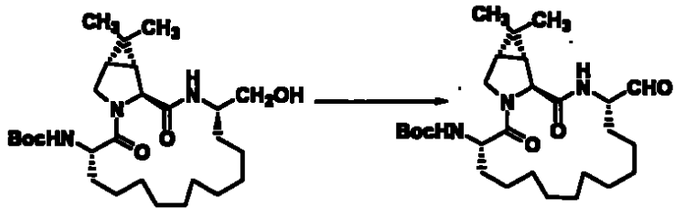
Paso A



1l 2a

Una solución del alcohol **1l** (1,1g, 2,25 mmol) en metanol (30 ml) se trató con Pd/C (10% p/p, 100 mg) y se hidrogenó a 4,14 x 10^5 Pa (60 psi) durante 3 h. La mezcla de reacción se filtró a través de un tapón de celite, se concentró in *vacuo* para dar **2a**, que se usó en el siguiente paso sin otra purificación.

Paso B

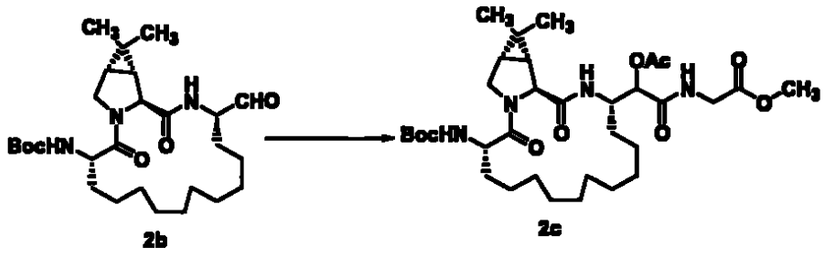


2a 2b

Se oxidó **2a** del paso A usando reactivo de Dess-Martin (1,14 g, 2,68 mmol) siguiendo el procedimiento similar al paso H (ejemplo Preparativo 1) para dar **2b** (760 mg) como una espuma incolora.

MS (ESI), m/z, Intensidad relativa 1005 [$(2M+Na)^+$, 10], 530 [$(M+K)^+$, 20], 514. [$(M+Na)^+$, 90], 492 [$(M+1)^+$, 30], 436 (40), 392 (100).

Paso C



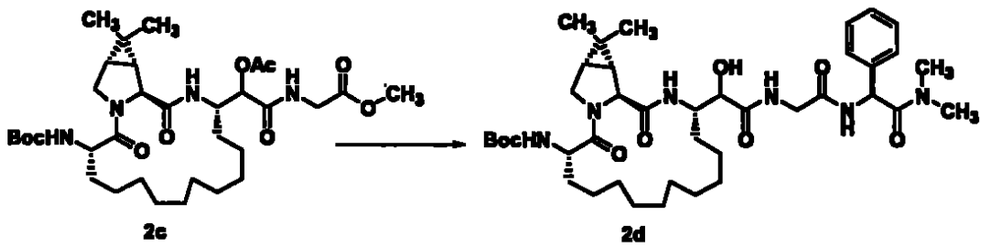
2b 2c

Se convirtió el compuesto **2b** (200 mg, 0,41 mmol) del paso B en **2c** (250 mg) usando CH_3COOH (60 mg) y metilisocianoacetato (99 mg, 1 mmol) siguiendo el procedimiento similar al paso I (ejemplo Preparativo 1) como una mezcla de diastereómeros.

^{1}H RMN ($CDCl_3$, 300 MHz, mezcla de diastereómeros) 8,05, 7,93 (d, 1 H), 6,60 (d, 1 H, J=7,8 Hz), 5,20, 5,09 (d, 1 H), 4,58-4,49 (bt, 1 H), 4,34 (s, 1H), 4,34-4,31 (bt, 1H), 4,11-4,06 (m, 1H), 3,95-3,86 (m, 3 H), 3,73, 3,71 (s, 3 H), 2,21, 2,19 (s, 3H), 1,99-1,06 (m, 31 H), 0,99-0,94 (6 H).

MS (ESI), m/z, intensidad relativa 689 [$(M+K)^+$, 5], 673 [$(M+Na)^+$, 30], 651 [$(M+1)^+$, 35], 551 (100).

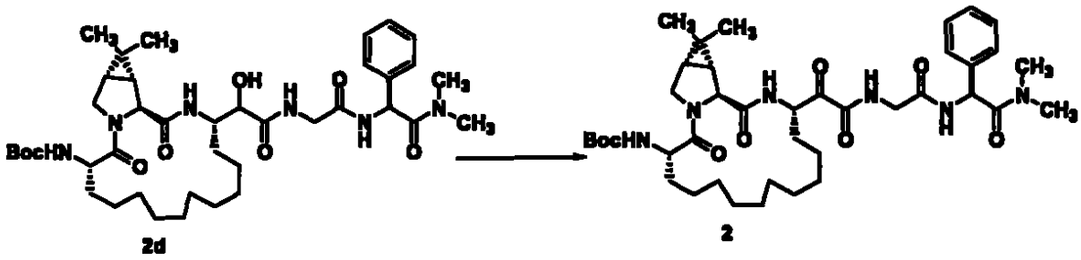
Paso D



2c 2d

Se hidrolizó el metil éster **2c** (250 mg, 0,39 mmol) al ácido usando $LiOH{\cdot}H_2O$ (42 mg, 1 mmol) y se acopló a H-Phg-$N(CH)_2$ ·HCl (90 mg, 0,42 mmol) usando NMM (126 mg, 1,26 mmol) y HATU (160 mg, 0,42 mmol) según se señaló en el Ejemplo Preparativo 1, paso J para dar **2d** bruto usado directamente para oxidación.

Paso E

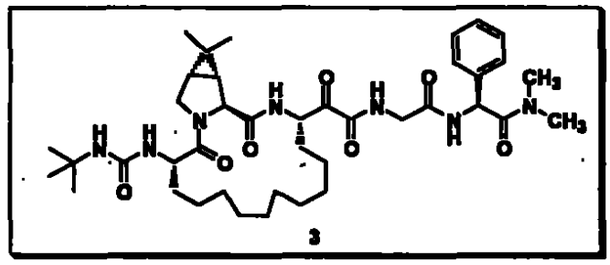


2d 2

Se oxidó la hidroxi amida **2d** usando reactivo de Dess-Martin (200 mg, 0,48 mmol) purificándose mediante cromatografía (SiO_2, acetona/CH_2Cl_2 1:4) para dar **2** (110 mg) como un sólido incoloro.

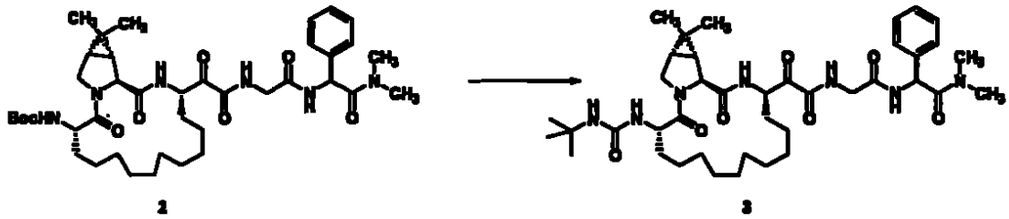
MS (ESI), m/z, intensidad relativa 775 [$(M+Na)^+$, 60], 753 [$(M+1)^+$, 50], 653 (100), 277 (80), 232 (60), 162 (30), 162 (40), 148 (80), 217 (95).

Ejemplo Preparativo 3



3

Paso A



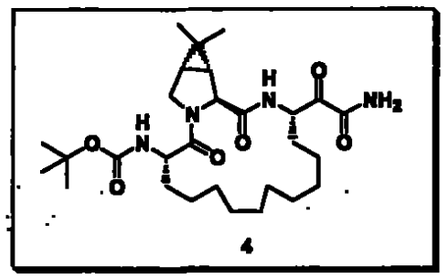
2 3

Una solución de **2** (40 mg, 0,0053 mmol) en HCOOH (2 ml) se agitó a ta. durante 2 h y se concentró in *vacuo*. El residuo se disolvió repetidamente en tolueno y se secó in *vacuo* para eliminar el ácido fórmico residual. El residuo se disolvió en CH_2Cl_2/DMF (1 ml de cada uno) y se trató con ^tBuNCO (10 μl) y NMM (15 μl) a 0°C y se dejó en refrigerador durante 12 h. La mezcla de reacción se concentró in *vacuo* y se purificó mediante cromatografía (SiO_2, acetona/hexanos 1:2) para dar **3** (21 mg) como un sólido incoloro.

459
456

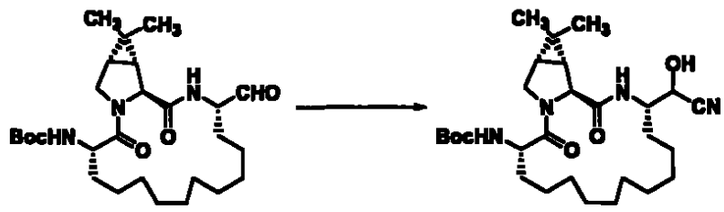
MS (ESI), m/z, intensidad relativa 774 [$(M+Na)^+$, 50], 752 [$(M+1)^+$, 70], 653 (90), 420 (30), 297 (30), 148 (100), 134 (40).

Ejemplo Preparativo 4



4

Paso A

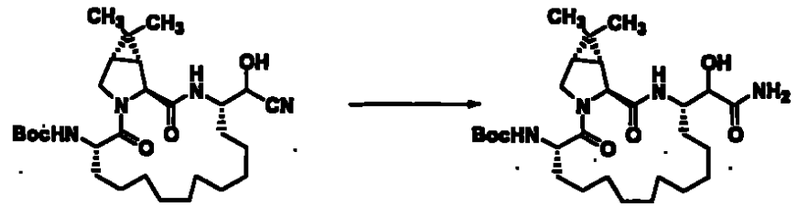


2b 4a

Se trató una solución del aldehído **2b** (100 mg, 0,2 mmol) en CH_2Cl_2 (2 ml) con Et_3N (50 mg, 0,5 mmol) y cianhidrina de la acetona (43 mg, 0,5 mmol). La mezcla de reacción se agitó a ta. durante 2 h y se concentró in *vacuo*. El residuo se purificó mediante cromatografía (SiO2, acetona/hexanos 1:4) para dar **4a** (100 mg) como un sólido incoloro.

MS (ESI), m/z, intensidad relativa 541 [$(M+Na)^+$, 60], 519 [$(M+1)^+$, 10], 463 (30), 419 (100).

Paso B

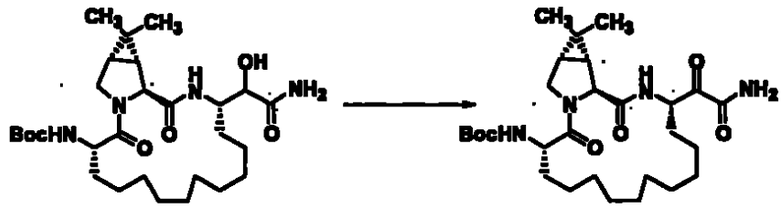


4a 4b

Se trató una solución de la cianhidrina **4a** (100 mg, 0,2 mmol) en DMSO (3 ml) con H_2O_2 (35%, 0,3 ml) y K_2CO_3 (43 mg, 0,3 ml) y se agitó a t.a. durante 4 h.

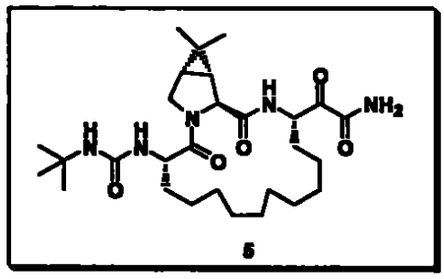
La mezcla de reacción se diluyó con CH_2Cl_2 (150 ml) y se lavó con solución de $Na_2S_2O_3$ acuoso (10%, 30 ml) y salmuera (30 ml). La mezcla de reacción se secó (MgSO4) se filtró, se concentró in *vacuo* y se usó directamente en el paso C sin otra purificación.

Paso C

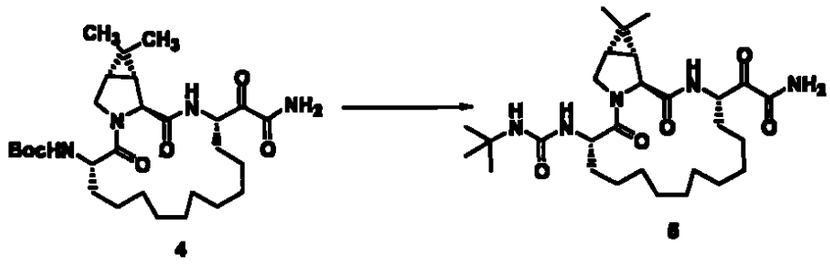


Se trató una solución de la hidroxi amida **4b** (100 mg, 0,18 mmol) en tolueno/DMSO (1:1, 5 ml) a 0°C con EDCI (356 mg, 1,86 mmol) y $Cl_2CHCOOH$ (120 mg, 0,93 mmol) y se agitó a 0°C durante 3 h. La mezcla de reacción se diluyó con EtOAc (150 ml) y se lavó con $NaHCO_3$ acuoso saturado (100 ml) y salmuera (100 ml). La capa de acetato de etilo se secó ($MgSO_4$), se concentró y se purificó mediante cromatografía (SiO_2, acetona/hexanos 2:3) para dar **4** (20 mg) como un sólido incoloro. **MS** (ESI), m/z, intensidad relativa 435 [$(M+1)^+$, 85], 390 (100).

Ejemplo Preparativo 5



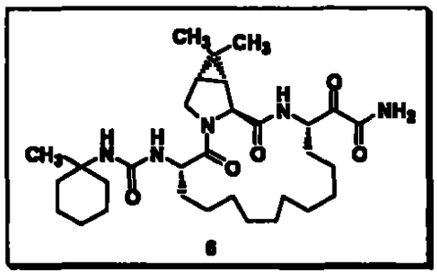
Paso A



4 5

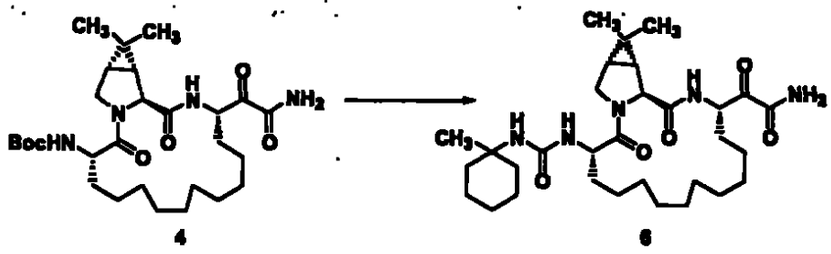
Se convirtió el carbamato 4 (40 mg, 0,1 mmol) en la urea 5 (7,5 mg) siguiendo el procedimiento similar al ejemplo Preparativo 3, Paso A.

Ejemplo Preparativo 6



6

Paso A

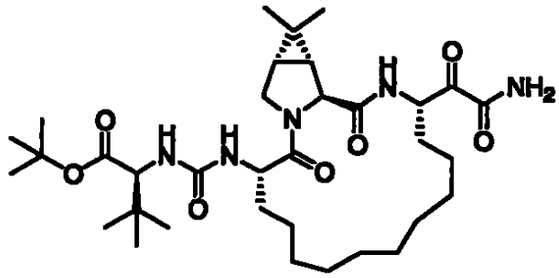


4 6

Se logró la síntesis de 6 usando el procedimiento similar a la síntesis de 5. Se agitó una solución de 4 (180 mg 0,34 mmol) en HCOOH (3,0 ml) a ta. durante 3 h y se concentró in *vacuo*. El residuo se secó in *vacuo* y se tomó en CH_2Cl_2 (4 ml) y se trató con metil ciclohexilisocianato (72 mg, 0,52 mmol) y Et_3N (52 mg, 0,52 mmol). La mezcla de reacción se agitó a 0°C durante 16 h y se concentró in *vacuo*. El residuo se purificó mediante cromatografía (SiO_2, acetona/hexanos 1:3) para dar 6 (10 mg) como un sólido incoloro

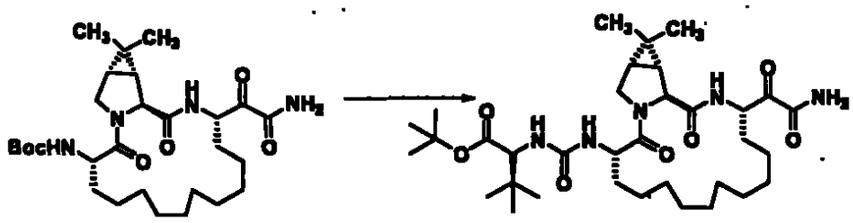
MS (ESI), m/z, intensidad relativa 574 [$(M+1)^+$, 20], 435 (100), 390 (50).

Ejempl Preparativo 7



7

Paso A

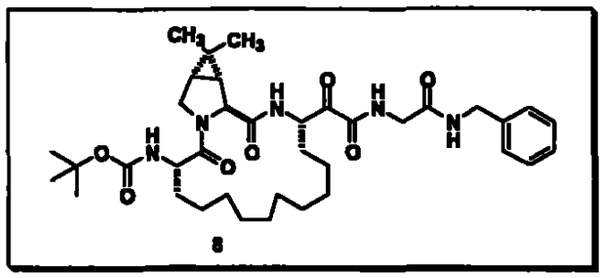


4 7

La síntesis de **7** se logró usando el procedimiento similar a la síntesis de **5**, Se agitó una solución de **4** (180 mg 0,34 mmol) en HCOOH (3,0 ml) a ta. durante 3 h y se concentró in *vacuo*. Se secaron 50 mg (0,12 mmol) de este residuo in *vacuo* y se tomaron en CH_2Cl_2 (4 ml) y se trataron con isocianato del *ter*-butil éster de *ter-butil* glicina (74mg, 0,0,35 mmol) y Et_3N (35 mg, 0,0,35 mmol). La mezcla de reacción se agitó a 0°C durante 16 h y se concentró in *vacuo*. El residuo se diluyó con CH_2Cl_2 y se lavó con HCl acuoso, $NaHCO_3$ acuoso saturado y salmuera. Las capas orgánicas se secaron ($MgSO_4$) y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 1:3) para dar **7** (15 mg) como un sólido incoloro.

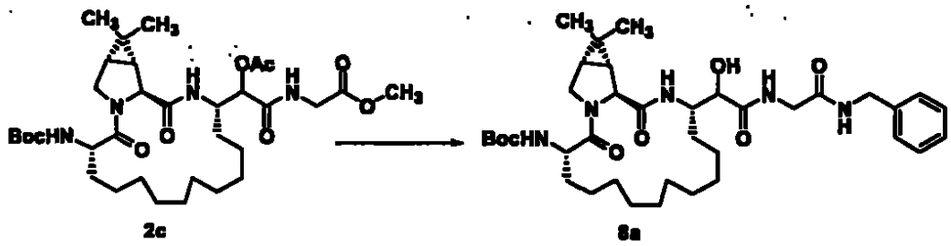
MS (ESI), m/z, intensidad relativa 648 [$(M+1)^+$, 45], 592 (25), 435 (100).

Ejemplo Preparativo 8



8

Paso A

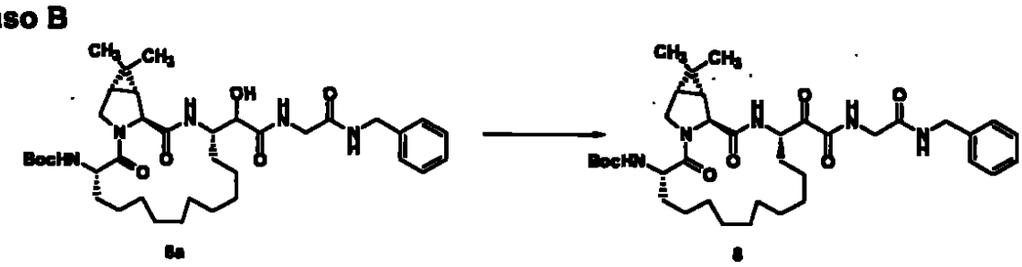


2c 8a

Se trató una solución del metil éster **2c** (100 mg, 0,15 mmol) en THF (2 ml), H_2O (2 ml) y CH_3OH (2 ml) con $LiOH{\cdot}H_2O$ (41 mg, 1,0 mmol) y se agitó a t.a. durante 2 h. Una vez completada la reacción, esta se acidificó con HCl acuoso (2 ml) y se concentró in *vacuo*. El residuo se secó in *vacuo* y se usó como tal sin otra purificación.

El ácido se disolvió en CH_2Cl_2 (2 ml), DMF (2 ml) y se trató con bencil amina (107 mg, 0,22 mmol), NMM (42 mg, 0,42 mmol) HATU (53 mg, 0,14 mmol) y se agitó a 0°C durante 24 h. La solución de color amarillo se concentró in *vacuo* y se diluyó con CH_2Cl_2 (100 ml). Las capas orgánicas se lavaron con $NaHCO_3$ acuoso saturado, HCl acuoso y salmuera. La mezcla de reacción se secó ($MgSO_4$) se filtró, se concentró in *vacuo* y se usó como tal en el siguiente paso (63 mg).

Paso B



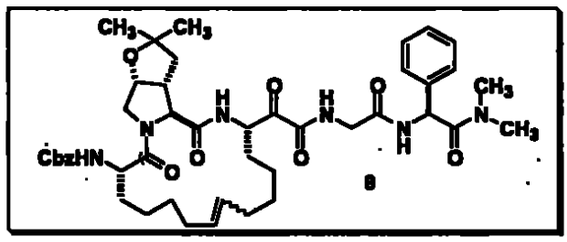
8a 8

464
461

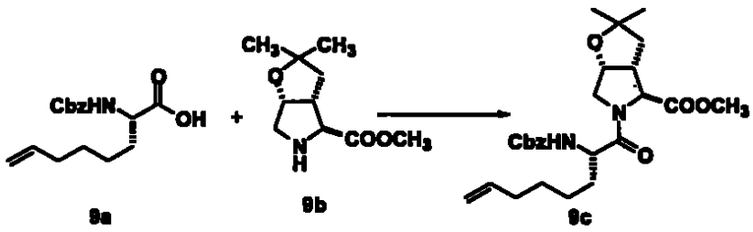
Se trató la hidroxiamida **8a** (62 mg) en CH_2Cl_2 (3 ml) con reactivo de Dess-Martin (62 mg, 0,15 mmol) y se agitó a t.a. durante 1,5 h. La mezcla de reacción se diluyó con CH_2Cl_2 (20 ml) y se trató con solución acuosa de $Na_2S_2O_3$ (10%, 25 ml) y $NaHCO_3$ saturado (25 ml) y se agitó durante 20 min. La capa acuosa se separó y se extrajo una vez más con CH_2Cl_2. Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, se concentraron in *vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 1:2) para dar **8** como un sólido incoloro (21 mg).

MS (ESI), m/z, intensidad relativa 704 [$(M+Na)^+$, 40], 682 [$(M+1)^+$, 20], 582 (100), 150 (70), 117 (30).

Ejemplo Preparativo 9



Paso A

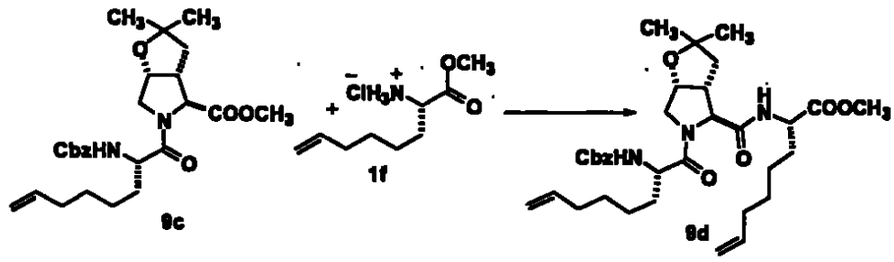


Una solución del ácido **9a** (3,6 g, 18,1 mmol), la amina **9b** (5,53 g, 18,1 mmol) HATU (8,59 mmol, 22,62 mmol) y NMM en CH_2Cl_2 (50 ml), DMF (50 ml) se agitó a 0°C hasta el día siguiente. La mezcla de reacción se concentró in *vacuo* y se diluyó con HCl acuoso (1M, 500 ml) y se extrajo con CH_2Cl_2 (3x250 ml). Las capas orgánicas combinadas se lavaron con HCl acuoso (500 ml), $NaHCO_3$ acuoso saturado (500 ml), salmuera (300 ml) y se purificaron mediante

cromatografía (SiO_2, acetona/hexanos 1:4) para dar **9c** (6,7 g) como un sólido incoloro.

MS (ESI), m/z, intensidad relativa 495 $(M+Na)^+$, 90], 473 [$(M+1)^+$, 60], 429 (70), 391 (40), 200 (100), 140 (30).

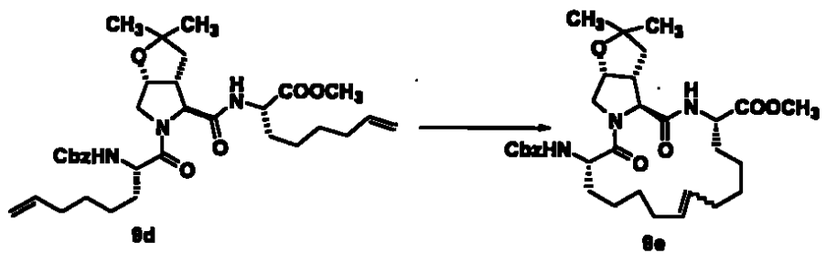
Paso B



Una solución del metil éster **9c** (5,5 g, 11,59 mmol) en $CH_3OH/THF/H_2O$ (300 ml) se trató con $LiOH.H_2O$ (700 mg, 16,7 mmol) y se agitó a t.a. durante 1,5 h. La mezcla de reacción se diluyó con HCl acuoso y se extrajo en CH_2Cl_2 (700 ml). La capa orgánica se secó con $MgSO_4$ se filtró, se concentró in *vacuo y* se usó como tal en pasos posteriores.

Se trató una solución del ácido bruto en CH_2Cl_2 (50 ml), DMF (50 ml) con HATU (5,5 g, 17,35 mmol), NMM (4,07 g, 40,32 mmol) y se agitó a 0°C durante 24 h. La mezcla de reacción se concentró in vacuo y se tomó en HCl acuoso (300 ml). las capas ácidas se extrajeron en CH_2Cl_2 (2x200 ml) y las capas orgánicas combinadas se lavaron con $NaHCO_3$ saturado, salmuera y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 4:1) para dar **9d** (7,1 g) como un sólido incoloro.

Paso C



465

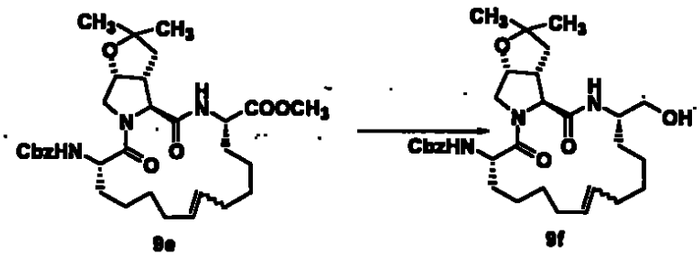
463

Se trató una solución del dieno **9d** (2,0 g, 3,2 mmol) en CH_2Cl_2 (64 ml) con catalizador de Grubbs ($[(Cy)_3RuCl_2{=}CHC_6H_5$, 404 mg, 0,48 mmol) y se agitó a t.a. durante 24 h. La mezcla de reacción se concentró in *vacuo* y se purificó mediante cromatografía (SiO_2, EtOAc/Hex 1:3) para dar **9e** (1,1 g) como un sólido marrón y mezcla de isómeros *E/Z*.

^{1}H RMN ($CDCl_3$, 300 MHz) δ, 7,36 (bm, 5 H), 7,13 (d, 1 H, 4,5 Hz), 5,73 (d, 1 H, J=8,1Hz), 5,28 (m, 2 H), 5,10 (s, 2 H), 4,75 (m, 1 H), 4,65 (m, 2 H), 4,52- 4,46 (m, 1 H), 3,90 (bd, 1 H), 3,74 (s, 3 H), 3,61 (dd, 1 H, J= 15,6, 11,1 Hz), 3,44 (dd, 1 H, J=6,9, 7,2 Hz), 2,12-2,01 (m, 5 H), 1,79-1,67 (m, 3 H), 1,49-1,43 (m, 3 H), 1,361,34 (m, 4 H), 1,26 (bs, 5 H), 1,16 (bs, 3 H).

MS (ESI), m/z, intensidad relativa 606 [$(M+Na)^+$ 70], 584 (100), 540 (30).

Paso D

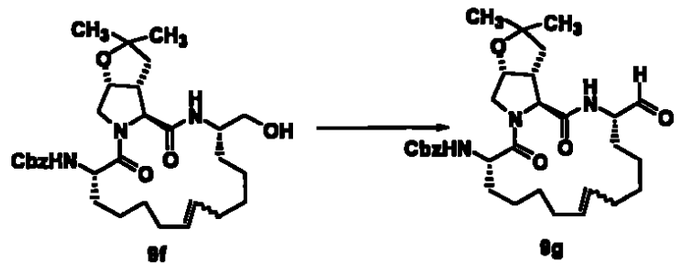


Se trató una solución del éster **9e** (200 mg, 0,32 mmol) en THF seco (5 ml) con $LiBH_4$ (solución de 2M en THF, 0,32 ml) y se agitó a t.a. durante 3 h. La mezcla de reacción se desactivó con HCl acuoso (1M, 100 ml) y se extrajo con CH_2Cl_2 (3x50 ml). Las capas orgánicas combinadas se lavaron con $NaHCO_3$ acuoso (100 ml), salmuera, se secaron con $MgSO_4$, se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 1:3) para dar **9f** (2,1 g).

^{1}H RMN ($CDCl_3$, 300 MHz) δ.

MS (ESI), m/z, intensidad relativa 578 [$(M+Na)^+$, 40], 556 [$(M+1)^+$, 80], 512, (30), 295 (100).

Paso E



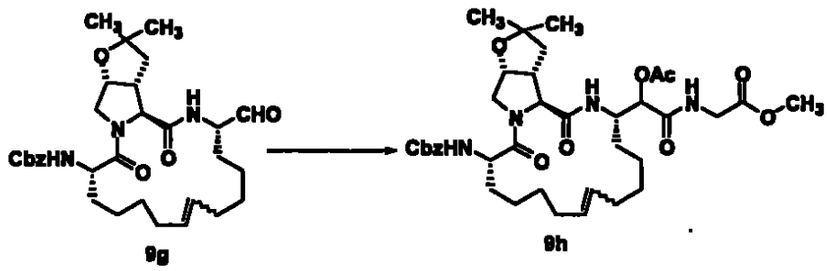
9f 9g

Se trató una solución del alcohol **9f** (100 mg, 0,19 mmol) en CH_2Cl_2 (3 ml) con reactivo de Dess-Martin (106 mg, 0,25 mmol) y se agitó a t.a. durante 2 h. La mezcla de reacción se desactivó con solución de $Na_2S_2O_3$ (10%, 10 ml) y solución saturada de $NaHCO_3$ (10 ml) y se agitó a t.a. durante 0,2 h. La mezcla de reacción se extrajo con CH_2Cl_2. La capa orgánica se secó con $MgSO_4$, se filtró, se concentró *in vacuo* y se purificó mediante cromatografía (SiO_2, acetona/hexanos 3:1) para dar **9g** (80 mg).

^{1}H RMN ($CDCl_3$, 300 MHz) δ 9,52 (s, 1 H), 7,36 (bs, 5 H), 7,11 (d, 1 H, J=7,2 Hz), 5,67 (d, 1 H, J=7,8 Hz), 5,24-5,11 (m, 2 H), 5,11 (s, 2 H), 4,77-4,45 (m, 5 H), 3,92 (d, 1 H, J=12 Hz), 3,58 (dd, 1 H, J=6,6, 5,5 Hz), 3,51-3,46 (m, 1 H), 2,17-1,00 (m, 25 H).

MS (ESI), m/z, intensidad relativa 576 [$(M+Na)^+$, 15], 554 [$(M+1)^+$, 100], 510 (40).

Paso F

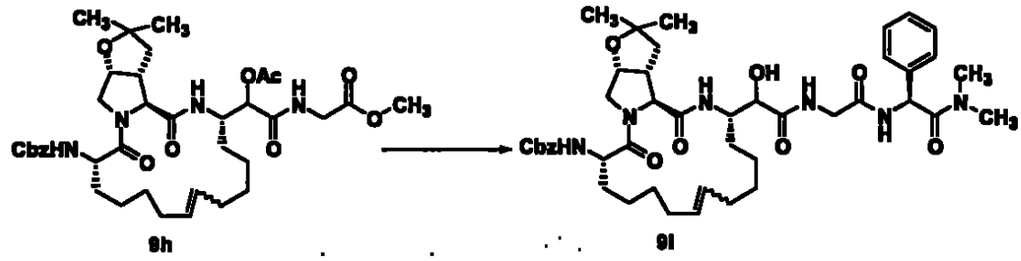


9g 9h

Se trató una solución del aldehído **9g** (80 mg, 0,15 mmol) en CH_2Cl_2 seco (2 ml) con CH_3COOH (30 mg, 0,50 mmol) y metilisocianoacetato (50 mg, 0,50 mmol). La mezcla de reacción se agitó a ta. durante 24 h y se concentró *in vacuo* . El residuo se purificó mediante cromatografía (SiO_2, acetona/hexanos 1:3) para dar **9h** como una mezcla de diastereómeros.

MS (ESI), m/z, intensidad relativa 735 [(M+Na)$^+$, 70], 713 [(M+1)$^+$, 100].

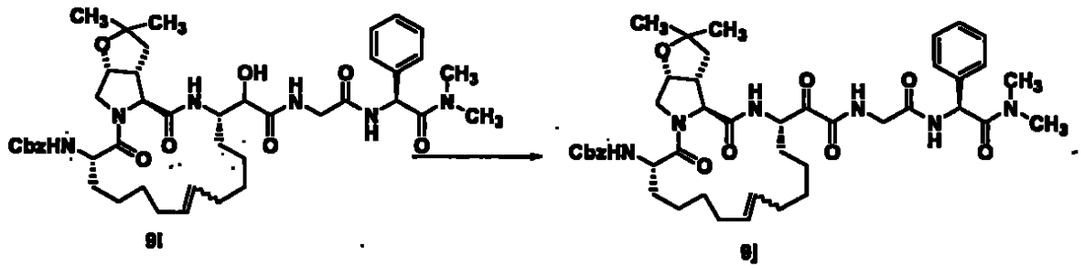
Paso F



9h **9i**

Se hidrolizó el metil éster **9h** (600 mg, 0,92 mmol) al ácido usando $LiOH{\cdot}H_2O$ y se acopló a H-Phg-$N(CH)_2{\cdot}HCl$ (235 mg, 1,09 mmol) usando NMM (303 mg, 3,0 mmol) y HATU (437 mg, 1,15 mmol) según se indicó en el ejemplo Preparativo 1, paso J, para dar **9i**, que se empleó directamente para la oxidación.

Paso G

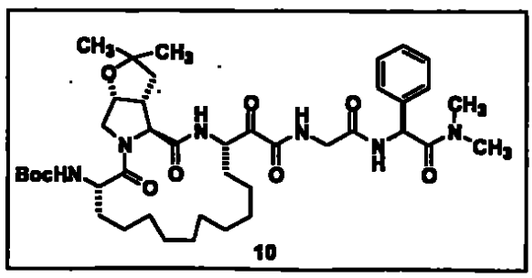


9i **9j**

Se oxidó **9j** bruto (470 mg, 0,58 mmol) del paso F usando reactivo de Dess-Martin (424 mg, 1,00 mmol) siguiendo el procedimiento similar al paso H (ejemplo Preparativo 1) para dar **9j** (310 mg) como un sólido incoloro.

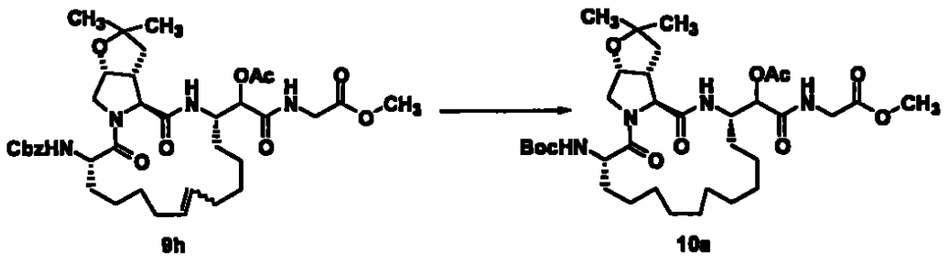
MS (ESI), m/z, intensidad relativa 869 [(M+CH_3OH+Na)$^+$, 100], 815 [(M+1)$^+$, 40], 770 (30).

Ejemplo Preparativo 10



10

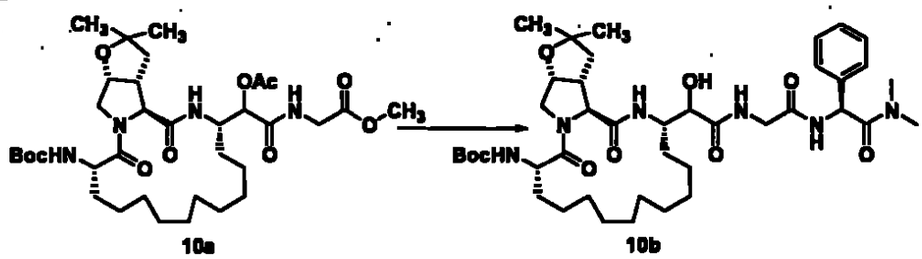
Paso A



9h 10a

Se trató una solución de **9h** (200 mg, 0,3 mmol) en metanol (5 ml) con Pd(OH)2/C (húmedo, 10%) y se hidrogenó durante 3h. La mezcla de reacción se filtró a través de un tapón de Celite y el filtrado se concentró *in vacuo* . El residuo se disolvió en cloruro de metileno y se trató con diterbutildicarbonato (200 mg, 0,92 mmol). La mezcla de reacción se agitó a ta. durante 24 h y se purificó mediante cromatografía (SiO_2, acetona/Hexanos 1:2) para dar **10a** (85 mg) como un sólido incoloro.

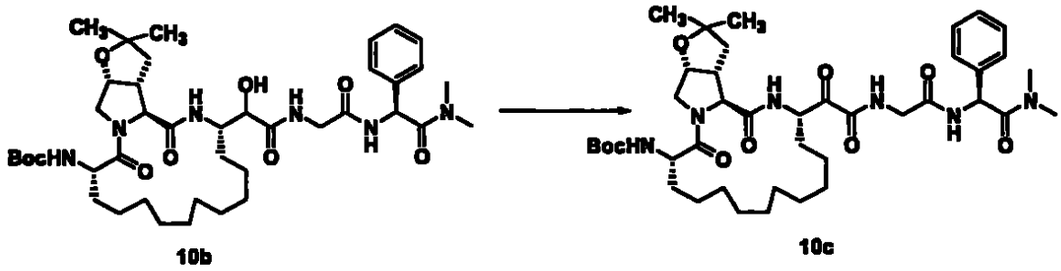
Paso B



10a 10b

Se hidrolizó el metil éster **10a** (80 mg, 0,15 mmol) al ácido usando $LiOH{\cdot}H_2O$ (41 mg, 1 mmol) y se acopló a H-Phg-$N(CH)_2$ ·HCl (32 mg, 0,15 mmol) usando NMM (40 mg, 0,40 mmol) y HATU (64,6 mg, 0,17 mmol) según se indicó en el ejemplo Preparativo 1, paso J, para dar **10b**, que se empleó directamente para la oxidación.

Paso C

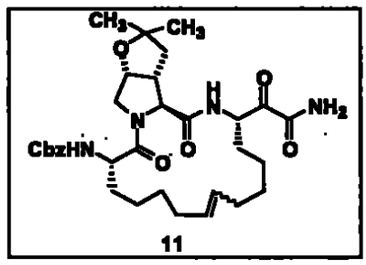


10b 10c

Se hidrolizó la hidroxi amida **10b** (60 mg, 0,08 mmol) usando reactivo de Dess-Martin (60 mg, 0,14 mmol) purificándose mediante cromatografía (SiO_2, acetona/CH_2Cl_2 1:2) para dar **10c** (21 mg) como un sólido incoloro.

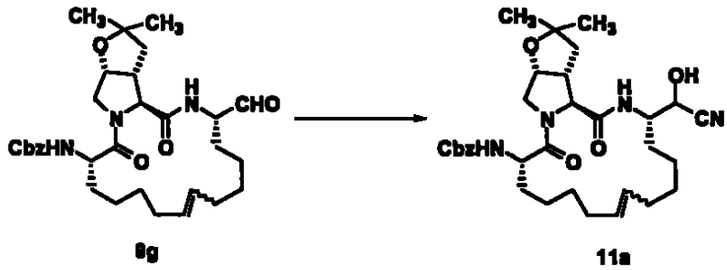
MS (ESI), m/z, intensidad relativa 805 [$(M+Na)^+$, 20], 783 [$(M+1)^+$, 20], 683 (30), 369 (40), 210 (70), 116 (100).

Ejemplo Preparativo 11



11

Paso A



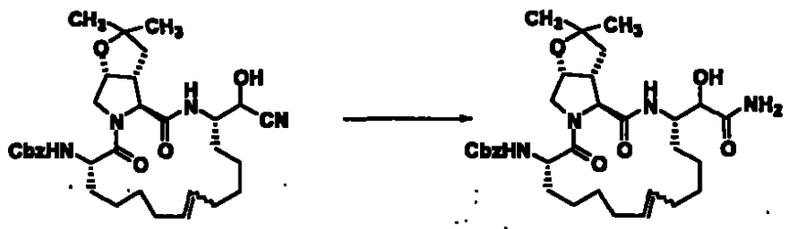
9g 11a

Se trató una solución del aldehído **9g** (400 mg, 0,73 mmol) en CH_2Cl_2 con Et_3N (150 mg, 1,5 mmol) y cianhidrina de acetona (170 mg, 1,5 mmol). La mezcla de reacción se agitó a ta. durante 3 h y se concentró *in vacuo*. El residuo se purificó mediante cromatografía (SiO_2, acetona/hexanos 1:4) para dar **4a** (286 mg) como un sólido incoloro.

477
468

MS (ESI), m/z, intensidad relativa 603 [(M+Na)$^+$, 60], 581 [(M+1)$^+$, 70], 464 (50), 420 (100).

Paso B

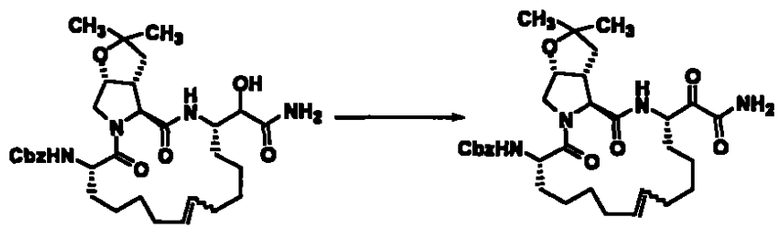


11a **11b**

Se trató una solución de la cianhidrina **11a** (600 mg, 1,1 mmol) en DMSO (12 ml) con H_2O_2 (35%, 1,0 ml) y K_2CO_3 (43 mg, 0,3 ml) y se agitó a t.a. durante 8 h. La mezcla de reacción se diluyó con CH_2Cl_2 (150 ml) y se lavó con solución de $Na_2S_2O_3$ acuoso (10%) y salmuera (30 ml). La mezcla de reacción se secó ($MgSO_4$), se filtró, se concentró *in vacuo* y se empleó directamente en el paso C sin otra purificación.

MS (ESI), m/z, intensidad relativa 621 [(M+Na)$^+$, 70], 599 [(M+1)$^+$, 100], 554 (40).

Paso C

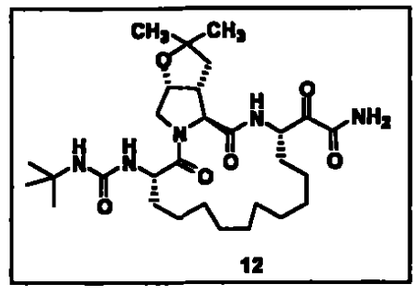


11b **11**

Se trató una solución de la hidroxi amida **11b** (320 mg, 0,54 mmol) en tolueno/DMSO (1:1, 10 ml) a 0°C con EDCI (1,1 g, 5,40 mmol) y $Cl_2CHCOOH$ (350 mg, 2,7 mmol) y se agitó a t.a. durante 4 h. La mezcla de reacción se diluyó con CH_2Cl_2 (150 ml) y se lavó con $NaHCO_3$ acuoso saturado y salmuera. La capa orgánica se secó ($MgSO_4$), se concentró y se purificó mediante cromatografía (SiO_2, acetona/hexanos 1:2) para dar **11** (173 mg) como un sólido incoloro.

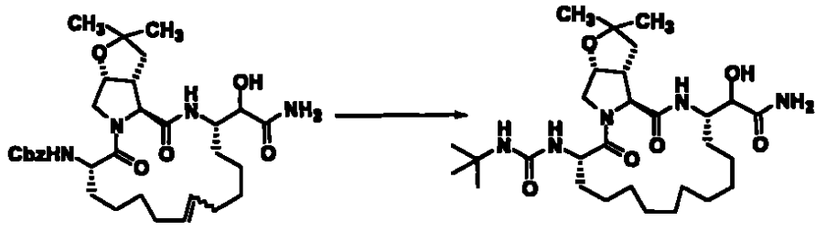
MS (ESI), m/z, intensidad relativa 619 [(M+1)$^+$, 20], 597 (100).

Ejemplo Preparativo 12



12

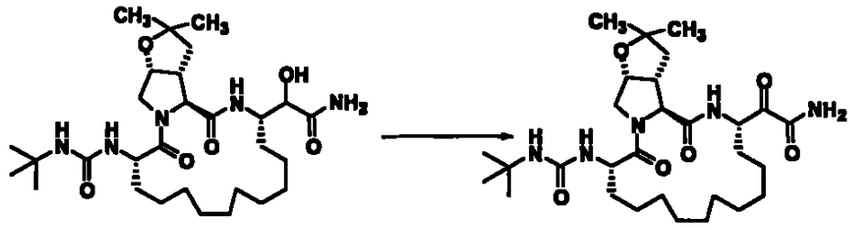
Paso A



11a 11b

Se hidrogenó una solución de **11a** usando Pd/C y la amina obtenida se disolvió en CH_2Cl_2 y se trató con ter-butilisocianuro a 0°C. La mezcla de reacción se agitó a ta. durante 12 h y se diluyó con agua. La mezcla de reacción se extrajo con CH_2Cl_2 (30 ml) y las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* para obtener **11b**, que se empleó en la oxidación sin otra purificación.

Paso B



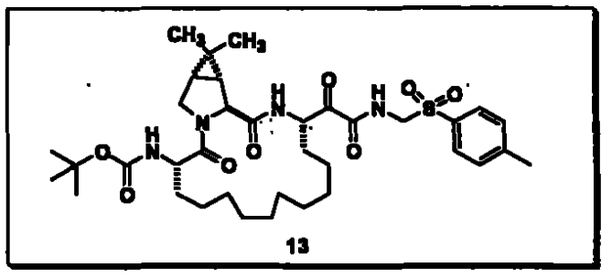
11b 12

Se trató una solución de la hidroxi amida **11b** (320 mg, 0,54 mmol) en tolueno/DMSO (1:1, 10 ml) a 0°C con EDCI (1,1 g, 5,40 mmol) y $Cl_2CHCOOH$ (350 mg, 2,7 mmol) y se agitó a t.a. durante 4 h. La mezcla de reacción se diluyó con CH_2Cl_2 (150 ml) y se lavó con $NaHCO_3$ acuoso saturado y salmuera. La capa

orgánica se secó ($MgSO_4$), se concentró y se purificó mediante cromatografía (SiO_2, acetona/hexanos 1:2) para dar **11** (173 mg) como un sólido incoloro.

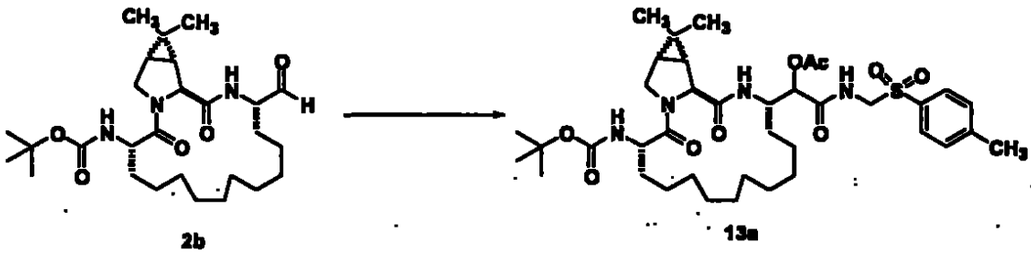
MS (ESI), m/z, intensidad relativa 619 [$(M+1)^+$, 20], 597 (100).

Ejemplo Preparativo 13



13

Paso A

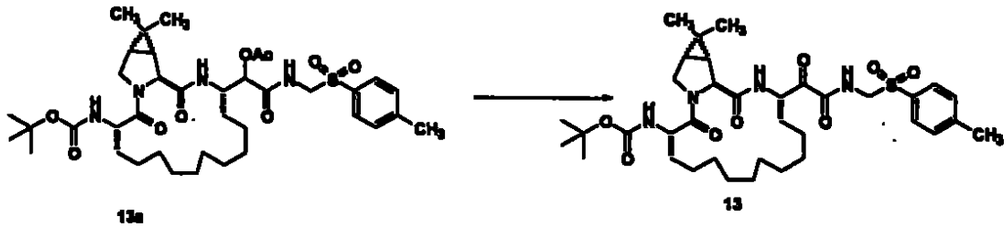


2b **13a**

Se trató una solución del aldehído **2b** (50 mg, 0,1 mmol) en CH_2Cl_2 seco (5 ml) con CH_3COOH (21 mg, 0,3 mmol) y TOSMIC (59 mg, 0,3 mmol, 3,0 eq.). La mezcla de reacción se agitó a ta. durante 40 h y se concentró *in vacuo* . El residuo se purificó mediante cromatografía (SiO_2, EtOAc/hexanos 2:3) para dar **1k** (60 mg) como una mezcla de diastereómeros.

MS (ESI), m/z, intensidad relativa 769 [$(M+Na)^+$, 30], 747 [$(M+1)^+$, 20], 647 (100).

Paso B



13a **13**

Se trató una solución de **13a** (60mg, 0,08 mmol) en metanol con 8 gotas de HCl concentrado y se agitó a t.a. durante 12 h. El éster acetato se hidrolizó con la

474

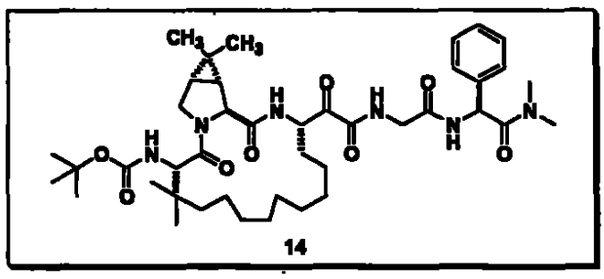
471

desprotección parcial del grupo Boc, que se desprotegió con diterbutildicarbonato (16 mg, 0,073 mmol).

Se trató la hidroxiamida (46 mg, 0,07 mmol) en CH_2Cl_2 con reactivo de Dess-Martin (55 mg, 0,13 mmol) y se agitó a t.a. durante 10 min. Se agregó $Na_2S_2O_3$ acuoso saturado y la mezcla de reacción se extrajo en CH_2Cl_2. La mezcla de reacción se secó ($MgSO_4$), se filtró, se concentró *in vacuo* y se purificó mediante cromatografía para dar **13** (61 mg).

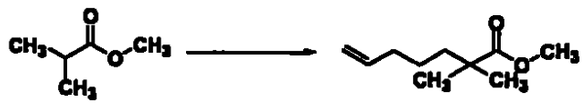
MS (ESI), m/z, intensidad relativa 703 [$(M+1)^+$, 11], 603 (100).

Ejemplo Preparativo 14



14

Paso A



14a

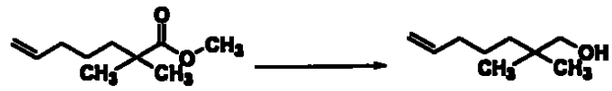
Se agregó una solución de isobutirato de metilo (2,0g, 19,5 mmol) gota a gota en THF a una solución de KHMDS en THF (4,65 g, 23,5 mmol) a –78°C y se agitó durante 0,5 h. La mezcla de reacción se trató con 5-bromo-1-penteno (3,5 g, 23,5 mmol) y se agitó a t.a. durante 1 h. La mezcla de reacción se desactivó con HCl acuoso y se extrajo en éter (150 ml). La capa orgánica se secó ($MgSO_4$), se filtró, se concentró *in vacuo* y se purificó mediante cromatografía (EtOAc/Hexano 1:19) para dar 2,1 g de **14b** como líquido incoloro .

^{1}H RMN: ($CDCl_3$, 300 MHz) δ 5,83-5,70 (m, 1 H), 5,00-4,91 (dd, 2 H), 3,65 (s, 3 H), 2,01 (dt, 2 H), 1,53-1,48 (m, 2 H), 1,35-1,30 (m, 2 H), 1,1 (s, 9 H).

Paso B

475

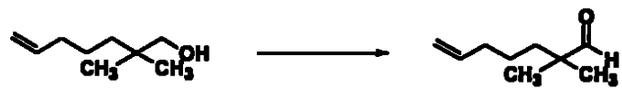
472



14b 14c

Se trató una solución del éster (2, 6 g, 16 mmol) en éter (30 ml) con $LiAlH_4$ (solución 1M en THF, 20 ml) a –78°C y se calentó hasta ta. La mezcla de reacción se desactivó con una solución de $KHSO_4$ y se filtró a través de un tapón de Celite y $MgSO_4$. El filtrado se concentró *in vacuo* y se usó tal cual en el siguiente paso.

Paso C

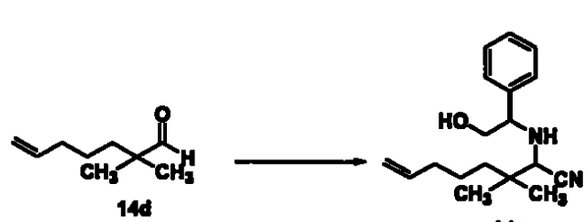


14c 14d

Se trató una solución de cloruro de oxalilo (1,48 g, 11,7 mmol) en CH_2Cl_2 seco con DMSO (1,53 g, 19,5 mmol) a –78°C y se agitó durante 15 min. A esta mezcla se agregó el alcohol **14c** (1,1 g, 7,8 mmol) y se agitó a –78°C durante 15 min. Se agregó trietilamina (5,0 ml, 35,5 mmol) y la mezcla de reacción se calentó a ta. La mezcla de reacción se acidificó y se extrajo con EtOAc (200 ml). Las capas orgánicas combinadas se lavaron con HCl acuoso, se secaron ($MgSO_4$), se filtraron y se concentraron *in vacuo* y se usaron en la siguiente reacción.

^{1}H RMN ($CDCl_3$, 300 MHz) δ 9,42 (s, 1 H), 5,82-5,68 (m, 1 H), 5,00-4,91 (m, 2 H), 2,03 (dt, 2 H), 1,48-1,23 (m, 4 H), 1,03 (s, 3 H).

Paso D



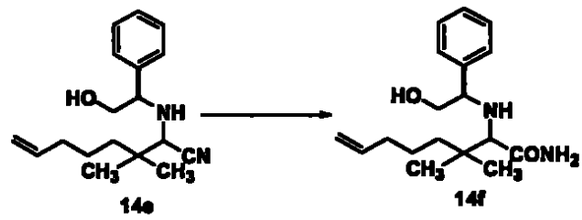
14d 14e

Se trató una solución del aldehído **14d** (18g, 129 mmol) en CH_2Cl_2 (150 ml) con (R)-feniglicinol (20,33 g, 148,3 mmol) y se agitó a 0°C durante 1 h. La mezcla de reacción se trató con TMS-CN (25,6g, 258 mmol) y se agitó a t.a. durante 12 h. La mezcla de reacción se desactivó con $NaHCO_3$ acuoso saturado y se extrajo

~~475~~
473

con EtOAc (3x150 ml). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y el residuo se disolvió en THF (100 ml) y se trató con HCl acuoso (100 ml). La capa acuosa se alcalinizó con NaOH acuoso (1 M) y se extrajo con (EtOAc, 450 ml). Las capas orgánicas combinadas se secaron, se filtraron, se concentraron *in vacuo* y se purificaron por cromatografía (SiO_2, EtOAc/Hexanos 6:1) para dar **14e** 21 g como un aceite incoloro.

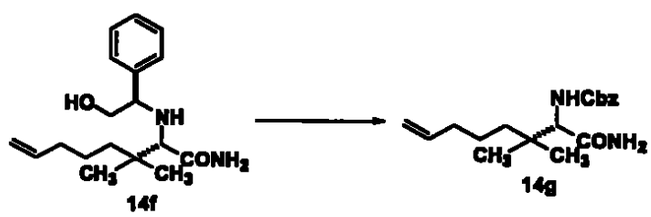
Paso E



Se trató una solución de **14e** (20 g) en CH_3OH (200 ml) con H_2O_2 (60 ml) y $LiOH.H_2O$ (5,88 g, 209,6 mmol) a 0°C. La mezcla de reacción se agitó a ta. durante 12 h y se enfrió hasta 0°C y se desactivó cuidadosamente con solución de $Na_2S_2O_3$ acuoso (10%). La mezcla de reacción se concentró *in vacuo* y se extrajo la capa acuosa con EtOAc (600 ml). Las capas orgánicas combinadas se lavaron intensamente con $Na_2S_2O_3$ acuoso, se secaron ($MgSO_4$), se concentraron *in vacuo* y se purificaron mediante cristalización (EtOAc/Hexanos) para dar el diastereómero usado directamente puro en la siguiente reacción.

^{1}H RMN ($CDCl_3$, 300 MHz) δ 7,30 (bs, 5 H), 6,25 (s, 1 H), 6,17 (s, 1 H), 5,79-5,66 (m, 2 H), 4,98-4,89 (m, 2 H), 3,71-3,60 (m, 3 H), 2,68 (bs, 1 H), 1,98-1,90 (3 H), 1,03 (s, 3 H), 0,99 (s, 3 H), 1,03-0,99 (m, 1 H).

Paso F



Se trató una solución de la amida **14f** (8,00g, 26,3 mmol) en CH_2Cl_2 (160 ml), CH_3OH (80 ml) a 0°C con $Pb(OAc)_4$ (13,45 mmol, 30,3 mmol), a 0°C durante 1 h. La solución amarilla se trató con $NaHCO_3$ acuoso (250 ml, y se agitó durante 15 min. La mezcla de reacción se filtró y se concentró *in vacuo*. La capa preponderantemente acuosa se extrajo en CH_2Cl_2 (3x300 ml), se concentró *in vacuo* y se usó directamente en otra reacción.

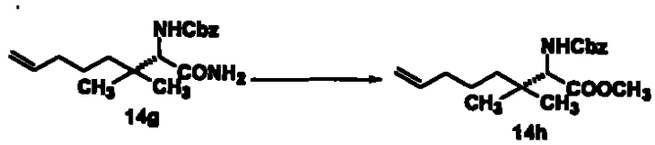
Una solución de la imina bruta se tomó en THF (200 ml) y se trató con HCl acuoso (1 M, 200 ml) y se agitó a t.a. durante 1 h. La mezcla de reacción se concentró *in vacuo* y se extrajo con éter (2x250 ml). La capa acuosa se alcalinizó con NaOH acuoso (50%) a 0°C y se extrajo con CH_2Cl_2 (600 ml). Las capas orgánicas combinadas se extrajeron con salmuera, se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se usó directamente en la siguiente reacción.

El residuo se disolvió en CH_2Cl_2 (200 ml) y se enfrió a –78°C y se trató con NMM (4,2 g, 40 mmol) y Cbz-Cl (5,4g, 31,58 mmol). La mezcla de reacción se agitó a ta. durante 12 h y se lavó con HCl acuoso. La capa orgánica se separó y la capa acuosa se extrajo con CH_2Cl_2 (200 ml) Las capas orgánicas combinadas se extrajeron con salmuera, se secaron y se purificaron mediante cromatografía (SiO_2, EtOAc/Hexanos 2:3) para dar **14g** (6,8 g) como un sólido incoloro.

^{1}H RMN ($CDCl_3$, 300 MHz) δ 7,37-7,30 (m, 5 H), 6,23 (bs, 1 H), 5,86 (bs, 1 H), 5,82- 5,64 (m, 1 H), 5,63 (d, 1 H, J= 9,3 Hz), 5,12-4,93 (m, 4 H), 4,07 (d, 1 H, J=9 Hz), 2,0-1,9(m, 2 H), 1,42- 1,30 (m, 4 H), 0,96 (s, 6 H).

MS (ESI), m/z, intensidad relativa 341[M+Na)$^+$, 100], 319 [(M+1)+, 30], 274 (50), 230 (70), 213 (30), 140 (30).

Paso G



478

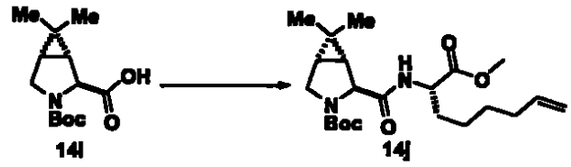
475

Se trató una solución de amida **14 g** (6,8 g, 21,4 mmol) en CH_2Cl_2 (200 ml) con Me_3OBF_4 (10,36 g, 69,9 mmol) y K_3PO_4 (12,11 g, 69,52 mmol) y se agitó a t.a. durante 12 h. La mezcla de reacción se concentró *in vacuo* y se disolvió en CH_3OH (280 ml) y HCl acuoso (140 ml, 1 M) y se calentó a reflujo durante 1 h. La mezcla de reacción se concentró y la capa acuosa se extrajo además con CH_2Cl_2 (3x150 ml). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, EtOAc/hexanos 1:19) para dar **14h** (5,6g) como aceite incoloro.

^{1}H RMN ($CDCl_3$, 300 MHz) δ 7,36 (bs, 5 H), 5,85-5,71 (m, 1 H), 5,32 (d, 1 H, J=9,9 Hz), 5,10 (dd, 2 H, J= 12, 3,9 Hz), 5,03-4,93 (m, 2 H), 4,27 (d, 1 H, J=9,9 Hz), 3,72 (s, 3 H), 2,05—1,98 (m, 2 H), 1,47-1,24 (m, 4 H), 0,93 (s, 9 H).

MS (ESI), m/z, intensidad relativa 356 [M+Na)$^+$, 95], 334 [(M+1)+, 10], 290 (100), 230 (60), 213 (20).

Paso H



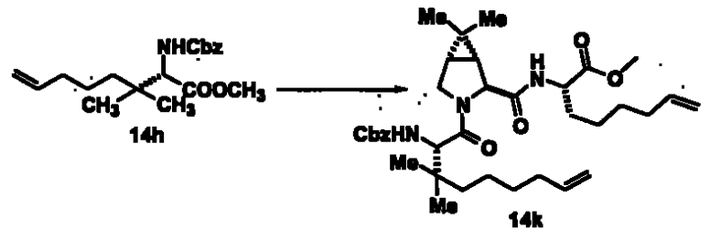
Se trató una solución del ácido **14l** (4,5g, 17,64 mmol) y la amina **1f** (3,66 g, 17,64 mmol) en CH_2Cl_2 (50 ml), DMF (50 ml) a 0°C con HATU (8,39 g, 22,05 mmol) y NMM (5,35 g, 52,92 mmol) y se agitó hasta el día siguiente a 0°C. La mezcla de reacción se concentró *in vacuo* y se diluyó con 450 ml de CH_2Cl_2. La capa acuosa se lavó con HCl acuoso (1M, 2x300 ml), NaHCO3 acuoso (1M, 2x300 ml). Las capas orgánicas se secaron con $MgSO_4$, se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, Acetona/Hexanos 5:1) para dar **14j** como un aceite incoloro (5,8 g).

^{1}H RMN ($CDCl_3$, 300 MHz) δ 7,03, 6,39 (d, 1 H, J = 7,5 Hz), 5,8-5,7 (m, 1 H), 4,99-4,90 (m, 2 H), 4,66 –4,54 (m, 1 H), 3,72 (s, 3 H), 3,62-3,42 (m, 2 H), 2,01 (bs, 2

H), 1,88-1,63 (m, 4 H), 1,61, 1,43 (s, 9 H), 1,6-1,3 (m, 4 H), 1,02 (s, 3 H), 0,90 (s, 3H).

MS (ESI), m/z, intensidad relativa 431 [$(M+Na)^+$, 60], 409 [$(M+1)^+$, 40], 353 (40), 309 (100), 110 (80).

Paso I



Una solución del éster **14h** (5,4g, 16,2 mmol) en H_2O (30 ml), THF (30 ml) y CH_3OH (30 ml) se agitó con $LiOH{\cdot}H_2O$ (1,36 g, 32,42 mmol) durante 24 h y se concentró *in vacuo*. La capa acuosa se acidificó con HCl acuoso (1M) y se extrajo en CH_2Cl_2 (400 ml). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, se concentraron *In vacuo* y se usaron tal cual en reacciones posteriores.

Se trató una solución de ácido (4,0 g, 12,5 mmol) y de amina desprotegida* en CH_2Cl_2 (30 ml), DMF (30 ml) a 0°C con HATU (7,15 g, 18,79 mmol) y NMM (4,5 g, 45,0 mmol) y se agitó a 0°C durante 48 h, y 25°C durante 24 h. La mezcla de reacción se concentró *in vacuo* y se diluyó con 300 ml de CH_2Cl_2. La capa acuosa se lavó con HCl acuoso (1M, 3x100 ml), $NaHCO_3$ acuoso (saturado, 3x100 ml). Las capas orgánicas se secaron con $MgSO_4$, se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, EtOAc/Hexanos 3:1) para dar **14k** como un aceite incoloro (4 g de 14k puro y 2 g de 14k parcialmente impuro).

^{1}H RMN ($CDCl_3$, 300 MHz) δ 7,34-7,32 (bs, 5 H), 6,92 (d, 1H, J=7,5Hz), 5,48-5,69 (m, 2 H), 5,37 (d, 1 H, J=9,9 Hz), 5,08-4,92 (m, 6 H), 4,56-4,33 (M, 1 h), 3,97-3,93 (m, 2 H), 3,84-3,80 (m, 2 H), 3,74 (s, 3 H), 2,03-1,97 (m, 4 H), 1,86-1,87-1,39 (m, 12 H), 1,12 (s, 3 H), 0,98 (s, 6 H), 084 (s, 3 H)

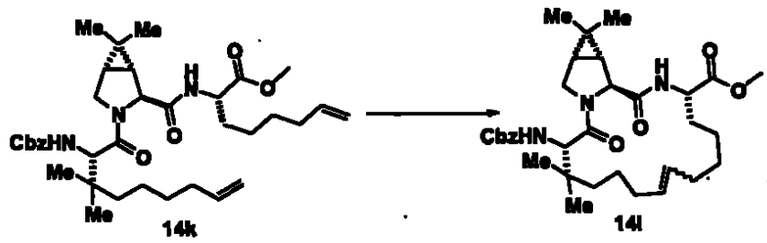
480

477

MS (ESI), m/z, intensidad relativa 632 [(M+Na)$^+$, 20], 610 [(M+1)$^+$, 100], 309 (60).

* la amina se obtuvo por degradación de **14j** con HCl 4 M en dioxano.

Paso J

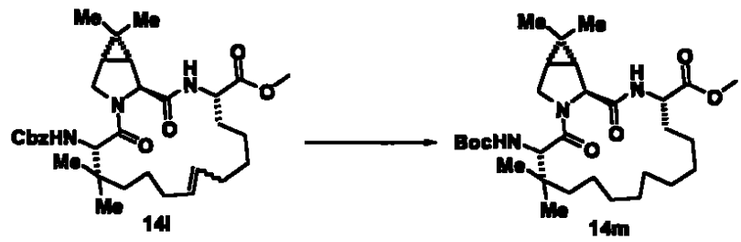


Se saturó una solución del dieno **14k** (4,00 g, 6,57 mmol) en CH_2Cl_2 (65,0 ml) a ta. con N_2 y se trató con catalizador de Grubbs (551 mg, 0,657 mmol) y se agitó durante 24 h. La mezcla de reacción se concentró *in vacuo* y se purificó mediante cromatografía (SiO_2, EtOAc/hexanos 1:3) para dar **14l** (1,7 g) como un sólido de color canela.

^{1}H RMN ($CDCl_3$, 300 MHz) δ 7,34-7,31 (bs, 5 H), 7,08 (d, 1 H, J = 7,8 Hz), 5,43 (d, 1 H, J = 10,2 Hz), 5,28 (m, 2 H), 5,13-5,02 (m, 2 H), 4,56-4,32 (m, 1 H), 4,49-4,28 (m, 2 H), 3,96-3,79 (m, 2 H), 3,74 (s, 9 H), 2,05-1,29 (m, 16 H), 1,0 (s, 3 H), 0,96 (s, 3 H), 0,94 (s, 3 H), 0,86 (s, 3 H).

MS (ESI), m/z, intensidad relativa 550 [(M+1)$^+$, 50], 450 (100).

Paso K

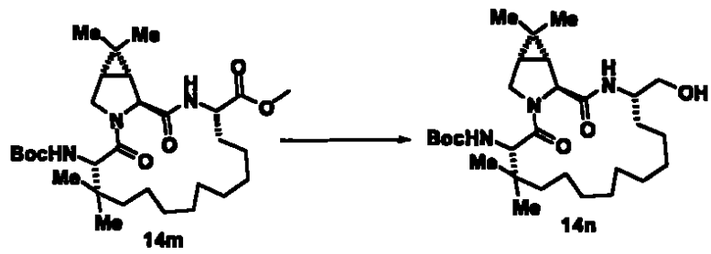


Se trató una solución del alqueno **14l** (200 mg, 0,35 mmol) en CH3OH (2 0 ml) con Pd/C (5%, 200 mg), diterbutildicarbonato (200 mg, 0,92 mmol) y se hidrogenó a t.a. durante 12 h. La mezcla de reacción se filtró a través de un tapón de Celite y se concentró *In vacuo*. La mezcla de reacción se purificó mediante cromatografía (SiO_2, acetona/hexanos 1:5) para dar **14m** (81 mg).

^{1}H RMN ($CDCl_3$, 300 MHz) δ 6,84 (d, 1 H, J=7,8 Hz), 5,14 (d, 1 H), 4,61-4,55 (m, 1 H), 4,31 (s, 1 H), 4,22 (d, 1 H, J=10 Hz), 4,03 (d, 1 H, J=10,5 Hz), 3,88-3,85 (m, 1 H), 3,75(s, 3 H), 1,89-1,76 (m, 1 H), 1,59-1,76 (m, 28 H), 1,02 (s, 3 H), 0,97 (s, 3 H), 0,94 (s, 3 H), 0,86 (s, 3 H).

MS (ESI), m/z, intensidad relativa 610 [(M+AcOH+1)$^+$, 40], 550 [(M+1)$^+$, 50], 450 (100), 309 (20).

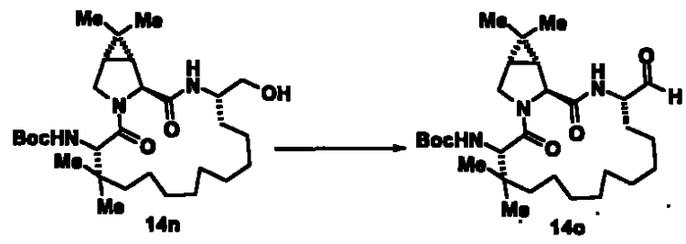
Paso L



Una solución del éster **14m** (80 mg, 0,15 mmol) en THF seco (2 ml) se trató con $LiBH_4$ (solución 2M en THF, 0,1 ml) y se agitó a t.a. durante 4 h. La mezcla de reacción se desactivó con HCl acuoso (1M, gotas) y se extrajo con CH_2Cl_2 (3x30 ml). Las capas orgánicas combinadas se lavaron con $NaHCO_3$ acuoso (100 ml), salmuera, se secaron con $MgSO_4$, se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 1:3) para dar **14n** (70 mg) como un sólido amorfo.

MS (ESI), m/z, intensidad relativa 544 [(M+Na)$^+$, 30], 522 [(M+1)$^+$, 40], 422 (100).

Paso M

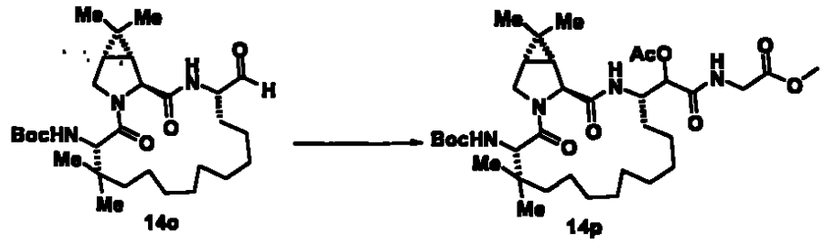


Se trató una solución del alcohol **14n** (30 mg, 0,05 mmol), en CH_2Cl_2 (2 ml) con reactivo de Dess-Martin (30 mg, 0,07 mmol) y se agitó a t.a. durante 2 h. La mezcla de reacción se desactivó con solución de $Na_2S_2O_3$ (10%, 10 ml) y solución

saturada de $NaHCO_3$ (10 ml) y se agitó a t.a. durante 0,5 h. La mezcla de reacción se extrajo con CH_2Cl_2 (3x10 ml). La capa orgánica se secó con $MgSO_4$, se filtró, se concentró *in vacuo* y se usó tal cual en la siguiente reacción.

MS (ESI), m/z, intensidad relativa 552 [$(M+1)^+$, 100], 248 (40).

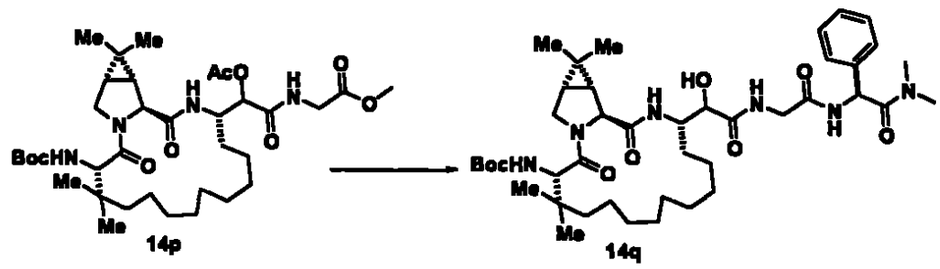
Paso N



El compuesto **14o** del paso **M** se convirtió en **14p** (40 mg) usando CH_3COOH (20 µl) y metilisocianoacetato (20 µl) siguiendo el procedimiento similar al paso I (ejemplo Preparativo 1) dando una mezcla de diastereómeros.

MS (ESI), m/z, intensidad relativa 711 [$(M+1)^+$, 100], 240 (20).

Paso O

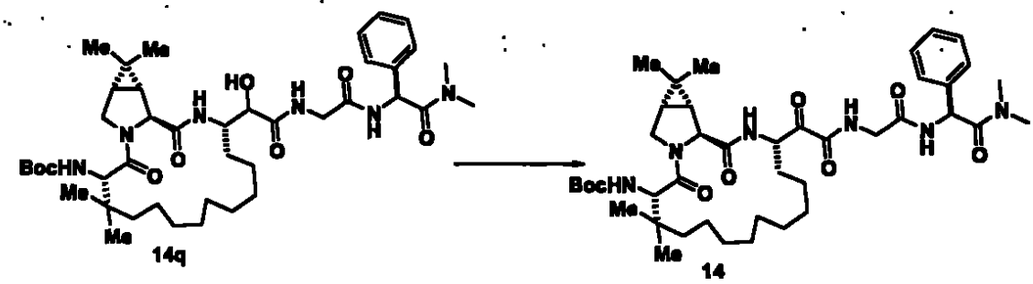


Se trató una solución del metil éster **14p** (80 mg, 0,12 mmol) en THF (3 ml), H_2O (3 ml) y CH_3OH (3 ml) con $LiOH{\cdot}H_2O$ (41 mg, 1 mmol) y se agitó a t.a. durante 2 h. Una vez completada la reacción, la reacción se acidificó con HCl acuoso (15 ml) y se extrajo con CH_2Cl_2 (3x30 ml). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron *in vacuo* . El residuo se secó *in vacuo* y se usó tal cual sin otra purificación.

El ácido se disolvió en CH_2Cl_2 (2 ml), DMF (2 ml) y se trató con H-Phg-$N(CH)_2{\cdot}HCl$ (40 mg, 0,2 mmol), NMM (40 mg, 0,4 mmol) HATU (68 mg, 0,16

mmol) y se agitó a 0°C durante 24 h. La solución de color amarillo se concentró *in vacuo* y se diluyó con CH_2Cl_2 (75 ml). Las capas orgánicas se lavaron con NaHCO3 acuoso saturado, HCl acuoso y salmuera. La mezcla de reacción se secó ($MgSO_4$), se filtró, se concentró *in vacuo* y se usó tal cual en el paso siguiente (90 mg).

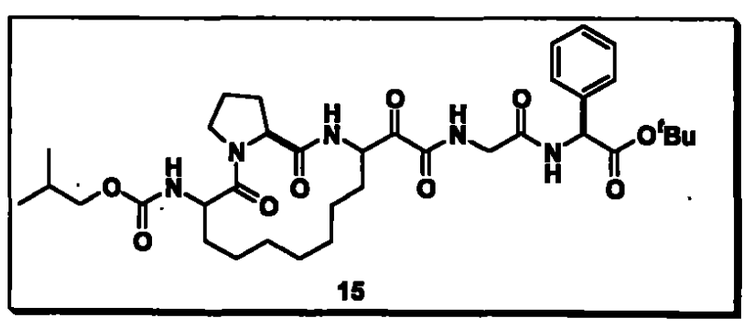
Paso P



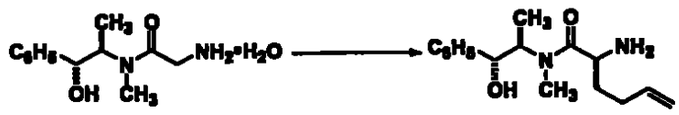
Se trató una solución del alcohol **14q** (90 mg, 0,11 mmol) en CH_2Cl_2 (2 ml) con reactivo de Dess-Martin (100 mg, 0,24 mmol) y se agitó a t.a. durante 2 h. La reacción se diluyó con solución acuosa de $Na_2S_2O_3$ (30 ml) y solución acuosa de $NaHCO_3$ (30 ml cada una) y se extrajo con CH_2Cl_2 (50 ml). La capa orgánica se lavó con $NaHCO_3$ saturado, salmuera, se secó con $MgSO_4$, se filtró, se concentró *in vacuo* y se purificó mediante cromatografía (acetona/hexanos 2:3) para dar **14** (22 mg) como un sólido incoloro.

MS (ESI), m/z, intensidad relativa 813 [$(M+1)^+$, 100], 768 (20).

Ejemplo Preparativo 15



Paso A



1a 15a

A 45 ml de THF, diisopropilamina (4,70 ml, 33,51 mmol, 2 eq.) y LiCl (4,26 g, 6 eq) a –78°C se agregó nBuLi (20,4ml, 1,95 eq) bajo atmósfera de nitrógeno. 10 min. más tarde, la solución de **1a**/30 ml de THF se transfirió a la solución anterior durante 10 min. Después de 20 min, la mezcla amarilla amarronada se calentó hasta 0°C. Otros 20 min. más tarde, la solución se tornó de color amarillo brillante opaco y se agregó 4-yodo-1-buteno (3,35 g, 1,1 eq) gota a gota. La solución se tornó aún más brillante y 60 min. más tarde se agregaron 115 ml de HCl 1 M para desactivar la reacción. Se eliminó el THF y se agregaron 150 ml de EtOAc para extracción. La capa orgánica también se lavó con 115 ml de HCl 1M. Las capas acuosas se combinaron y se ajustaron a pH 14 con NaOH 6M a 0°C. La extracción se realizó con 110 ml x 4 de diclorometano. La capa orgánica se secó sobre carbonato de sodio. La filtración a través de Celite y la eliminación del solvente dieron 4 g del aceite que, tras el reposo, se tornó sólido. La cromatografía flash con Et_3N/MeOH/DCM 5:5:90 dio 2,63 g de **15a** puro con 57% de rendimiento. (R_f = 0,64, Et_3N/MeOH/DCM 5:5:90)

^{1}H RMN (relación de rotámeros 4:1. * indica picos del rotámero menor. $CDCl_3$): δ 0,96* (d, 3H, J = 6,7 Hz) 1,15 (d, 3H, J = 6,9 Hz) 1,45-1,55 (m, 2H) 2,05-2,20 (m, 2H) 2,80 (s, 3H) 2,92* (s, 3H) 3,55-3,60 (m, 2H) 4,00* (m, 1H) 4,35-4,45* (m, 1H) 4,60-4,65 (m, 2H) 4,92-5,02 (m, 2H) 5,68-5,80 (m, 1H) 7,20-7,40 (m, 5H).

^{13}C RMN ($CDCl_3$): δ 11,26 15,68 31,11 35,67 47,17 52,22 76,92 116,46 127,50 128,67 129,34 138,60 143,19 178,08.

MS: $C_{16}H_{24}N_2O_2$: 277 $(M+H)^+$;

HRMS: calculado: 277,1916; experimental: 277,1917.

Paso B



15a 15b

Se trataron 1,9 g de **15a** (6,88 mmol, 1 eq) con NaOH 2N (7,0 ml, 2 eq), 7 ml de agua y se reflujó a 100°C durante 3 h. La mezcla se enfrió a temperatura ambiente. Se agregaron 20 ml de DCM, 10 ml de agua y se separó la capa orgánica. La capa acuosa se lavó con 20 ml de DCM. Las capas orgánicas combinadas también se lavaron con 10 ml de agua. La capa acuosa combinada se trató con 1,3 ml de HCl 12 N. Se agregaron 20 ml de dioxano y se ajustó la solución a un pH 8-9 mediante el agregado de $NaHCO_3$ saturado. Se agregaron 1,48 g de iBOC-OSU (1 eq) y se agitó la mezcla hasta el día siguiente. Después de disminuir el volumen del solvente a la mitad, se agregaron 10 ml de agua y 10 ml de DCM para la extracción. La capa acuosa se trató entonces con HCl 12 N gota a gota hasta que precipitó (pH 2). La extracción con 40 ml x 2 de EtOAc seguida de secado sobre $MgSO_4$ y filtración por Celite dio 1,52 g de aceite incoloro **15b** con 90% de rendimiento.

^{1}H RMN ($CDCl_3$): δ 0,88 (d, 6 H, J = 6,6 Hz) 1,78-2,00 (m, 3 H) 2,10-2,20 (m, 2 H) 3,80-3,82 (m, 2 H) 4,40 (m, 1 H) 5,00-5,06 (m, 2 H) 5,10 (m, 1 H) 5,80 (m, 1 H).

^{13}C RMN ($CDCl_3$): δ 20,0 26,2 29,0 32,8 54,2 72,8 117,0 138,0 157,8 177,6.

MS para $C_{11}H_{19}NO_4$: 230 $(M+H)^+$.

Paso C

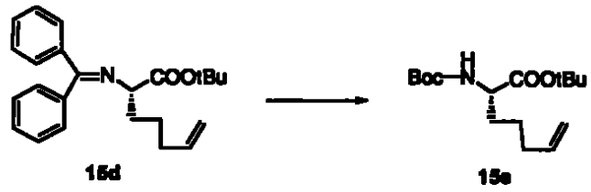


15c 15d

Se mezcló la imina **15c** (9,42 g, 31,88 mmol, 1 eq) con catalizador de Corey (*J. Am. Chem. Soc.*, 1997, *119*, 12414) (1,93 g, 0,1 eq), monohidrato de

hidróxido de cesio (53,55 g, 10 eq) en 150 ml de DCM. La solución se enfrió hasta –60°C seguido del agregado de 5-yodo-1-penteno (25 g, 4 eq) bajo nitrógeno. El producto bruto se agitó durante 60 h cuando se agregaron 100 ml de etil éter. Después de lavar con agua 100 ml x 2 y salmuera 70 ml x 1, la capa orgánica se secó sobre $MgSO_4$. La filtración por Celite y la eliminación del solvente dio 28,56 g de producto bruto. Se sometieron a cromatografía 5,1 g del bruto con hexano puro en primer lugar y luego EtOAc/hexano 1:40 a 1:20. Se obtuvo una mezcla de 2,56 g de **15d**, 5-yodo-1-penteno y benzofenona (1:2,5:0,8). (**15d**: R_f = 0,39, EtOAc/hexano1:20)

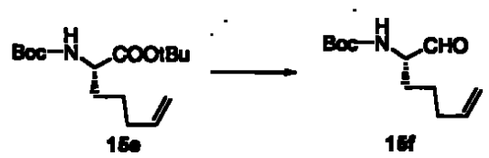
Paso D



15d 15e

Se trataron 0,5 g del producto **15d** bruto anterior (2,56 g) con 4 ml de HOAc/THF/agua 1:1:1 durante 90 min. cuando la TLC muestra la desaparición del material de partida. Se agregaron dos pipetas llenas de $NaHCO_3$ saturado. Se agregaron 10 ml de agua y 20 ml de hexano para extracción. Luego, la capa acuosa también se alcalinizó a pH 9-10. Se agregaron $(Boc)_2O$ (0,15 g) y 4 ml de dioxano y después de 2,5 h, se eliminó el solvente y el pH de la solución se ajustó a 3-4. La extracción con éter seguida de cromatografía con EtOAc/hexano 1:10 dio 0,16 g de **15e** con 48 % de rendimiento total a partir de **15c**. (R_f = 0,44, EtOAc/hexano 1:10)

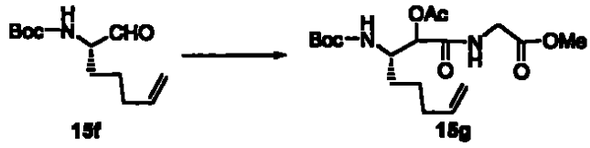
Paso E



15e 15f

Se disolvieron 4,88 g de **15e** (13,87 mmol) en 20 ml de tolueno a –78°C y se trataron con 21 ml de $LiAlH_4$ (1 M en Et_2O, 1,6 eq) durante 40 min. La mezcla se calentó hasta 0°C y se desactivó mediante EtOAc y 20 ml de $NaHSO_4$ 5%. La extracción con éter, la filtración a través de Celite y la eliminación del solvente dieron el residuo que se sometió a cromatografía con EtOAc/hexano 1/5. Se obtuvieron 2,8 g del aldehído deseado **15f** (R_f = 0,4) junto con el alcohol (1,43 g, R_f = 0,04). Este último se pudo convertir en el aldehído mediante la reacción de Dess-Martin.

Paso F



15f **15g**

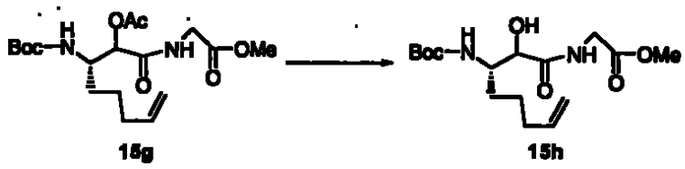
Se mezclaron 1,26 g de **15f** (5,55 mmol, 1 eq), metil isocianoacetato (0,50 ml, 1 eq), ácido acético (0,32 ml, 1 eq) en 20 ml de DCM y se agitó durante 80 h. La eliminación del solvente y la cromatografía flash dieron 1,10 g de **15g** con 51% de rendimiento. (R_f = 0,29, EtOAc/hexano 1:1).

^{1}H RMN ($CDCl_3$): δ 1,42 (s, 9 H) 1,50-1,60 (m, 2 H) 1,99-2,20 (m, 4 H) 2,18 (s, 3 H) 3,76 y 3,78 (dos singuletes, 3 H, diastereómeros 1:1) 3,90-4,20 (m, 4 H) 4,90-5,00 (m, 2 H) 5,20 (br s, 1 H) 5,70 (m, 1 H) 6,62 (br s, 1 H).

^{13}C RMN ($CDCl_3$): δ 21,93 26,26 29,46 31,25 34,41 41,99 52,53 53,50 75,57 80,41 115,74 139,14 156,28 168,91 169,38 170,79.

HRMS para $C_{18}H_{30}N_2O_7$: calculado: 387,2131 $(M+H)^+$; experimental 387,2133.

Paso G



15g **15h**

485

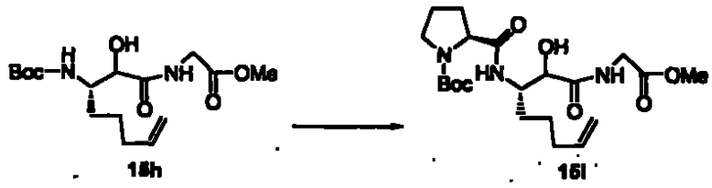
Se agitó **15g** (1,08 g, 2,8 mmol, 1 eq), 60 mg K_2CO_3 (0,15 eq) en 6 ml de MeOH a temperatura ambiente durante 1 h y luego otras 2 h a 40°C. La remoción del sólido seguida de cromatografía flash dio el producto deseado **15h** como sólido blanco (0,65 g, 68% de rendimiento).

^{1}H RMN ($CDCl_3$): δ 1,40 (s, 9 H) 1,40-1,70 (m, 4 H) 1,99-2,10 (m, 2 H) 3,70(s, 3 H) 3,80 (br, 1 H) 4,00-4,25 (m, 4 H) 4,90-5,00 (m, 2 H) 5,10 (br s, 1 H) 5,30 (m, 1 H) 5,78 (m, 1 H) 7,40 (br s, 1 H).

^{13}C RMN ($CDCl_3$): δ 26,83 29,48 30,76 34,53 42,03 53,51 54,95 75,05 81,07 115,76 139,30 157,92 170,84 174,16. $C_{16}H_{28}N_2O_6$: 345 $(M+H)^+$.

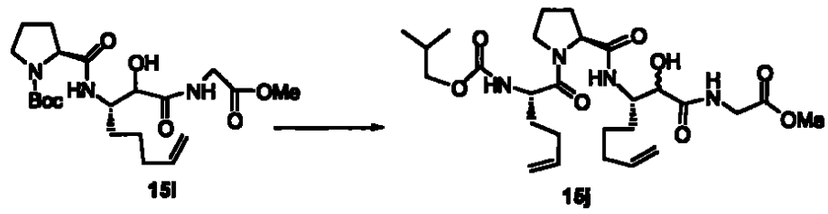
HRMS: calculado: 345,2026; experimental: 345,2033.

Paso H



El compuesto **15h** (0,39 g, 1,13 mmol) se agitó con HCl 4 M en dioxano (4 ml) a temperatura ambiente durante 2 h cuando se formaron precipitados sólidos. El solvente se eliminó y se agregaron 20 ml de DCM. El pH se ajustó a 7 usando la base de Hunig. Luego, el solvente se eliminó y el residuo se trató con 10 ml de THF, Boc-Pro-OH (0,73 g, 3 eq), HATU (1,29 g, 3 eq), base de Hunig (1,18 ml, 6 eq) y 1 ml de DMF. Después de agitar a temperatura ambiente durante 7 h, el solvente se eliminó *in vacuo*. El residuo se disolvió en 20 ml de EtOAc y se lavó con 10 ml de $NaHCO_3$ saturado, 10 ml de HCl 0,5 M dos veces, 20 ml de agua y 5 ml de salmuera. La cromatografía dio 0,68 g de **15i** (Rf = 0,31, 5% MeOH en DCM).

Paso I



15l 15j

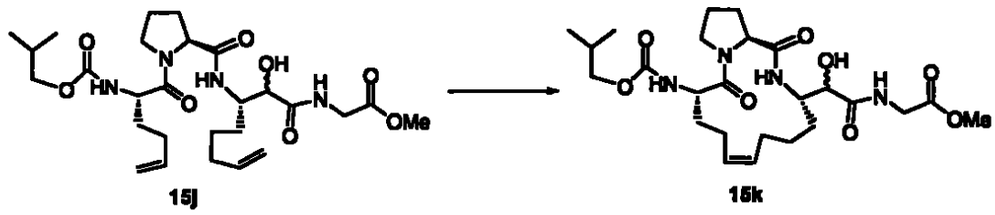
Se trató **15l** con 2 ml de DCM, 3 ml de HCl 4 M en dioxano durante 1 h. Se agregaron 30 ml de DCM seguido de neutralización con base de Hunig a 0°C. El solvente se eliminó y se disolvió el producto bruto en 5 ml de DCM, 10 ml de THF. Después de la adición de **15b** (0,26 g, 1 eq), HATU (0,43 g, 1 eq) y base de Hunig (0,41 ml, 2,1 eq) y agitación durante 4 h, el solvente se eliminó y se agregaron 30 ml de EtOAc. Luego, la solución se lavó con 10 ml de $NaHCO_3$ saturado, 10 ml de HCl 1 M, 10 ml de HCl 0,5 M, 20 ml de agua, 5 ml de salmuera. La cromatografía dio el producto deseado **15j** (0,3 g, 48% a partir de **15h**).

^{13}C RMN ($CDCl_3$): δ 20,20 26,26 26,72 29,18 29,55 30,58 33,25 34,60 41,95 48,57 52,90 53,00 53,40 54,68 61,56 72,34 75,68 115,64 116,73 138,07 139,33 157,47 171,04 171,15 173,06 174,23.

$C_{27}H_{44}N_4O_8$: 553 $(M+H)^+$.

HRMS: calculado: 553,3237; experimental: 553,3259.

Paso J



15j 15k

Se trató el compuesto **15j** (0,37 g, 0,67 mmol) con 0,138 g de catalizador de Grubbs (0,25 eq) en 223 ml de DCM bajo argón. Después de agitar a temperatura ambiente durante 65 h, la RMN muestra que la mezcla contiene material de partida **15j**, el producto deseado **15k** (alrededor de 20% de rendimiento) y $PO(C_6H_{11})_3$. Los R_f para estos tres compuestos son 0,34, 0,24,

490
487

0,74, respectivamente en 5% HOAc/EtOAc. La cromatografía flash reiterada pudo dar la muestra pura de **15k**.

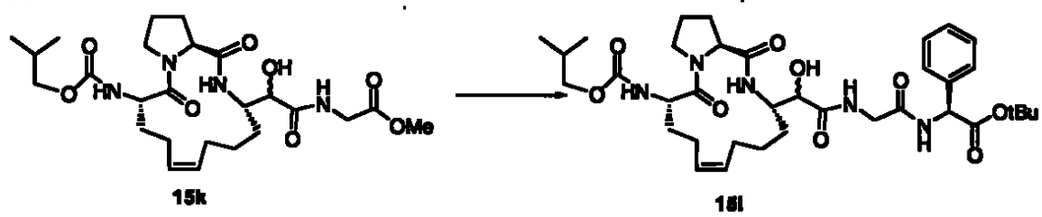
^{1}H RMN ($CDCl_3$): δ 0,90 (d, 6 H, J = 6,6 Hz) 1,40-2,00 (m, 14 H) 2,05-2,50 (m, 3 H) 3,60 (m, 1 H) 3,70 (s, 3 H) 3,75-4,00 (m, 3 H) 4,00-4,20 (m, 2 H) 4,50 (m, 1 H) 4,70 (d, 1 H, J = 7,5 Hz, diastereómero) 4,81 (d, 1 H, J = 7,9 Hz, otro diastereómero) 5,38 (m, 1 H) 5,58 (m, 1 H) 5,65 (br s, 1 H) 7,20 (d, 1 H J = 7,0 Hz) 7,38 (d, 1 H, J = 7,1 Hz).

^{13}C RMN ($CDCl_3$): δ 20,26 23,05 26,54 27,02 27,67 27,73 29,21 31,06 34,03 41,97 48,71 52,40 52,80 53,.53 60,54 72,43 75,08 130,44 130,56 157,02 171,13 172,01 173,13 173,38.

LC/MS: Tr = 5,11 min. (gradiente A (acetonitrilo)/B (agua con 0,1% de TFA): de A/B 5% a A/B 95% en 10 min.) $C_{25}H_{40}N_4O_8$: 525 $(M+1)^+$

HRMS: calculado: 525,2924; experimental: 525,2908.

Paso K



15k 15l

Se agitaron el compuesto **15k** (92 mg, 0,18 mmol, 1 eq), 60 mg de K_2CO_3 (2,5 eq) en 5 ml de MeOH a 40°C durante 2 h cuando la TLC muestra la desaparición completa del material de partida. Después de la eliminación del solvente, se agregaron 44 ml de HCl 0,01 M en DCM (2,5 eq) para neutralizar la solución. El solvente se eliminó seguido del agregado de 10 ml de THF, 1 ml de DMF, PhG-O-tBu (sal de HCl, 51 mg, 1,2 eq), 80 mg de HATU (1,2 eq), 0,11 ml de base de Hunig (3,5 eq). La mezcla se agitó durante 12 h. Después de la eliminación del solvente, la cromatografía directa dio el producto **15l** (97 mg, 79% de rendimiento a partir de **15j**. Rf = 0,32, 5% de MeOH/DCM).

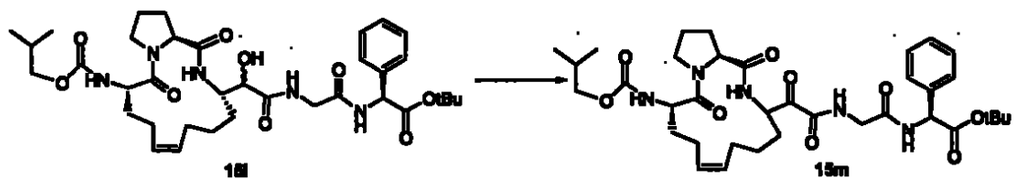
491
488

^{1}H RMN ($CDCl_3$): δ 0,90 (d, 6 H, J = 6,6 Hz) 1,30 (s, 9 H) 1,40-2,00 (m, 14 H) 2,15-2,20 (m, 1 H) 3,60 (m, 1 H) 3,75-3,90 (m, 3 H) 4,00-4,09 (m, 1 H) 4,10-4,35 (m, 2 H) 4,50 (m, 1 H) 4,62 (d, 1 H, J = 7,5 Hz, diastereómero) 4,72 (d, 1 H, J = 7,9 Hz, otro diastereómero) 5,20-5,38 (m, 1 H) 5,44 (d, 1 H, J = 6,6 Hz) 5,50 (m, 1 H) 5,98 (m, 1 H) 7,30 (m, 5 H) 7,45 (d, 1H, J = 7,0 Hz) 7,55 (d, 1 H, J = 7,1 Hz) 7,70 (br s, 1 H).

^{13}C RMN ($CDCl_3$): δ 20,30 23,35 26,38 26,78 27,29 28,02 29,18 31,42 34,89 43,97 48,70 51,90 52,93 58,22 60,40 72,44 74,96 75,93 83,80 120,88 128,10 128,12 129,63 129,70 130,33 137,74 157,20 169,32 170,69 173,70 174,47.

LC/MS: Tr = 6,61 min. (gradiente A (acetonitrilo)/B (agua con 0,1% de TFA): de A/B 5% a A/B 95% en 10 min.) MS: $C_{36}H_{53}N_5O_9$: 700 $(M+H)^+$.

Paso L



15l 15m

Se trató el compuesto **15l** (90 mg, 0,13 mmol) con 109 mg del reactivo de Dess-Martin (2 eq) en 10 ml de DCM a temperatura ambiente durante 12 h. Después de la eliminación del solvente, la cromatografía directa con EtOAc/hexano 7:3 dio **15m** (40%) como sólido blanco.

^{1}H RMN ($CDCl_3$): δ 0,95 (d, 6 H, J = 6,6 Hz) 1,40 (s, 9 H) 1,50-2,10 (m, 14 H) 2,20-2,30 (m, 1 H) 3,60(m, 1 H) 3,75-3,90 (m, 3 H) 3,93 (dd, 1 H, J = 5,9, 16,8 Hz) 4,10 (m, 1 H) 4,50 (dd, 1 H, J = 8,0, 13,9 Hz) 4,80 (d, 1 H, J = 6,6 Hz) 5,20-5,40 (m, 3 H) 5,41 (d, 1 H, J = 6,6 Hz) 5,60 (dd, 1 H, J = 7,3, 10 Hz) 6,82 (d, 1 H, J = 7,3 Hz) 7,30 (m, 5 H) 7,50 (m, 1H) 7,80 (d, 1 H, J = 6,7 Hz).

^{13}C RMN ($CDCl_3$): δ 20,29 23,65 26,34 26,75 29,02 29,20 30,37 30,95 31,56 35,07 43,71 48,83 52,95 54,20 58,14 60,23 72,54 84,15 128,03 129,41

492

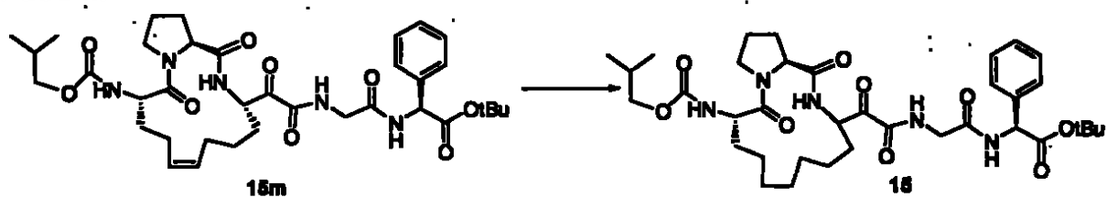
489

129,68 129,87 130,62 137,60 156,99 160,33 167,41 171,37 173,84 187,26 196,36.

LC/MS: Tr = 6,81 min. (gradiente A (acetonitrilo)/B (agua con 0,1% de TFA): de A/B 5% a A/B 95% en 10 min.) MS: $C_{36}H_{51}N_5O_9$: 698 $(M+H)^+$

HRMS: calculado 698,3765 experimental 698,3762.

Paso M



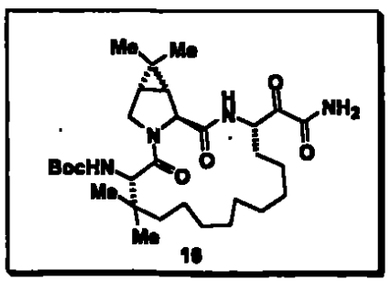
Se trató el compuesto **15m** (4 mg) con 5 ml de MeOH, 2 mg de Pd-C bajo globo de hidrógeno durante 1,5 h. La solución se filtró a través de Celite. El filtrado se secó *in vacuo* y la RMN muestra la formación exclusiva de **15.**

^{1}H RMN ($CDCl_3$): δ 0,95 (d, 6 H, J = 6,6 Hz) 1,40 (s, 9 H) 1,50-2,10 (m, 16 H) 2,20-2,30 (m, 1 H) 3,60(m, 1 H) 3,75-3,90 (m, 3 H) 3,93 (dd, 1 H, J = 5,9, 16,8 Hz) 4,10 (m, 1 H) 4,50 (dd, 1 H, J = 8,0, 13,9 Hz) 4,80 (d, 1 H, J = 6,6 Hz) 5,30 (m, 1 H) 5,41 (d, 1 H, J = 6,6 Hz) 5,55 (d, 1 H, J = 7,0 Hz) 6,82 (d, 1 H, J = 7,3 Hz) 7,30 (m, 5 H) 7,50 (m, 1H) 7,80 (d, 1 H, J = 6,7 Hz).

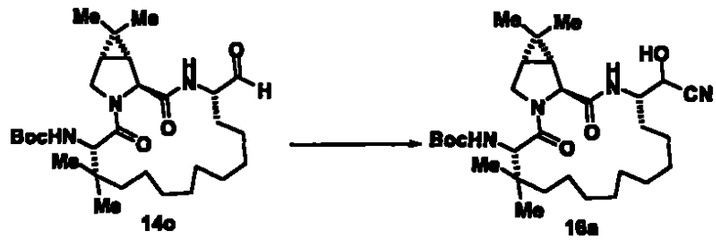
LC/MS: Tr = 5,26 min. (gradiente A (acetonitrilo)/B (agua con 0,1% de TFA): de A/B 5% a A/B 95% en 10 min.) MS: $C_{36}H_{53}N_5O_9$: 700 $(M+H)^+$.

HRMS: calculado: 700,3922; experimental: 700,3925.

Ejemplo Preparativo 16



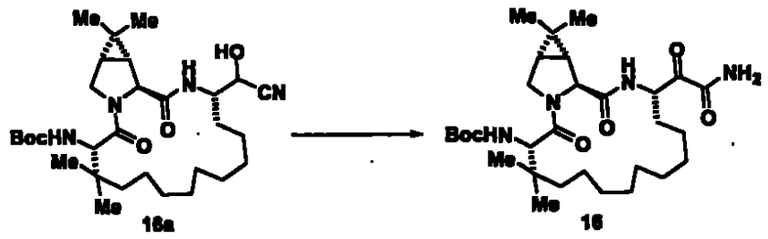
Pas A



Se trató una solución del aldehído **14c** (590 mg, 1,15 mmol) en CH_2Cl_2 (10 ml) con Et_3N (240 mg, 2,4 mmol) y cianhidrina de acetona (240 mg, 2,82 mmol). La mezcla de reacción se agitó a t.a. durante 2 h y se concentró *in vacuo*. El residuo se purificó mediante cromatografía (SiO_2, acetona/hexanos 1:4) para dar **16a** (600 mg) como un sólido incoloro.

MS (ESI), m/z, intensidad relativa 569 [$(M+Na)^+$, 20], 547 [$(M+1)^+$, 40], 447 (100).

Paso B

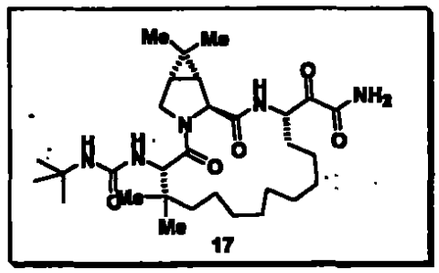


Se trató una solución de la cianhidrina **16a** (600 mg, 1,1 mmol) en DMSO (10 ml) con H_2O_2 (35%, 1,5 ml) y K_2CO_3 (252 mg, 1,83 mmol) y se agitó a t.a. durante 15 h. La mezcla de reacción se diluyó con CH_2Cl_2 (200 ml) y se lavó con solución acuosa de $Na_2S_2O_3$ (10%, 50 ml) y salmuera (30 ml). La mezcla de reacción se secó ($MgSO_4$), se filtró, se concentró *in vacuo* y se usó directamente en la oxidación sin otra purificación.

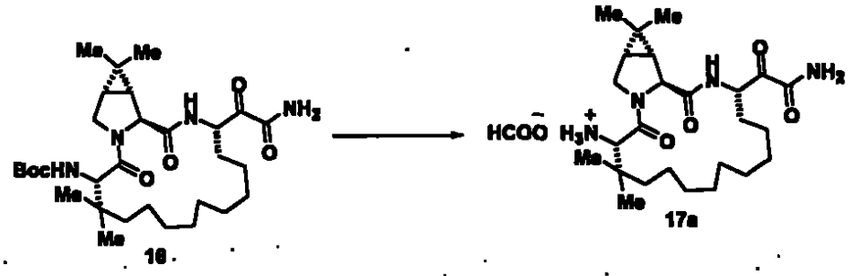
Se trató una solución de hidroxi amida en tolueno/DMSO (2:1, 15 ml) con EDCI (1,9 g, 10,00 mmol) y $Cl_2CHCOOH$ (317 mg, 2,49 mmol) y se agitó a 0°C durante 3 h. La mezcla de reacción se diluyó con CH_2Cl_2 (300 ml) y se lavó con NaHCO3 acuoso saturado (2x100 ml) y salmuera (100 ml). La capa orgánica se secó ($MgSO_4$), se concentró y se purificó mediante cromatografía (SiO_2, acetona/hexanos 1:5) para dar **16** como un sólido incoloro.

MS (ESI), m/z, intensidad relativa 617 [$(M+CH_3OH+Na)^+$, 20], 595 [$(M+CH_3OH+1)^+$, 40], 507 [$(M+1)^+$, 20], 463 (100).

Ejemplo Preparativo 17

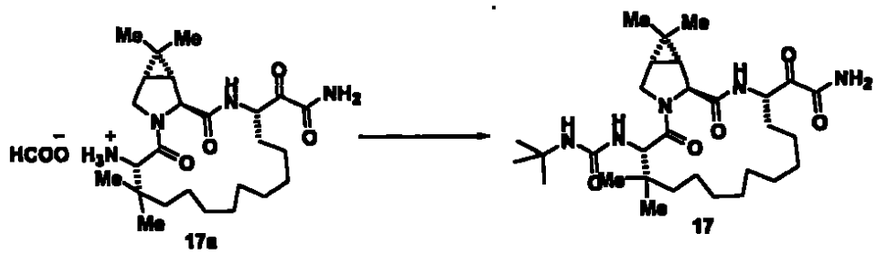


Paso A



Se agitó una solución de **16** (300 mg 0,54 mmol) en HCOOH (10,0 ml) a t.a. durante 2 h y se concentró *in vacuo* . El residuo se secó *in vacuo* y se usó en reacciones posteriores sin otra purificación.

Paso B

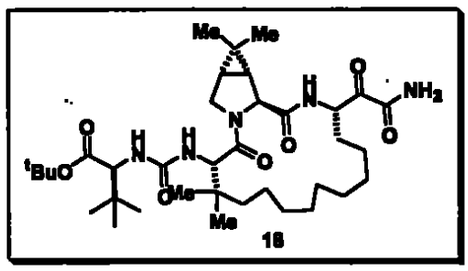


Se trató una solución de **17a** (100 mg) en DMF/CH_2Cl_2 (1:1, 3 ml) con ^{t}BuNCO (50 µl y NMM (52 mg, 0,52 mmol). La mezcla de reacción se agitó a t.a. durante 16 h y se concentró *in vacuo* y se diluyó con CH_2Cl_2 (60 ml) y se lavó con HCl acuoso (1M, 2x30 ml), se secó, se concentró *in vacuo* . El residuo se purificó

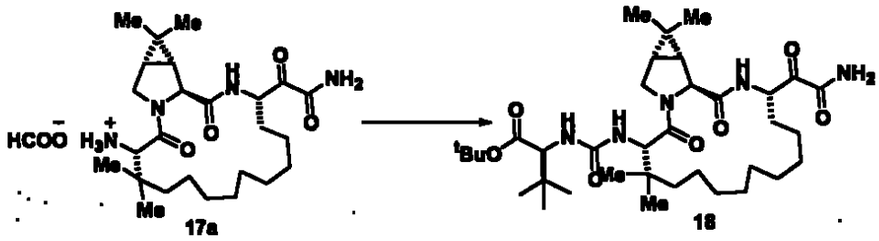
mediante cromatografía (SiO_2, acetona/hexanos 1:2) para dar **17** (34 mg) como un sólido incoloro.

MS (ESI), m/z, intensidad relativa 584 [$(M+1)^+$, 30], 463 (100).

Ejemplo Preparativo 18



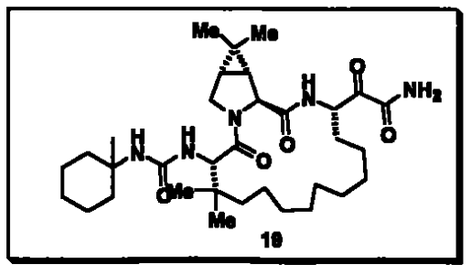
Paso A



Se trató una solución de **17a** (100 mg) en DMF/CH_2Cl_2 (1:1, 3 ml) con isocianato de terbutiléster de ter-butilglicina (100 mg, 0,46 mmol) y NMM (52 mg, 0,52 mmol). La mezcla de reacción se agitó a t.a. durante 16 h y se concentró *in vacuo*, se diluyó con CH_2Cl_2 (60 ml) y se lavó con HCl acuoso (1M, 2x30 ml), se secó, se concentró *in vacuo* . El residuo se purificó mediante cromatografía (SiO_2, acetona/hexanos 1:2) para dar **18** (42 mg) como un sólido incoloro.

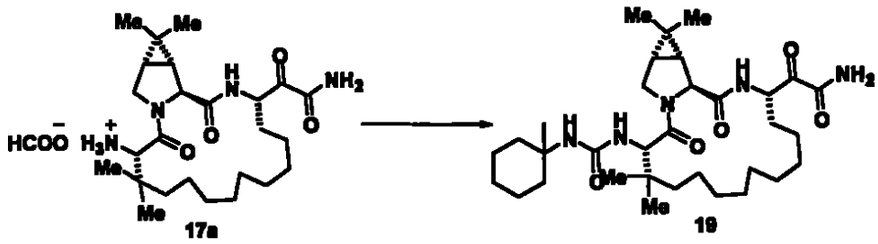
MS (ESI), m/z, intensidad relativa 698 [$(M+Na)^+$, 40], 676 [$(M+1)^+$, 100], 463 (20).

Ejemplo Preparativo 19



496
493

Paso A

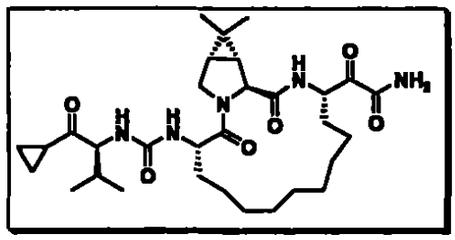


17a 19

Se trató una solución de **17a** (100 mg) en DMF/CH_2Cl_2 (1:1, 3 ml) con isocianato de α-metil-ciclohexilamina (100 µl) y NMM (52 mg, 0,52 mmol). La mezcla de reacción se agitó a t.a. durante 16 h y se concentró *in vacuo* , se diluyó con CH_2Cl_2 (60 ml) y se lavó con HCl acuoso (1M, 2x30 ml), se secó y se concentró *in vacuo*. El residuo se purificó mediante cromatografía (SiO_2, acetona/hexanos 1:2) para dar **20** (21 mg) como un sólido incoloro.

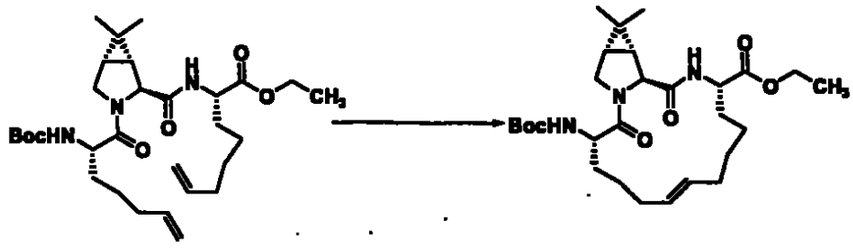
MS (ESI), m/z, intensidad relativa 624 [$(M+Na)^+$, 30], 602 [$(M+1)^+$, 15], 463 (100), 449 (20), 129 (30).

Ejemplo Preparativo 20



20

Paso A

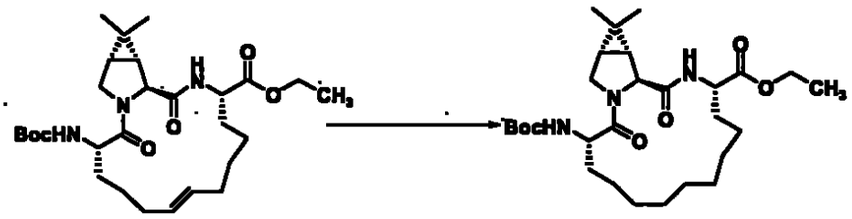


20a **20b**

Se trató una solución del dieno acíclico **20a** (6,00 g, 10,954 mmol) en tolueno seco (500 ml), se desgasificó con argón durante 0,5 h, se trató con

catalizador de Grubbs (1,35 g, 1,643 mmol) y se calentó a 60°C durante 12 h. La mezcla de reacción se concentró *in vacuo* y se purificó mediante cromatografía (SiO_2, EtOAc/hexanos 1:3) para dar **20b** como una espuma marrón.

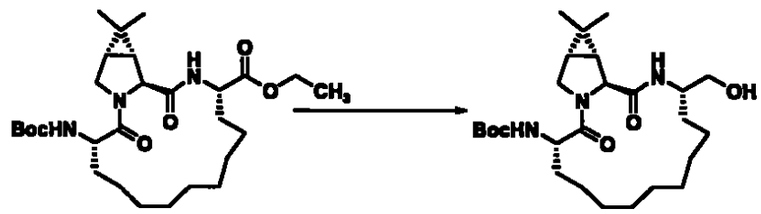
Paso B



20b **20c**

Se trató una solución del alqueno **20b** (5,00g mg, 0,865 mmol) en metanol (100 ml) con Pd/C (1,2g, 5% p/p) y se hidrogenó a 3,45 x 10^5 Pa (50 psi) durante 3 h. La reacción se filtró a través de un tapón de Celite y se concentró *in vacuo*. El residuo se purificó mediante cromatografía usando THF/hexanos con un gradiente de 10-40% para dar **20c** aislado (3,00 g) como un sólido incoloro.

Paso C



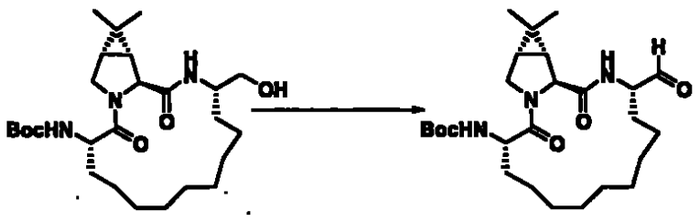
20c **20d**

Se trató una solución del éster **20c** (3,00 g, 5,75 mmol) en THF seco (50 ml) con $LiBH_4$ (solución 2M en THF, 3,5 ml, 6,90 mmol) y se agitó a t.a. durante 3 h. La reacción se monitoreó por TLC (EtOAc/Hexanos 1:2). La reacción se desactivó con metanol (2 ml) y se diluyó con HCl acuoso (1 M, 30 ml) y se extrajo en CH_2Cl_2 (3x100 ml). Las capas orgánicas combinadas se lavaron con $NaHCO_3$ acuoso saturado (30 ml), salmuera, se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2,

495

Acetona/Hexanos 1:2) para dar **20d** (2,21 g) como un sólido incoloro. MS (*m/z*, intensidad relativa) 518 [$(M+K)^+$, 15], 480 [$(M+H)^+$, 75], 380(100).

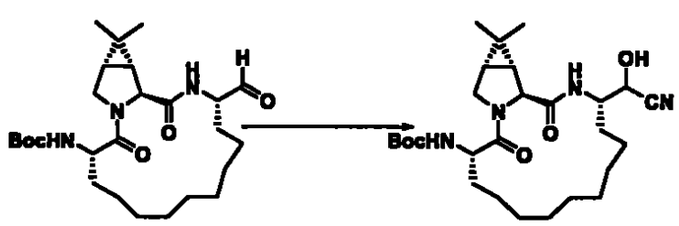
Paso D



20d **20e**

Se trató una solución del alcohol **20d** (2,2 g, 4,58 mmol) en CH_2Cl_2 seco (50 ml) con reactivo de Dess-Martin (2,91 g, 6,880 mmol) y se agitó a t.a. durante 2 h. La mezcla de reacción se diluyó con $Na_2S_2O_3$ acuoso (5%, 50 ml) y $NaHCO_3$ acuoso saturado (50 ml) y se agitó a t.a. durante 15 min. La mezcla de reacción se extrajo con CH_2Cl_2 (500 ml) y las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* para dar **20e** bruto (1,9 g), que se usó en la siguiente reacción sin otra purificación.

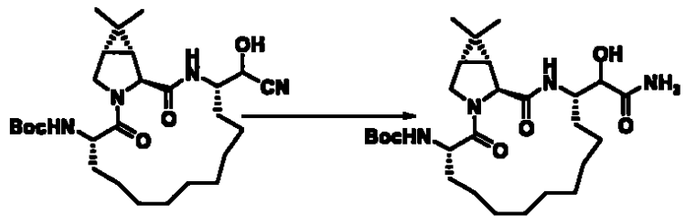
Paso E



20e **20f**

Se enfrió una solución de **20e** bruto (1,00 g, 2,094 mmol) en CH_2Cl_2 (15 ml) a 0°C y se trató con la cianhidrina de la acetona (356 mg, 4,187 mmol) y trietilamina (424 mg, 4,187 mmol). La mezcla de reacción se agitó a 0°C durante 12 h y se concentró *in vacuo*. El residuo se purificó mediante cromatografía (SiO_2, EtOAc/Hexanos 1:5-->1:1) para dar **20f** (500 mg) como un aceite incoloro.

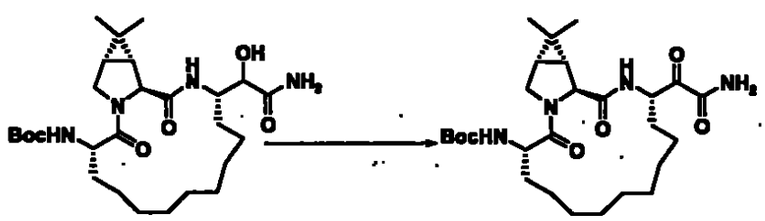
Paso F



20f **20g**

Se trató una solución de la cianhidrina **20f** (500 mg, ~1,00 mmol) en DMSO (5 ml) con H_2O_2 (5 ml), K_2CO_3 (276 mg, 2,00 mmol) y se agitó a t.a. durante 12 h. La mezcla de reacción se diluyó con $Na_2S_2O_3$ acuoso (5%, 100 ml) y se extrajo con CH_2Cl_2 (2x100 ml). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* para dar **20g** que se usó tal cual para la posterior oxidación sin purificación.

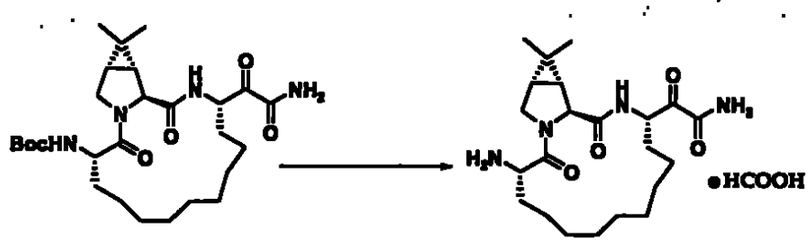
Paso G:



20g **20h**

Se trató una solución de la hidroxilamina **20g** (850 mg, 1,626 mmol) en tolueno (5 ml) y DMSO (5 ml) con EDCI (3,117 g, 16,26 mmol), y ácido dicloroacético (1,048 g, 8,13 mmol, 698μl) y se agitó a t.a. durante 3 h. La mezcla de reacción se diluyó con CH_2Cl_2 (200 ml) y se lavó con $NaHCO_3$ acuoso saturado (200 ml), HCl acuoso (1 M,200 ml), salmuera (30 ml), se secó ($MgSO_4$), se filtró, se concentró *in vacuo* y se purificó mediante cromatografía (SiO_2, acetona/Hexanos 1:2) para dar **20h** (300 mg) como un sólido incoloro.

Paso H:

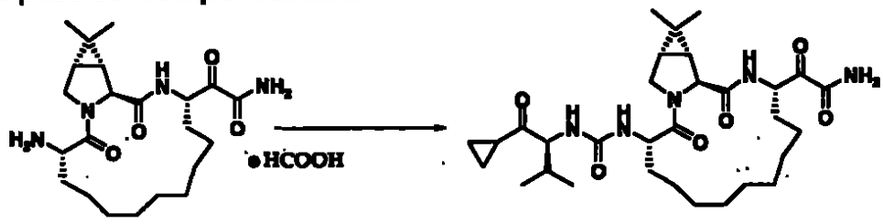


500

497

20h **20i**

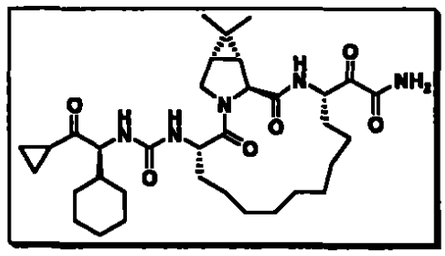
Se agitó una solución de la cetoamida protegida por Boc **20h** en ácido fórmico (5 ml) a t.a. durante 3 h y se concentró *in vacuo* y se usó tal cual en el siguiente paso sin otra purificación.



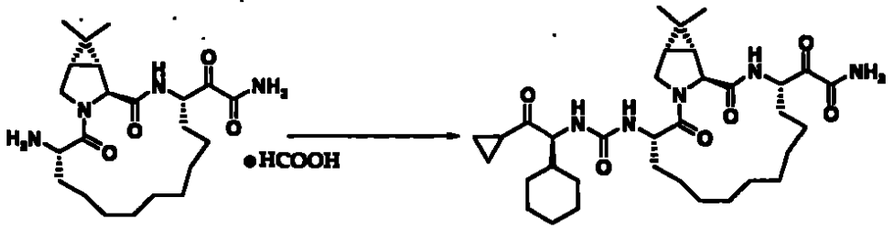
20i **20**

Se trató una solución de la amina **20i** (40 mg, 0,1 mmol) en cloruro de metileno (3,0 ml) con NMM (30 mg, 0,3 mmol) y se enfrió a 0°C. Se agregó una solución de isocianato en CH_2Cl_2 y la mezcla de reacción se agitó a ta. durante 1,5 h. La mezcla de reacción se diluyó con cloruro de metileno (60 ml) y se lavó con HCl acuoso (1 M, 30 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 20→50%) para dar ***20*** como un sólido incoloro. MS (*m/z*, intensidad relativa) 588 [$(M+H)^+$, 100], 421 (40). HRMS (ESI) Calculado. para $C_{31}H_{50}N_5O_6$: 588,3761 $(M+H)^+$; Experimental: 588,3751.

Ejemplo Preparativo 21:



21

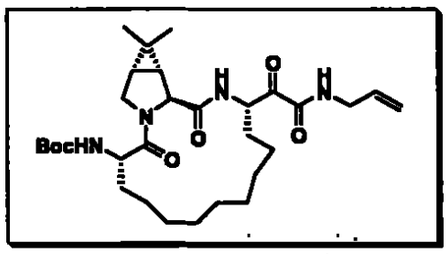


498

20l **21**

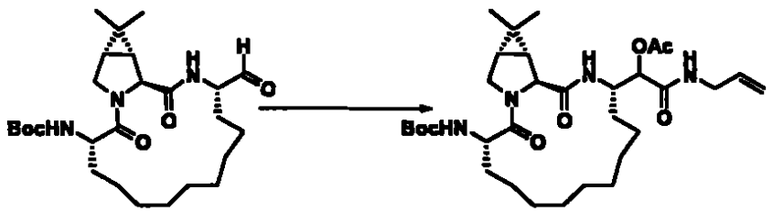
Se trató una solución de la amina **20l** (40 mg, 0,1 mmol) en cloruro de metileno (3,0 ml) con NMM (30 mg, 0,3 mmol) y se enfrió a 0°C. Se agregó una solución de 2-ciclohexil-1-ciclopropil-2-isocianato etanona (0,15 mmol) en CH_2Cl_2 y la mezcla de reacción se agitó a ta. durante 1,5 h. La mezcla de reacción se diluyó con cloruro de metileno (60 ml) y se lavó con HCl acuoso (1 M, 30 ml). Las capas orgánicas se secaron con ($MgSO_4$) se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 20 → 50%) para dar **21** como un sólido incoloro.

Ejemplo Preparativo 22



22

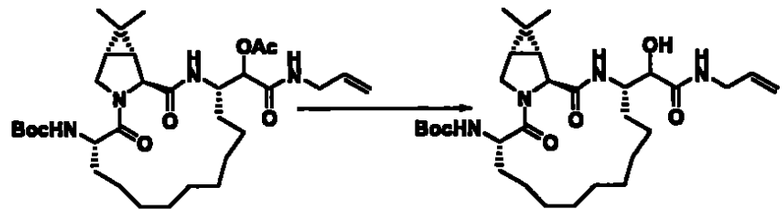
Paso A:



20e **22a**

Se trató una solución del aldehído **20e** (100 mg, 0,210 mmol) en cloruro de metileno (4 ml) con isocianuro de alilo (28,01 mg, 0,411 mmol) y ácido acético y se agitó a t.a. durante 12 h. La reacción se concentró *in vacuo* y se purificó mediante cromatografía (SiO_2, acetona/hexanos 1:4→1:1) para obtener **22a** (75 mg) como un sólido incoloro. MS (*m/z*, intensidad relativa) 605 [$(M+H)^+$, 100], 505 (98).

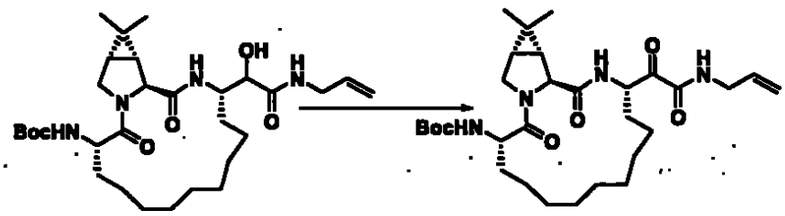
Paso B:



22a **22b**

Se trató una solución de **22b** (275 mg, 0,454 mmol) en metanol (4 ml), THF(4,0 ml) y agua (4,0 ml) con $LiOH \cdot H_2O$ (22 mg, 0,55 mmol) y se agitó a t.a. durante 2 h. La mezcla de reacción se diluyó con HCl acuoso (1 M, 30 ml) y se extrajo en CH_2Cl_2 (2x40 ml). La capa orgánica combinada se secó ($MgSO_4$), se filtró, se concentró *in vacuo*, y se usó tal cual en el siguiente paso sin otra purificación.

Paso C:

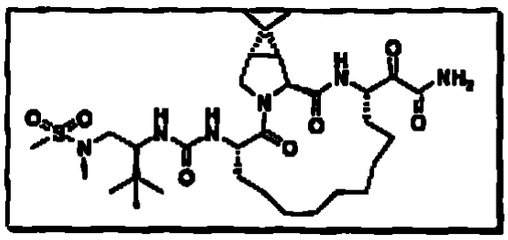


22b **22**

Se trató una solución del alcohol **22b** (300 mg, 0,534 mmol) en CH_2Cl_2 seco (15 ml) con reactivo de Dess-Martin (453 mg, 1,06 mmol) y se agitó a t.a. durante 2 h. La mezcla de reacción se diluyó con $Na_2S_2O_3$ acuoso (5%, 30 ml) y $NaHCO_3$ acuoso saturado (30 ml) y se agitó a t.a. durante 15 min. La mezcla de reacción se extrajo con CH_2Cl_2 (3x50 ml) y las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 0:1→1:1) para dar 22 como un sólido incoloro. MS (*m/z*, intensidad relativa) 561 [$(M+H)^+$, 100], 461 (99). HRMS (ESI) Calculado. para $C_{31}H_{50}N_5O_6$: 588,3761 $(M+H)^+$; Experimental: 588,3751.

Ejemplo Preparativo 23

500



23

Paso A:



23a 23b

Se trató una solución de amina 23a (900 mg, 3,40 mmol) en CH_2Cl_2 a 0°C con NMM (511 mg, 5,10 mmol) y cloruro metansulfonilo (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 exceso de HCl acuoso (1M, 500 ml). La capa orgánica se secó ($MgSO_4$), se filtró, se concentró *in vacuo*. y se purificó mediante cromatografía (SiO_2, Hex/EtOAc 1:9→1:1) para dar la metilsulfonamida 23b (1,00 g).

Paso B:



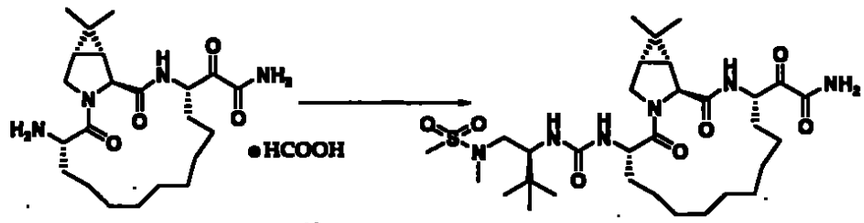
23b 23c

Se trató una solución de metansulfonamida 23b (1,0 g, 2,9 mmol) en metanol (30 ml) con paladio (200 mg, 10% en peso/C) y se hidrogenó a $4,14 \times 10^5$ Pa (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 usó directamente en otra reacción sin otra purificación.

Se trató una solución de la amina desprotegida en CH_2Cl_2 (10 ml) y $NaHCO_3$ acuoso saturado (10 ml) a 0°C con fosgeno (5 ml, solución 15% en tolueno) y se agitó a 0°C durante 2 h. La mezcla de reacción se diluyó con CH_2Cl_2 (50 ml) y la capa orgánica se lavó con $NaHCO_3$ acuoso frío. La capa orgánica se

secó ($MgSO_4$), se filtró y además se diluyó con 10 ml de tolueno, se concentró la capa de cloruro de metileno y se usó como una solución de **23c**.

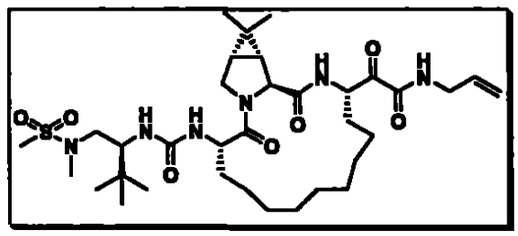
Paso C:



20I **23**

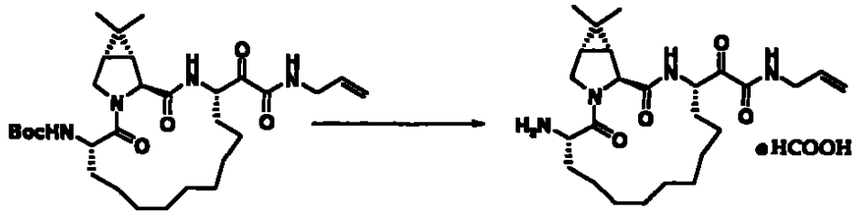
Se trató una solución de la amina **20I** (40 mg, 0,1 mmol) en cloruro de metileno (3,0 ml) con NMM (30 mg, 0,3 mmol) y se enfrió a 0°C. Se agregó una solución de isocianato **23** en CH_2Cl_2 y la mezcla de reacción se agitó a ta. durante 1,5 h. La mezcla de reacción se diluyó con cloruro de metileno (60 ml) y se lavó con HCl acuoso (1 M, 30 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 20→50%) para dar **23**, MS (*m/z*, intensidad relativa) 693 [$(M+K)^+$, 10], 677 [$(M+Na)^+$, 20], 655 [$(M+H)^+$, 100], 449 (30), 421 (30); HRMS (ESI) Calculado. para $C_{31}H_{54}N_6O_7SNa$ 677,3672 $(M+Na)^+$; Experimental: 677,3685.

Ejemplo Preparativo 24



24

Paso A:



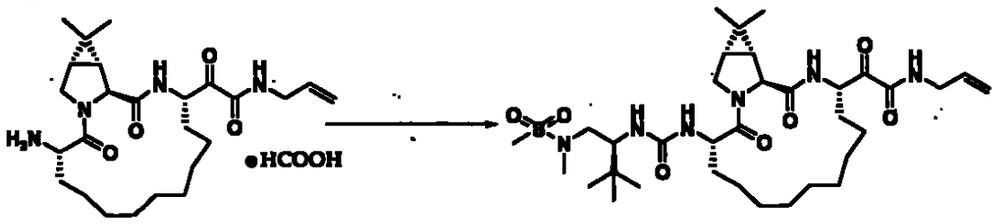
505.

502

22 24a

Se agitó una solución de la cetoamida protegida por Boc 22 (220 mg, 0,39 mmol) en ácido fórmico (5 ml) a ta. durante 3 h y se concentró *in vacuo* y se usó tal cual en el siguiente paso sin otra purificación.

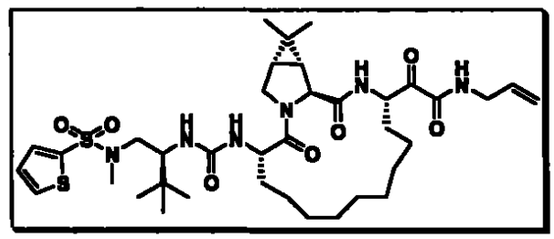
Paso B:



24a 24

Se trató una solución de la amina **24a** (40 mg, 0,1 mmol) en cloruro de metileno (3,0 ml) con NMM (30 mg, 0,3 mmol) y se enfrió a 0°C. Se agregó una solución de isocianato en CH_2Cl_2 y la mezcla de reacción se agitó a ta. durante 1,5 h. La mezcla de reacción se diluyó con cloruro de metileno (60 ml) y se lavó con HCl acuoso (1 M, 30 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *In vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 20→50%) para dar **24** (27 mg) MS (*m/z*, intensidad relativa) 734 [$(M+K)^+$, 10], 695 [$(M+H)^+$, 100], 461 (20), 443 (20); HRMS (FAB) Calculado para $C_{34}H_{59}N_6O_7S$ 695,4166 $(M+H)^+$; Experimental: 695,4161.

Ejemplo Preparativo 25



25

Paso A:



23a 25a

506

503

Se trató una solución de la amina **23a** (900 mg, 3,40 mmol) en CH_2Cl_2 a 0°C con NMM (511 mg, 5,10 mmol) y cloruro de tiofensulfonilo (928 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 acuoso en exceso (1M, 500 ml). La capa orgánica se secó ($MgSO_4$), se filtró, se concentró *in vacuo* y se purificó mediante cromatografía (SiO_2, Hex/EtOAc 1:9→1:1) para dar la sulfonamida **25a** (1,00 g), sólido incoloro.

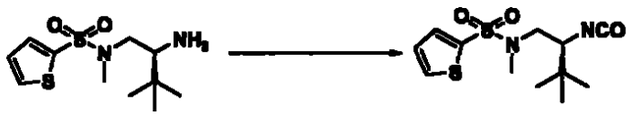
Paso B:



25a 25b

Se trató una solución de compuesto protegido por Cbz **25a** (1,00 g, 2,118 mmol) con TFA (30 ml) y sulfuro de dimetilo (7,78 ml) a 0°C y se agitó a t.a. durante 3 h. La mezcla de reacción se concentró *in vacuo* y se diluyó con NaOH acuoso (100 ml). La amina se extrajo con cloruro de metileno (2x100 ml) y las capas orgánicas combinadas se secaron con ($MgSO_4$) se filtraron, se concentraron *in vacuo* y para dar **25b** (800 mg) que se usó en otra reacción sin otra purificación. MS (*m/z*, intensidad relativa) 277 [$(M+H)^+$, 100], 190 (50).

Paso C:



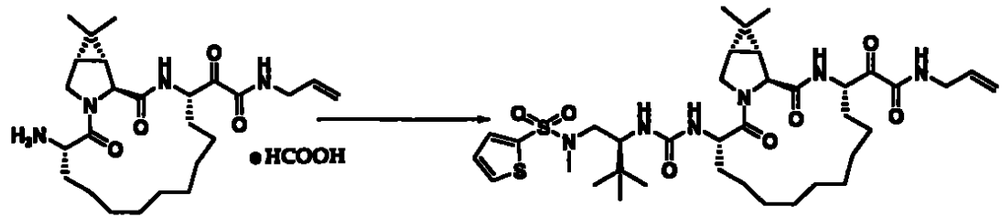
25b 25c

Se trató una solución de amina desprotegida **25b** (800 mg, 2,9 mmol) en CH_2Cl_2 (10 ml) y $NaHCO_3$ acuoso saturado (10 ml) a 0°C con fosgeno (5 ml, solución15% en tolueno) y se agitó a 0°C durante 2 h. La mezcla de reacción se diluyó con CH_2Cl_2 (50 ml) y la capa orgánica se lavó con $NaHCO_3$ acuoso frío. La capa orgánica se secó ($MgSO_4$), se filtró y también se diluyó con 10 ml de tolueno, se concentró la capa de cloruro de metileno y se usó como una solución de **25c.**

507

504

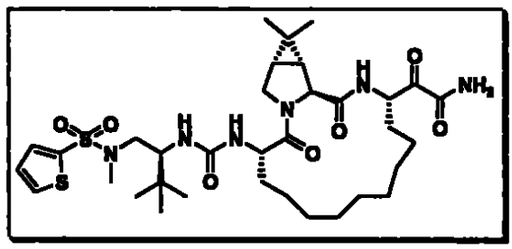
Paso D:



24a **25**

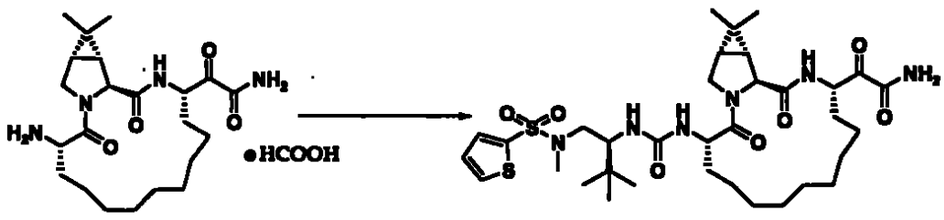
Se trató una solución de la amina **24a** (40 mg, 0,1 mmol) en cloruro de metileno (3,0 ml) con NMM (30 mg, 0,3 mmol) y se enfrió a 0°C. Se agregó una solución de isocianato en CH_2Cl_2 y la mezcla de reacción se agitó a ta. durante 1,5 h. La mezcla de reacción se diluyó con cloruro de metileno (60 ml) y se lavó con HCl acuoso (1 M, 30 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 20→ 50%) para dar **25** (39 mg) como un sólido incoloro. MS (*m/z*, intensidad relativa) 801 [$(M+K)^+$, 10], 763 [$(M+H)^+$, 100], 461 (15), 277 (20); HRMS (ESI) Calculado para $C_{37}H_{58}N_6O_7S_2Na$ 785,3706 $(M+Na)^+$; Experimental: 785,3706.

Ejemplo Preparativo 26



26

Paso A:

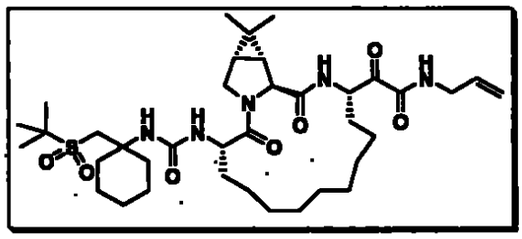


20i **26**

~~508~~
505

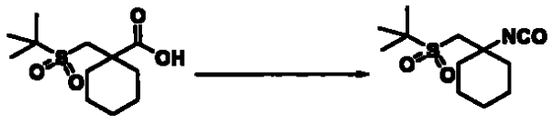
Se trató una solución de la amina **20l** (40 mg, 0,1 mmol) en cloruro de metileno (3,0 ml) con NMM (30 mg, 0,3 mmol) y se enfrió a 0°C. Se agregó una solución de isocianato en CH_2Cl_2 y la mezcla de reacción se agitó a ta. durante 1,5 h. La mezcla de reacción se diluyó con cloruro de metileno (60 ml) y se lavó con HCl acuoso (1 M, 30 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 20→ 50%) para dar **26** como un sólido incoloro (31 mg). MS (*m/z*, intensidad relativa) 761 [$(M+K)^+$, 10], 720 [$(M+H)^+$, 100], 421 (20); HRMS (ESI) Calculado para $C_{34}H_{54}N_6O_7S_2Na$ 745,3393 $(M+Na)^+$; Experimental: 745,3396.

Ejemplo Preparativo 27



27

Paso A:



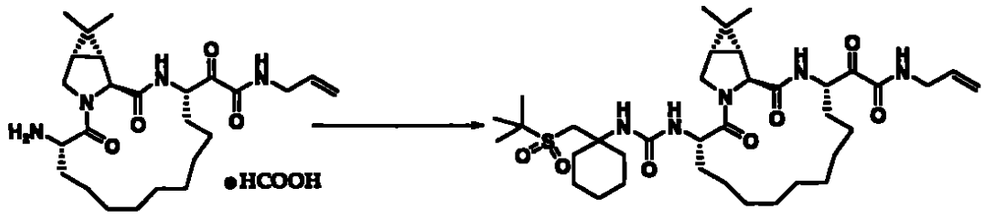
27a **27b**

Se trató una solución del ácido **27a** (100 mg, 0,385 mmol) en tolueno (5 ml) con DPPA (116,5 mg, 0,425 mmol) y Et_3N (42,5 mg, 0,425 mmol) y se agitó a reflujo durante 1,5 h. La mezcla de reacción se diluyó con $NaHCO_3$ saturado (30 ml) y se extrajo en CH_2Cl_2 (2x20 ml). Las capas orgánicas combinadas se lavaron con $NaHCO_3$ acuoso (30 ml), salmuera (30 ml), se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo*, y se usaron como una solución de isocianato en tolueno.

Paso B:

509

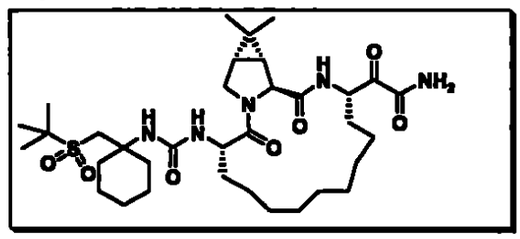
506



24a **27**

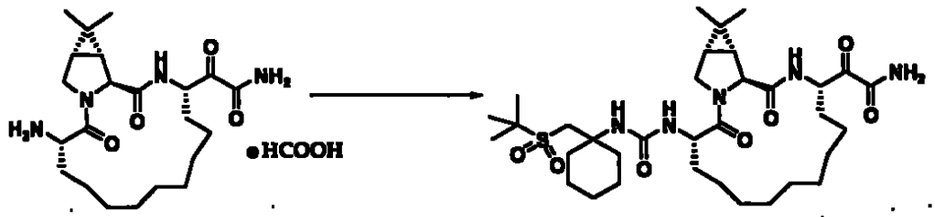
Se trató una solución de la amina **24a** (40 mg, 0,1 mmol) en cloruro de metileno (3,0 ml) con NMM (30 mg, 0,3 mmol) y se enfrió a 0°C. Se agregó una solución del isocianato **27b** (3 equiv) en CH_2Cl_2 y la mezcla de reacción se agitó a ta. durante 1,5 h. La mezcla de reacción se diluyó con cloruro de metileno (60 ml) y se lavó con HCl acuoso (1 M, 30 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 20→50%) para dar **27** como un sólido incoloro. MS (*m/z*, intensidad relativa) 720 [$(M+H)^+$, 85], 461(100); HRMS (ESI) Calculado para $C_{37}H_{61}N_5O_7SNa$ 742,4189 $(M+Na)^+$; Experimental: 742,4200.

Ejemplo Preparativo 28



28

Paso A:

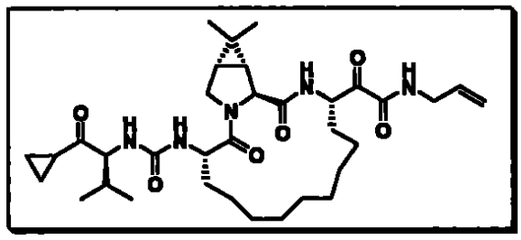


20i **28**

Se trató una solución de la amina **20i** (40 mg, 0,1 mmol) en cloruro de metileno (3,0 ml) con NMM (30 mg, 0,3 mmol) y se enfrió a 0°C. Se agregó una solución del isocianato **27b** (3,00 equiv) en CH_2Cl_2 y la mezcla de reacción se

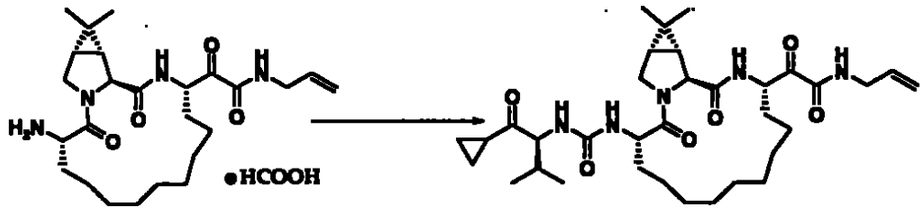
agitó a ta. durante 1,5 h. La mezcla de reacción se diluyó con cloruro de metileno (60 ml) y se lavó con HCl acuoso (1 M, 30 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 20→ 60%) para dar **28** (29 mg) como un sólido incoloro. MS (*m/z*, intensidad relativa) 718 [$(M+K)^+$, 10], 702 [$(M+Na)^+$, 20], 680 [$(M+H)^+$, 80], 421 (100); HRMS (ESI) Calculado para $C_{34}H_{57}N_5O_7SNa$ 702,3876 $(M+Na)^+$; Experimental: 702,3889.

Ejemplo Preparativo 29



29

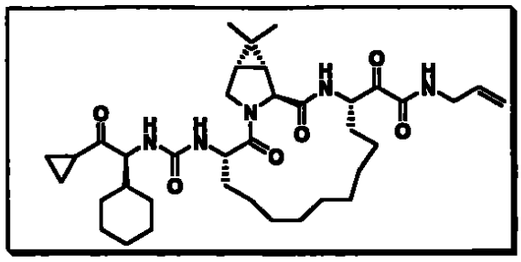
Paso A:



24a **29**

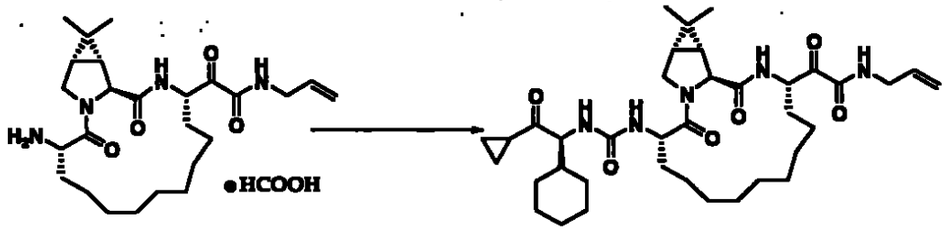
Se trató una solución de la amina **24a** (50 mg, 0,1 mmol) en cloruro de metileno (3,0 ml) con NMM (30 mg, 0,3 mmol) y se enfrió a 0°C. Se agregó una solución de isocianato en CH_2Cl_2 y la mezcla de reacción se agitó a ta. durante 1,5 h. La mezcla de reacción se diluyó con cloruro de metileno (60 ml) y se lavó con HCl acuoso (1- M, 30 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 20 → 50%) para dar **29** como un sólido incoloro (41 mg). MS (*m/z*, intensidad relativa) 628 [$(M+H)^+$, 100], 129 (35).

Ejemplo Preparativo 30



30

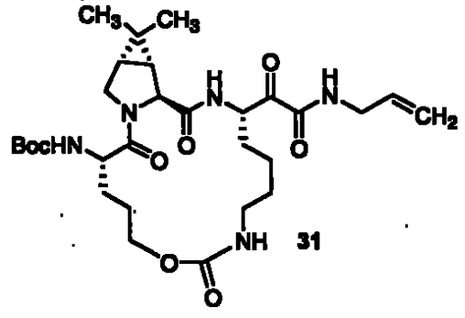
Paso A:



24a 30

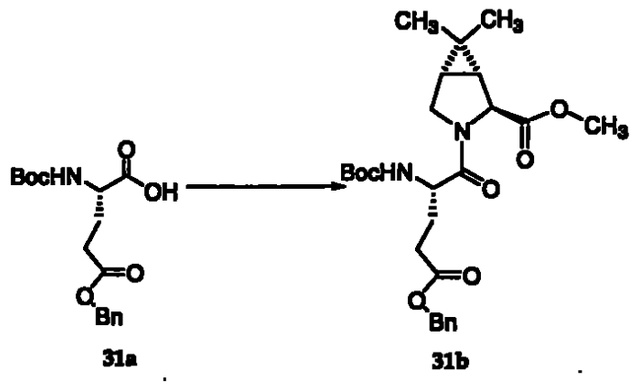
Se trató una solución de la amina **24a** (50 mg, 0,1 mmol) en cloruro de metileno (3,0 ml) con NMM (30 mg, 0,3 mmol) y se enfrió a 0°C. Se agregó una solución de isocianato (3,0 equiv.) en CH_2Cl_2 y la mezcla de reacción se agitó a ta. durante 1,5 h. La mezcla de reacción se diluyó con cloruro de metileno (60 ml) y se lavó con HCl acuoso (1 M, 30 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 20→ 50%) para dar **30** como un sólido incoloro. MS (*m/z*, intensidad relativa) 668 [$(M+H)^+$, 100], 169 (50), 128 (80).

Ejemplo Preparativo 31: Preparación de:



31

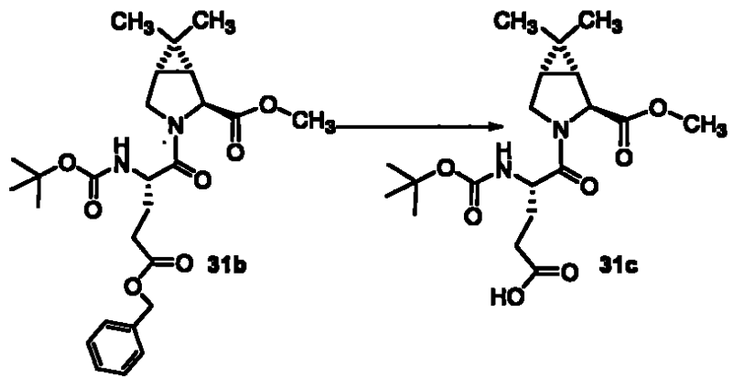
Paso A:



31a 31b

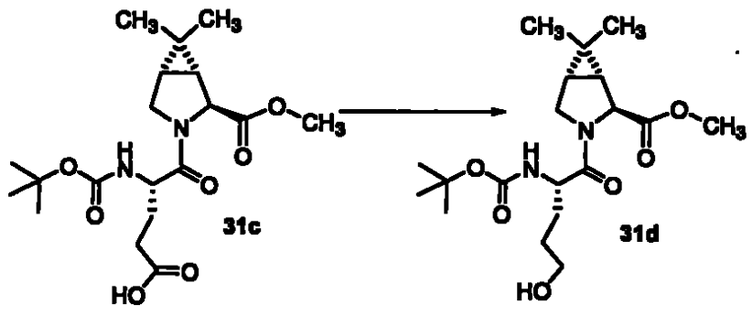
Se hizo reaccionar una solución de Boc-Glu-OBn **31a** (1,8 g, 5,36 mmol) y la amina **1d** (1 g, 4,87 mmol) como en el Ejemplo Preparativo 1, paso C, y se purificó mediante cromatografía en gel de sílice (EtOAc/hexanos 10% a 25%) para dar **31b** (1,28 g).

Paso B:



Se trató una solución del bencil éster **31b** (1,25 g, 2,56 mmol) con Pd/C 10% en EtOH y se hidrogenó [1,01 x 10^5 Pa (1 atm), ta.] durante 12 horas. La mezcla de reacción se filtró a través de un tapón de Celite y se concentró al vacío para dar **31c** (997 mg) que se usó en la siguiente reacción sin otra purificación.

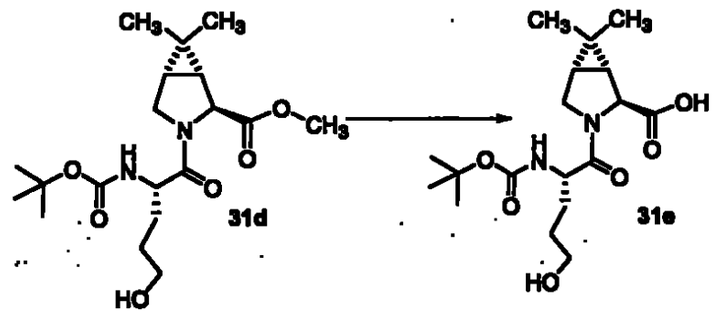
Paso C



513
516

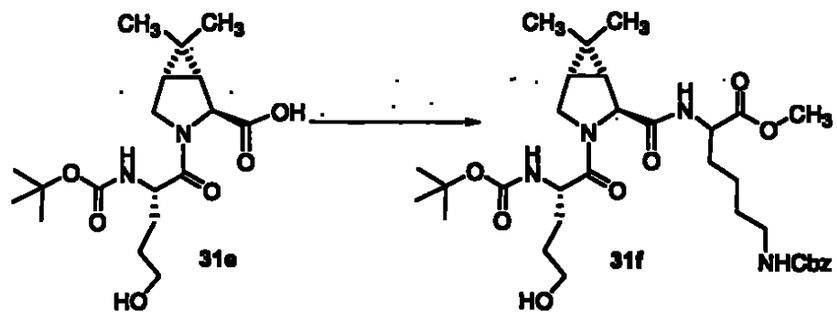
Se enfrió una solución del ácido **31c** (20,4 g, 48,7 mmol) en THF (300 ml) a 0°C y se trató con Et_3N (7,47 ml, 53,6 mmol) y cloroformiato de etilo (4,89 ml, 51,2 mmol) y se agitó durante 2 horas. El precipitado blanco formado se filtró y se lavó con THF frío. El filtrado se enfrió a 0°C y se agregó $NaBH_4$ (2,39 g, 63,4 mmol). Se agregó MeOH (20 ml) gota a gota durante 1 hora y se agitó durante un adicional de 2,5 horas. El solvente se eliminó al vacío, se agregó CH_2Cl_2 y se lavó con agua, salmuera y se secó sobre Na_2SO_4. Se filtró el Na_2SO_4 y se eliminó el solvente hasta sequedad. El residuo se purificó mediante cromatografía sobre gel de sílice (EtOAc/hexanos 50% a 90%) para dar **31d** (8,15 g).

Paso D:



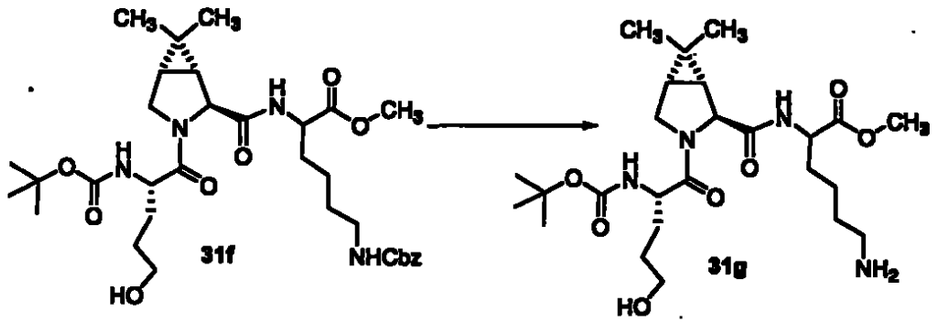
Se trató una solución del éster **31d** (8 g, 20,8 mmol) en MeOH (120 ml) y H_2O (24 ml) con $LiOH \cdot H_2O$ (2,62 g, 62,5 mmol) a temperatura ambiente durante 12 horas. Se eliminó el solvente al vacío hasta sequedad. Se agregó CH_2Cl_2 y se agitó durante 5 minutos con HCl 1N (72,9 mmol). Se separó la capa de CH_2Cl_2, se lavó con salmuera y se secó sobre Na_2SO_4. Se filtró el Na_2SO_4 y se eliminó el solvente hasta sequedad para dar el sólido blanco **31e** (7,65 g).

Paso E:



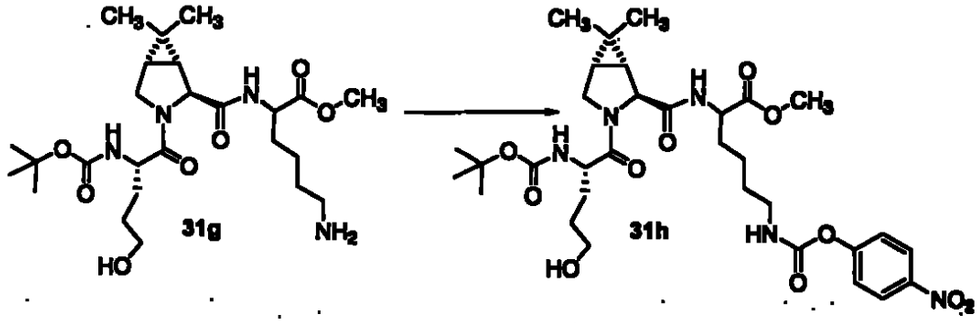
Se enfrió una solución del ácido **31e** en DMF anhidra (75 ml) y CH_2Cl_2 anhidro (75 ml) a 0°C y se agitó con HOOBt (3,68 g, 22,5 mmol), NMM (6,77 ml, 61,6 mmol) y EDCI (5,11 g, 26,7 mmol) durante 5 minutos. Se agregó H-Lys(Z)-OMe•HCl (7,13 g, 21,5 mmol) y se agitó durante 3,5 horas a 0°C. La reacción se mantuvo 12 horas a 5°C, después de las cuales se eliminó el CH_2Cl_2, se agregó EtOAc y se lavó con $NaHCO_3$ sat., H_3PO_4 5%, salmuera, y se filtró a través de Na_2SO_4. Se eliminó el solvente al vacío hasta sequedad para dar **31f** (12,7g).

Paso F



Se trató una solución de **31f** (5,5 g, 8,51 mmol) con Pd/C 10% en EtOH (100 ml) y se hidrogenó [1,01 x 10^5 Pa (1atm), ta.] durante 12 horas. La mezcla de reacción se filtró a través de un tapón de Celite y se concentró al vacío para dar **31g** (4,25 g).

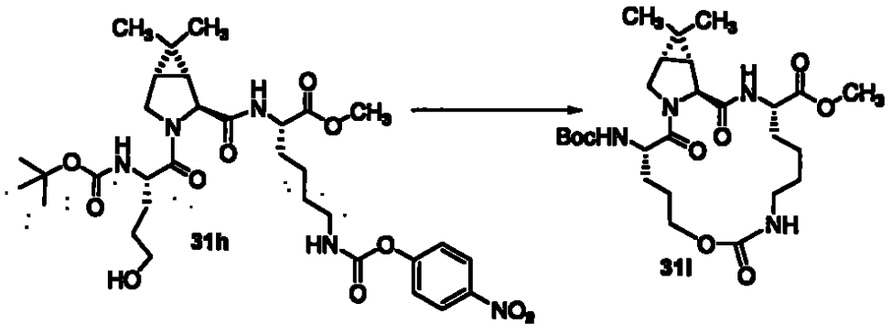
Paso G:



Se agitó una solución de la amina **31g** (4,25 g, 8,3 mmol) en CH_2Cl_2 anhidro (750 ml) con trietilamina (1,5 ml, 10,7 mmol) y cloroformiato de 4-nitrofenilo (2,0 g, 9,96 mmol) a temperatura ambiente durante 5 horas. Se eliminó el solvente al vacío hasta ~200 ml, luego se lavó con $NaHCO_3$ sat., agua, H_3PO_4

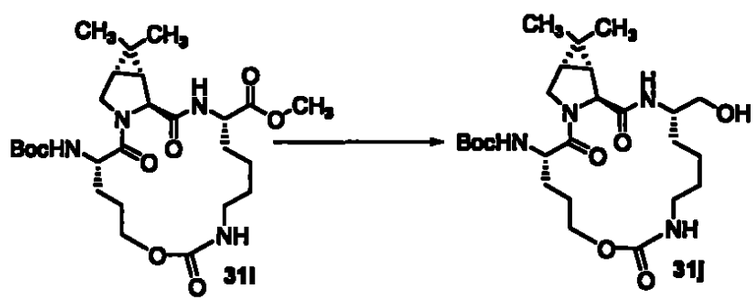
5%, salmuera y se filtró a través de Na_2SO_4. El Na_2SO_4 se filtró y se eliminó el solvente para dar **31h** (5,82 g).

Paso H:



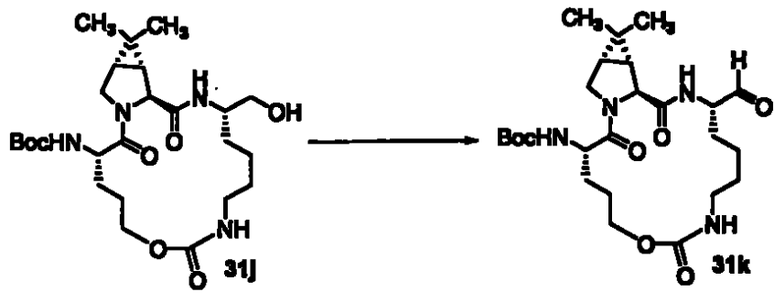
Se trató una solución de **31h** (5,8 g, 8,3 mmol) en THF anhidro (600 ml) con NaH 60% (996 mg, 24,9 mmol) a temperatura ambiente durante 22 horas. La reacción se desactivó mediante la adición de H_2O (5 ml), luego HCl 1N (50 ml) durante 3 minutos. Se eliminó el solvente al vacío, se agregó CH_2Cl_2 y se lavó con H_3PO_4 5%, salmuera, y se filtró a través de Na_2SO_4. Se filtró el Na_2SO_4, se eliminó el solvente y el residuo se sometió a cromatografía en columna sobre gel de sílice con MeOH/CH_2Cl_2 desde 0,25% hasta 3% para dar **31I** (2,86 g, 64% de rendimiento).

Paso I:



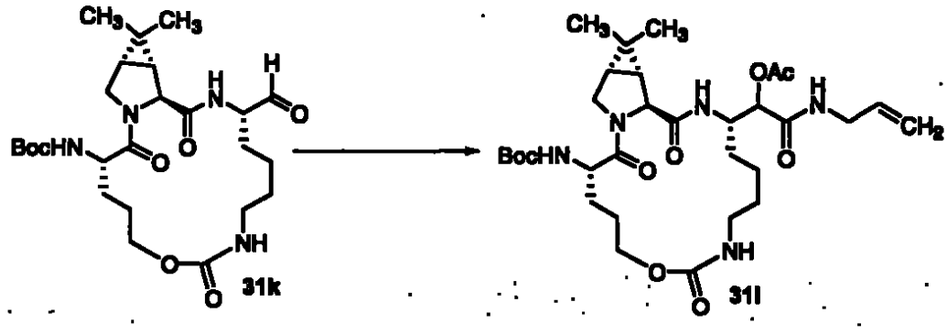
Se hizo reaccionar una solución de **31I** (613 mg, 1,13 mmol) como en el Ejemplo Preparativo 1, paso F, y se purificó mediante cromatografía sobre gel de sílice (MeOH/CH_2Cl_2 3% a 6%) para dar el alcohol **31J** (500 mg).

Paso J:



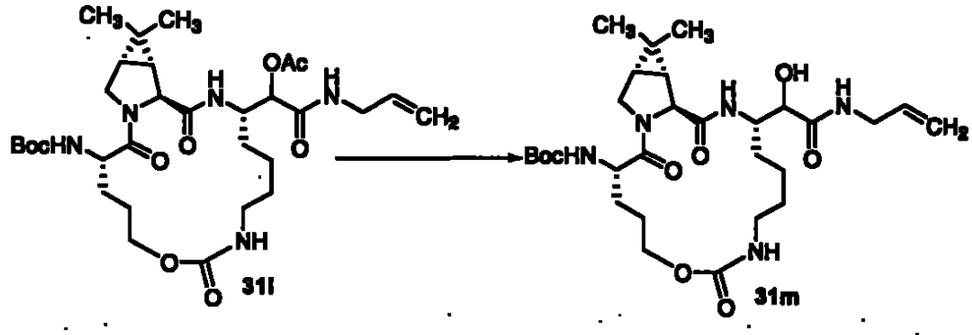
Se hizo reaccionar una solución del alcohol **31j** (480 mg, 0,94 mmol) como en el Ejemplo Preparativo 1, paso H, y se purificó mediante cromatografía sobre gel de sílice (acetona/hexanos 30% a 60%) para dar el aldehído **31k** (383 mg).

Paso K:



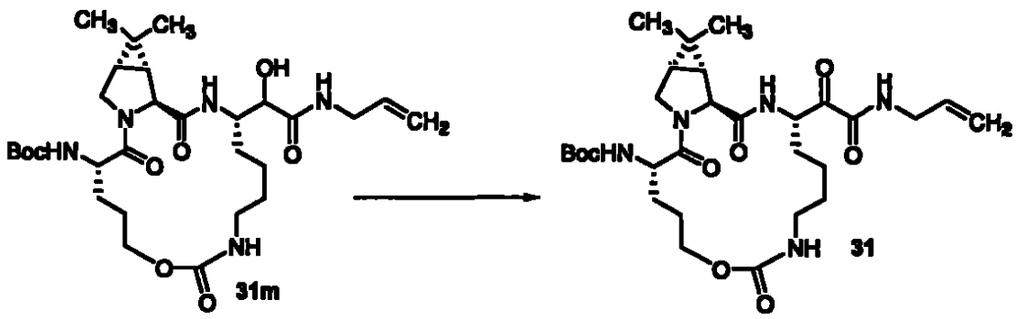
Se hizo reaccionar una solución del aldehído **31j** (365 mg, 0,71 mmol) como en el Ejemplo Preparativo 22, paso A, y se purificó mediante cromatografía sobre gel de sílice (acetona/hexanos 30% a 50%) para dar **31k** (426 mg).

Paso L:



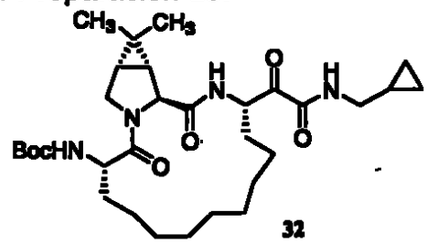
Se hizo reaccionar una solución de **31l** (357 mg, 0,56 mmol) como en el Ejemplo Preparativo 22, paso B, para dar **31m** (426 mg).

Paso M:

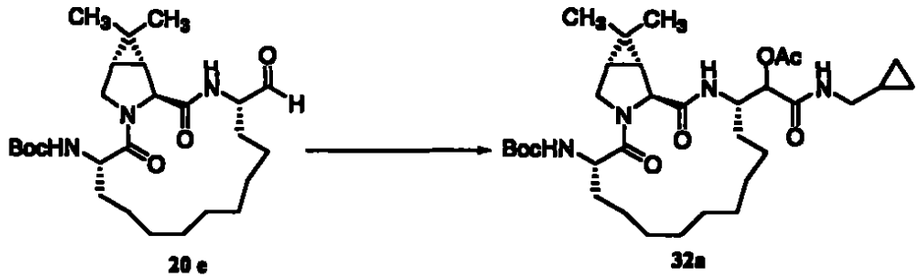


Se hizo reaccionar una solución de **31m** (350 mg, 0,59 mmol) como en el Ejemplo Preparativo 22, paso C, y se purificó mediante cromatografía sobre gel de sílice (acetona/hexanos 30% a 50%) para dar **31** (335 mg). MS (ES) *m/z* intensidad relativa 492 [(M-BOC+1)$^+$, 80]; 592 [(M+1)$^+$, 100]. Calculado para $C_{29}H_{46}N_5O_8$ [M+1]$^+$: 592,3346; Experimental 592,3359.

Ejemplo Preparativo 32: Preparación de:



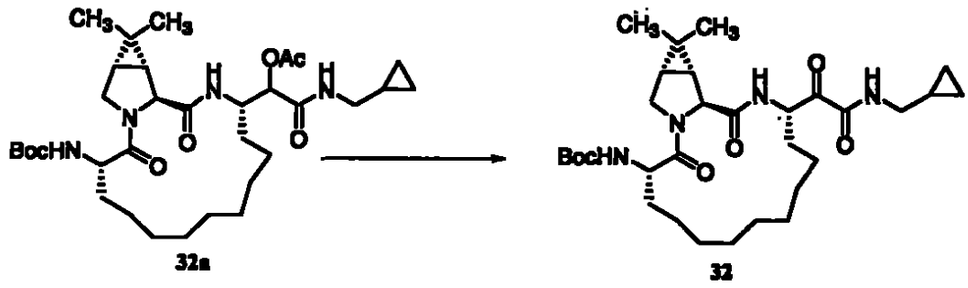
Paso A:



Se trató una solución del aldehído **20e** (200 mg, 0,42 mmol) en cloruro de metileno (10 ml) con isocianuro de ciclopropilmetilo (66,5 mg, 4,11 mmol) y ácido acético (50 mg, 0,82 mmol) y se agitó a t.a. durante 12 h. La reacción se concentró *in vacuo* y el residuo se purificó mediante cromatografía (SiO_2, acetona/hexanos 1:9→1:1) para obtener **32a** (230 mg).

MS (ES) *m/z* intensidad relativa 641 [(M+Na)$^+$, 70]; 619 [(M+1)$^+$, 100], 519 (50).

Paso B:



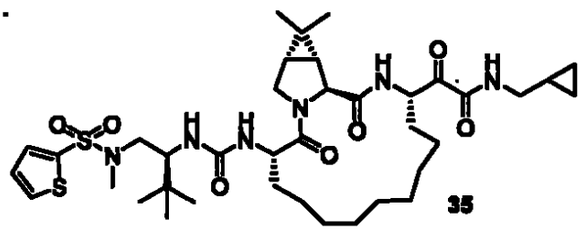
Se trató una solución del acetato **32a** (230 mg, 0,371 mmol) en metanol (5,0 ml), THF (5,0 ml) y agua (5,0 ml) con $LiOH \cdot H_2O$ (25 mg, 0,55 mmol) y se agitó a t.a. durante 1 h. La mezcla de reacción se diluyó con HCl acuoso (1 M, 30 ml) y se extrajo en CH_2Cl_2 (2 x 50 ml). La capa orgánica combinada se secó ($MgSO_4$), se filtró, se concentró *in vacuo* y se usó tal cual en el siguiente paso sin otra purificación.

Se trató una solución del alcohol en CH_2Cl_2 seco (15 ml) con reactivo de Dess-Martin (237 mg, 0,558 mmol) y se agitó a t.a. durante 2 h. La mezcla de reacción se diluyó con $Na_2S_2O_3$ acuoso (5%, 30 ml) y $NaHCO_3$ acuoso saturado (30 ml) y se agitó a t.a. durante 15 min. La mezcla de reacción se extrajo con CH_2Cl_2 (3x50 ml) y las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 0:1→1:1) para dar 32 como un sólido incoloro (275 mg).

MS (ES) *m/z* intensidad relativa 629 [(M+isobuteno)$^+$, 40], 575 [(M+1)$^+$, 100], 475 (90).

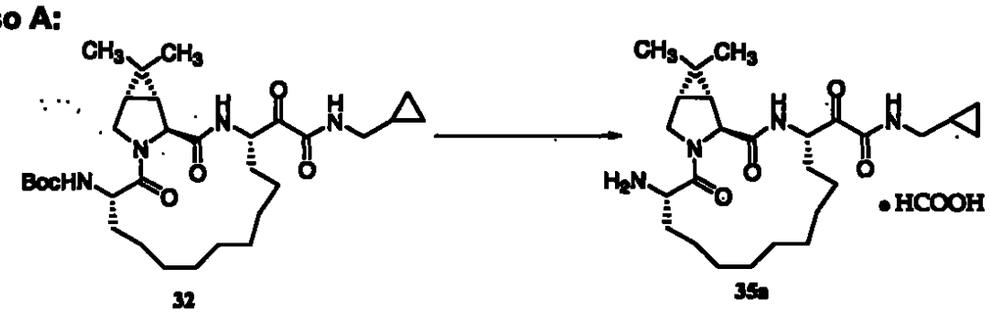
Se emplearon procedimientos similares para sintetizar los compuestos: 33 y 34 usando Isocianuro de ciclopropilo y etilo para el Paso A del Ejemplo Preparativo 32:

Ejemplo Preparativo 35: Preparación de:



35

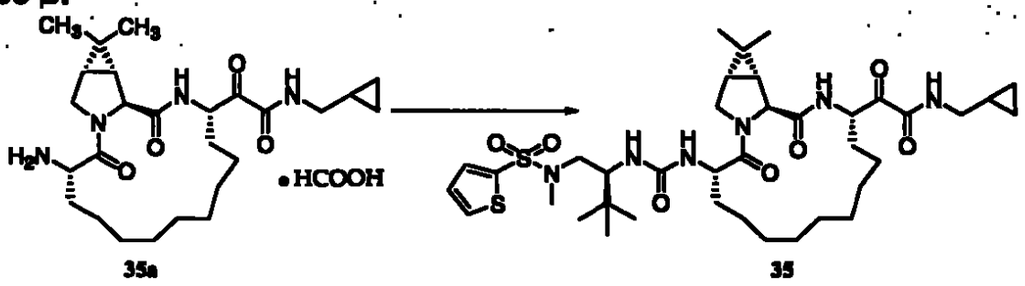
Paso A:



32 35a

Se desprotegió **32** (200 mg, 0,39 mmol) por disolución en 20 ml de ácido fórmico y reposo durante 2 h. La mezcla de reacción se concentró *in vacuo* para dar **35a** y se usó en posteriores reacciones sin purificación.

Paso B:



35a 35

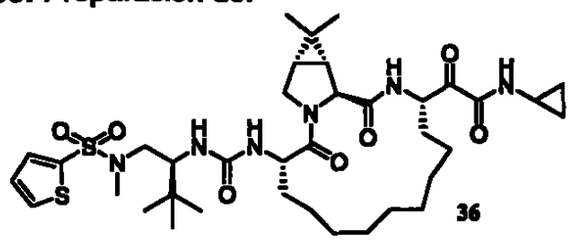
Se trató una solución de la amina **35a** (70 mg, 0,13 mmol) en cloruro de metileno (3,0 ml) con NMM (50 mg, 0,5 mmol) y se enfrió a 0°C. Se agregó una solución del isocianato **25c** (1 ml, 0,25 mmol) en CH_2Cl_2 y la mezcla de reacción se agitó a ta. durante 1,5 h. La mezcla de reacción se diluyó con cloruro de metileno (150 ml) y se lavó con HCl acuoso (1 M, 30 ml). Las capas orgánicas se secaron con ($MgSO_4$) se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, EtOAc/CH_2Cl_2 50→ 100%) para dar ***35*** como un sólido incoloro.

MS (ES) *m/z* intensidad relativa 799 [$(M+Na)^+$, 60]; 777 [$(M+1)^+$, 100].

520

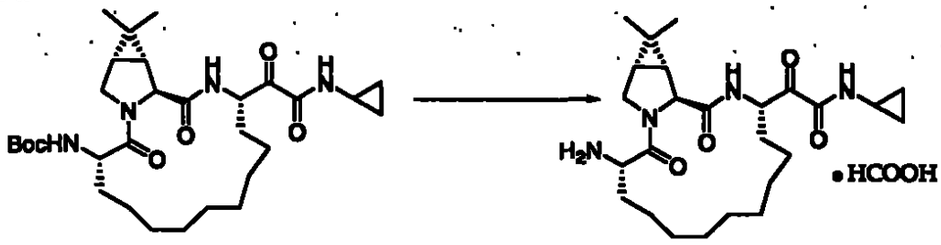
517

Ejemplo Preparativo 36: Preparación de:



36

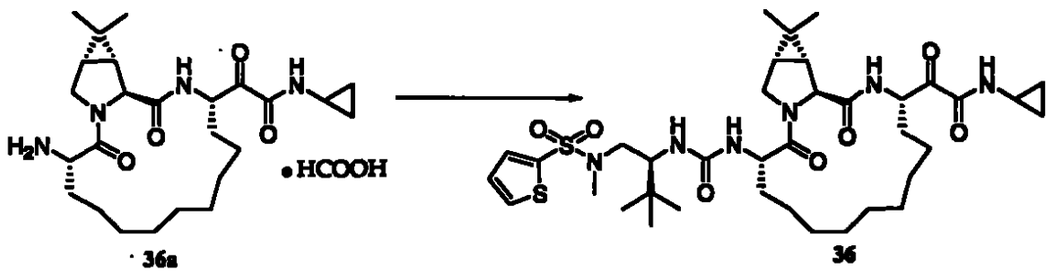
Paso A:



33 36a

Se desprotegió **33** (200 mg, 0,39 mmol) por disolución en 20 ml de ácido fórmico y reposo durante 2 h. La mezcla de reacción se concentró *in vacuo* para dar **36a** y se usó en posteriores reacciones sin purificación.

Paso B:



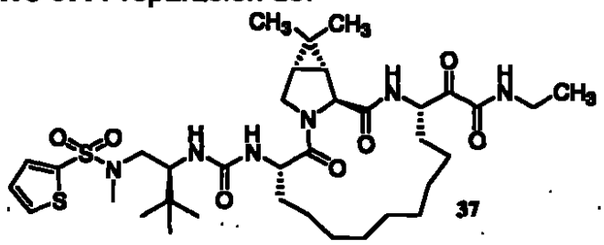
36a 36

Se trató una solución de la amina **36a** (70 mg, 0,13 mmol) en cloruro de metileno (3,0 ml) con NMM (50 mg, 0,5 mmol) y se enfrió a 0°C. Se agregó una solución del isocianato **25c** (1 ml, 0,25 mmol) en CH_2Cl_2 y la mezcla de reacción se agitó a ta. durante 1,5 h. La mezcla de reacción se diluyó con cloruro de metileno (150 ml) y se lavó con HCl acuoso (1 M, 30 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, EtOAc/CH_2Cl_2 0→100%) para dar **36** como un sólido

518

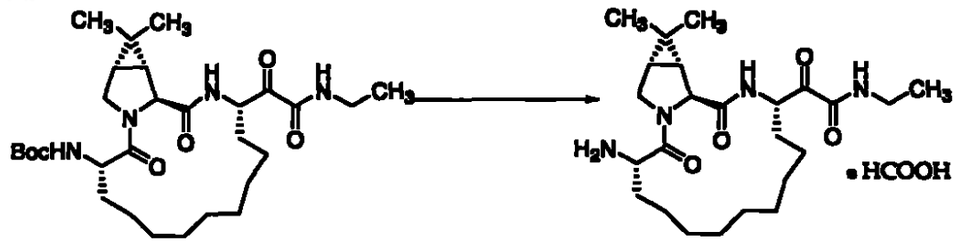
incoloro. MS (ES) *m/z* intensidad relativa 785 [(M+Na)$^+$, 50]; 763 [(M+1)$^+$, 100]; 593 (60).

Ejemplo Preparativo 37: Preparación de:



37

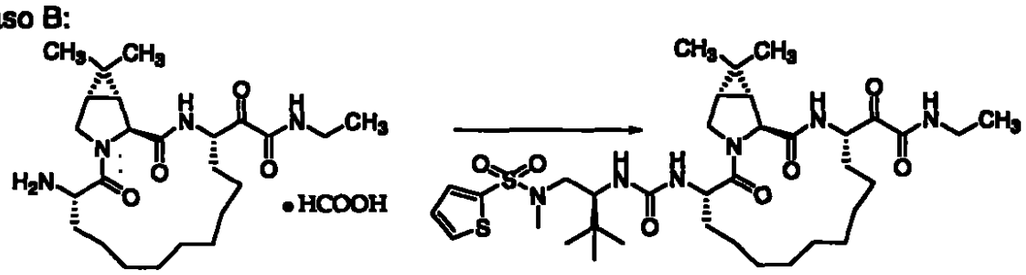
Paso A:



34 37a

Se desprotegió **34** (200 mg, 0,39 mmol) por disolución en 20 ml de ácido fórmico y reposo durante 2 h. La mezcla de reacción se concentró *in vacuo* para dar **37a** y se usó en posteriores reacciones sin purificación.

Paso B:



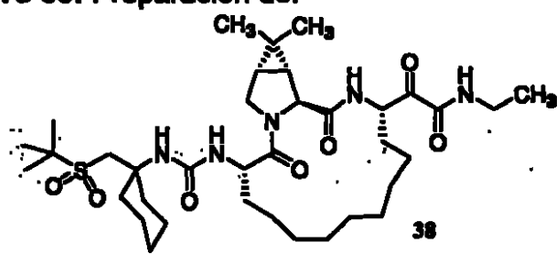
37a 37

Se trató una solución de la amina desprotegida **37a** (70 mg, 0,13 mmol) en cloruro de metileno (3,0 ml) con NMM (50 mg, 0,5 mmol) y se enfrió a 0°C. Se agregó una solución del isocianato **25c** (1 ml, 0,25 mmol) en CH_2Cl_2 y la mezcla de reacción se agitó a ta. durante 1,5 h. La mezcla de reacción se diluyó con cloruro de metileno (150 ml) y se lavó con HCl acuoso (1 M, 30 ml). Las capas

519

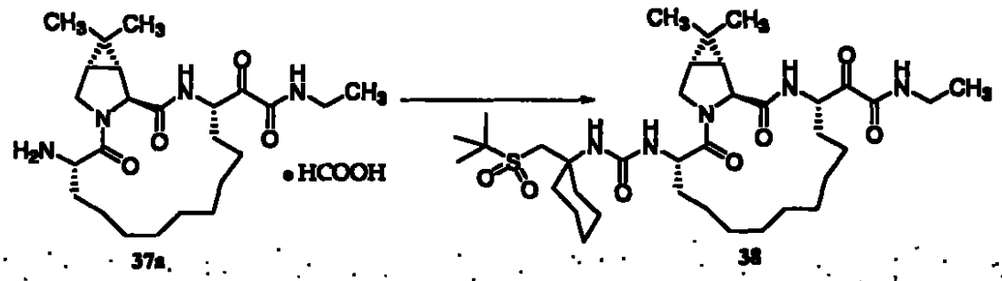
orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *In vacuo* y se purificaron mediante cromatografía (SiO_2, EtOAc/CH_2Cl_2 50→ 100%) para dar **37.** MS (ES) *m/z* intensidad relativa 773 [$(M+Na)^+$, 100]; 751 [$(M+1)^+$, 70].

Ejemplo Preparativo 38: Preparación de:



38

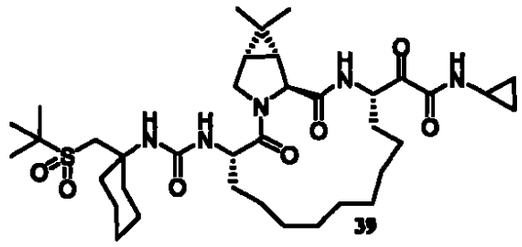
Paso A:



37a 38

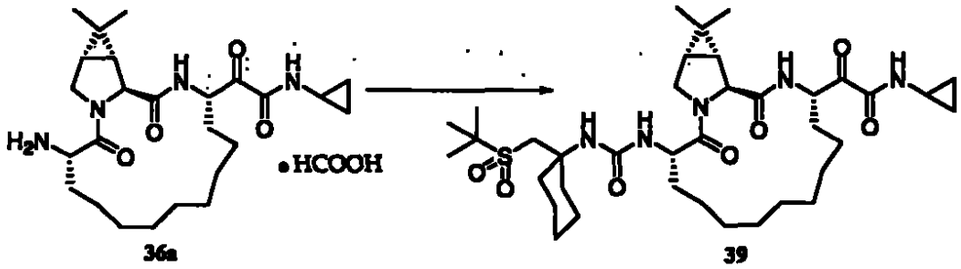
Se trató una solución de la amina desprotegida **37a** (70 mg, 0,13 mmol) en cloruro de metileno (3,0 ml) con NMM (50 mg, 0,5 mmol) y se enfrió a 0°C. Se agregó una solución del isocianato **27b** (1,5 ml, 0,25 mmol) en CH_2Cl_2 y la mezcla de reacción se agitó a ta. durante 1,5 h. La mezcla de reacción se diluyó con cloruro de metileno (150 ml) y se lavó con HCl acuoso (1 M, 30 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *In vacuo* y se purificaron mediante cromatografía (SiO_2, EtOAc/CH_2Cl_2 50→ 100%) para dar ***38*** como un sólido incoloro. MS (ES) *m/z* intensidad relativa 730 [$(M+Na)^+$, 30]; 708 [$(M+1)^+$, 100]; 409 (30).

Ejemplo Preparativo 39: Preparación de:



39

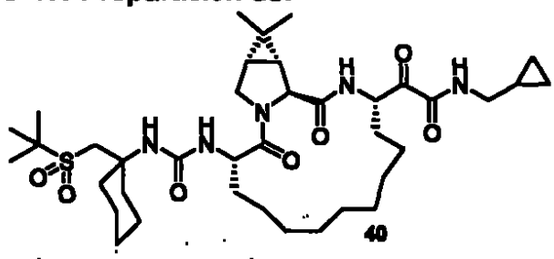
Paso A:



36a 39

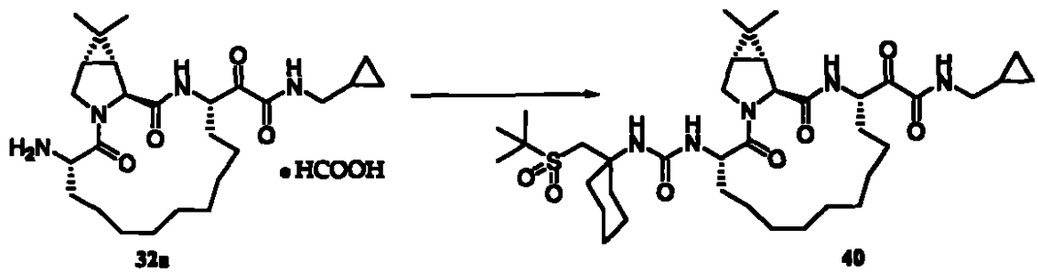
Se trató una solución de la amina **36a** (70 mg, 0,13 mmol) en cloruro de metileno (3,0 ml) con NMM (50 mg, 0,5 mmol) y se enfrió a 0°C. Se agregó una solución del isocianato **27b** (1 ml, 0,25 mmol) en CH_2Cl_2 y la mezcla de reacción se agitó a ta. durante 1,5 h. La mezcla de reacción se diluyó con cloruro de metileno (150 ml) y se lavó con HCl acuoso (1 M, 30 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, EtOAc/CH_2Cl_2 50→100%) para dar **39**, MS (ES) *m/z* intensidad relativa 742 [$(M+Na)^+$, 70]; 720 [$(M+1)^+$, 100]; 461 (40). HRMS Calculado para $C_{37}H_{62}N_5O_7S$ [$M+1]^+$: 720,4370; Experimental 720,4350.

Ejemplo Preparativo 40: Preparación de:



40

Paso A:



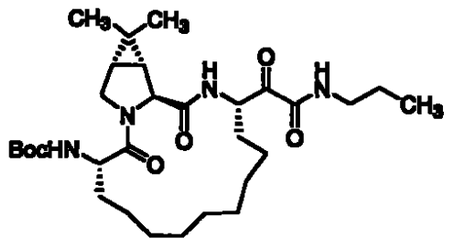
Se trató una solución de la amina **32a** (70 mg, 0,13 mmol) en cloruro de metileno (3,0 ml) con NMM (50 mg, 0,5 mmol) y se enfrió a 0°C. Se agregó una solución del isocianato **27b** (1 ml, 0,25 mmol) en CH_2Cl_2 y la mezcla de reacción se agitó a ta. durante 1,5 h. La mezcla de reacción se diluyó con cloruro de metileno (150 ml) y se lavó con HCl acuoso (1 M, 30 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, EtOAc/CH_2Cl_2 50→100%) para dar **40**.

^{1}H RMN (DMSO, 500 MHz), δ 8,80 (t, 1 H, *J*=6,0 Hz), 8,37 (d, 1 H, *J*=9,5 Hz), 6,22 (d, 1 H, *J*=8,8 Hz), 5,88 (s, 1 H), 5,31 (dt, 1 H, *J*=2,8 & 9,5 Hz), 4,35 (s, 1 H), 4,28-4,22 (m, 1 H), 3,85 (d, 1 H, *J*=10 Hz), 3,76 (q, 1 H, *J*=5,4 Hz), 3,59 (t, 1 H, *J*=13,5 Hz), 3,41 (d, 1 H, *J*=13,9 Hz), 3,07-2,95 (m, 2 H), 2,22-2,15 (m, 2 H), 1,69-1,00 (b, 23 H), 1,25 (s, 9 H), 0,99 (s, 3 H), 0,99-0,70 (m, 1 H), 0,88 (s, 3 H), 0,42-0,38 (m, 2 H), 0,21-0,18 (m, 2 H).

^{13}C RMN (DMSO, 125 MHz) δ 198,5, 172,1, 171,3, 162,0, 157,3, 60,5, 60,1, 54,4, 52,8, 51,5, 47,6, 43,8, 35,4, 35,1, 34,8, 32,3, 31,6, 31,4, 28,3, 28,0, 27,9, 27,3, 26,9, 26,6, 25,8, 25,6, 24,6, 23,4, 22,4, 21,5, 19,5, 13,7, 11,5, MS (ES) *m/z* intensidad relativa 756 [$(M+Na)^+$, 45]; 734 [$(M+1)^+$, 100]; 475 (20). HRMS calculado para $C_{38}H_{64}N_5O_7S$ [$M+1]^+$: 734,4526; Experimental 734,4535.

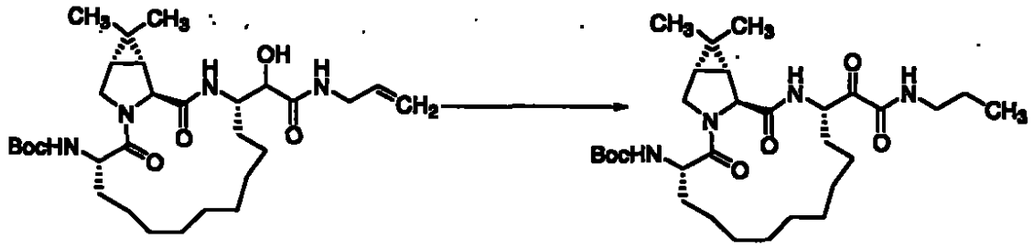
Ejemplo Preparativo 41: Preparación de:

525
522



41

Paso A:

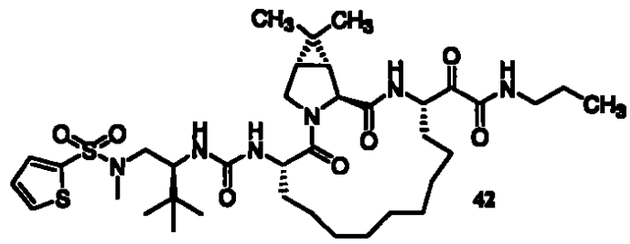


22b 41

Una solución del intermediario **22b** (300 mg, 0,54 mmol) se tomó en metanol (25 ml) y se trató con 10% de catalizador de Pearlman y se hidrogenó a 3,4 X 10^5 Pa (50 psi) durante 4 h. La mezcla de reacción se filtró a través de un tapón de Celite® y se concentró *in vacuo* para dar el producto reducido que se usó en una reacción posterior sin purificación.

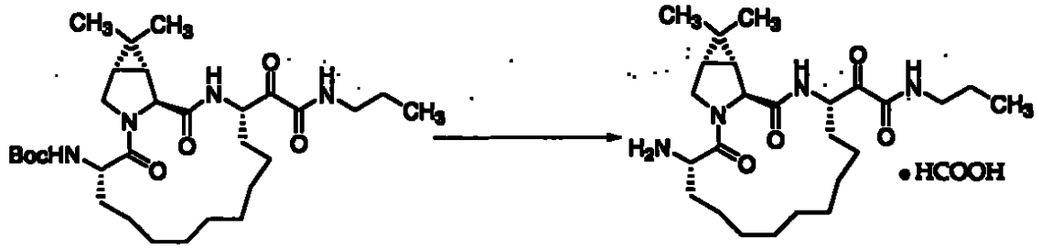
Se trató una solución del alcohol reducido en CH_2Cl_2 seco (5 ml) con reactivo de Dess-Martin (350 mg, 0,82 mmol) y se agitó a t.a. durante 2 h. La mezcla de reacción se diluyó con $Na_2S_2O_3$ acuoso (5%, 30 ml) y $NaHCO_3$ acuoso saturado (30 ml) y se agitó a t.a. durante 15 min. La mezcla de reacción se extrajo con CH_2Cl_2 (3x75 ml) y las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetona/hexanos 0:1→1:1) para dar **41** (270 mg) como un sólido incoloro.

Ejemplo Preparativo 42: Preparación de:



42

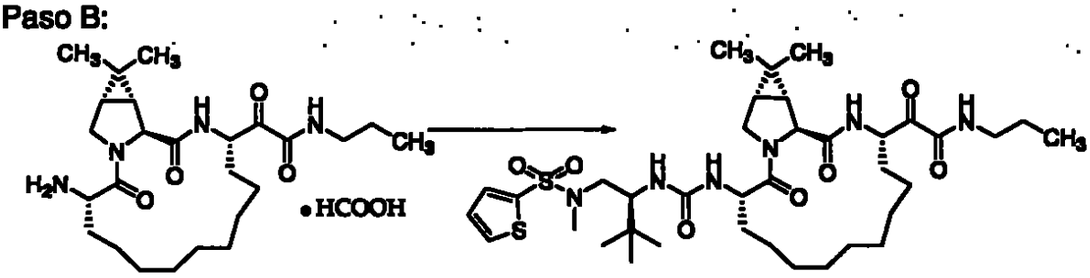
Paso A:



41 42a

Se desprotegió **41** por disolución en 20 ml de ácido fórmico y reposo durante 2 h. La mezcla de reacción se concentró *in vacuo* para dar **42a** y se usó en posteriores reacciones sin purificación.

Paso B:



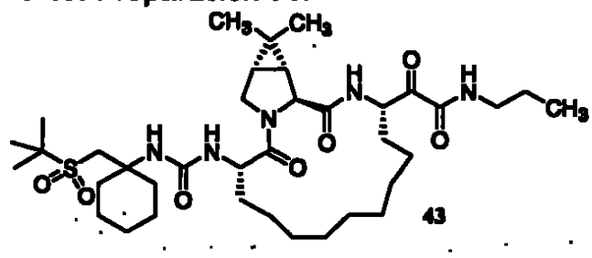
42a 42

Se trató una solución de la amina **42a** (100 mg, 0,196 mmol) en cloruro de metileno (3,0 ml) con NMM (60 mg, 0,6 mmol) y se enfrió a 0°C. Se agregó una solución deal isoclanato **25c** (1,5 ml, 0,25 mmol, 0,38 mmol) en tolueno y la mezcla de reacción se agitó a ta. durante 2 h. La mezcla de reacción se diluyó con cloruro de metileno (100 ml) y se lavó con HCl acuoso (1 M, 50 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, Acetato de etilo/hexanos 1:1→1:0) para dar **42** (65 mg) como un sólido incoloro. ^{1}H RMN (DMSO, 500 MHz), δ 8,71 (t, 1 H, *J*=6,3 Hz), 8,36 (d, 1 H, *J*=9 Hz), 8,00 (dd, 1 H, *J*=1,3 & 5,0 Hz), 7,65 (dd, 1 H,

524

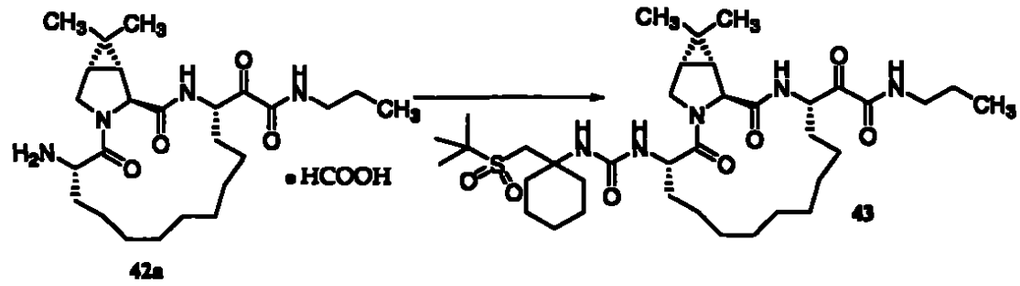
J=1,3 & 2,5 Hz), 7,25 (dd, 1 H, J= 3,8 &1,3 Hz), 6,15 (d, 1 H, J=9,0 Hz), 5,88 (d, 1 H, J=10 Hz), 5,31 (m, 1 H), 4,34 (s, 1 H), 4,30 (m, 1 H), 3,93 (d, 1 H, J=10,5 Hz), 3,79-3,75 (q, 1 H, J=5,0 Hz), 3,67-3,62 (dt, 1 H, J= 4,1 & 5,6 Hz), 3,12-3,05 (m, 2 H), 2,95-2,91 (m, 2 H), 2,67 (s, 3 H), 1,70-1,61 (m, 2 H) 1,40-1,00 (b, 20 H), 0,99 (s, 3 H), 0,85 (s, 3 H), 0,83 (s, 9 H), 0,83 (t, 3 H).^{13}C RMN (dmso, 125 MHz) δ, 198,5, 172,0, 171,7, 162,2, 158,3, 137,7, 133,9, 133,1, 129,0, 60,5, 55,8, 55,7, 52,7, 51,6, 51,5, 47,6, 36,0, 35,0, 32,2, 31,6, 31,3, 28,5, 27,9, 27,4, 27,1, 26,9, 26,7, 26,3, 24,4, 22,8, 22,3, 19,5, 13,7, 12,1, MS (ES) *m/z* intensidad relativa 788 [(M+Na)$^+$, 50]; 765 [(M+1)$^+$, 100].

Ejemplo Preparativo 43: Preparación de:



43

Paso A:



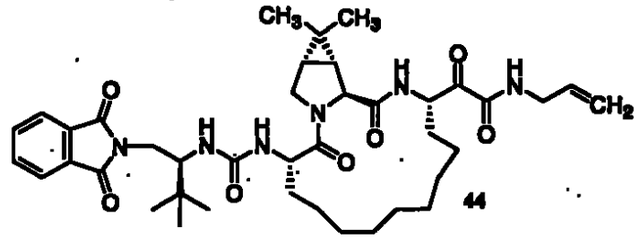
42a

Se trató una solución de LA amina **42a** (100 mg, 0,196 mmol) en cloruro de metileno (3,0 ml) con NMM (60 mg, 0,6 mmol) y se enfrió a 0°C. Se agregó una solución del isocianato **27b** (3 ml, solución de 0,1 M, 0,3 mmol) en tolueno y la mezcla de reacción se agitó a ta. durante 2 h. La mezcla de reacción se diluyó con cloruro de metileno (100 ml) y se lavó con HCl acuoso (1 M, 50 ml). Las capas orgánicas se secaron con ($MgSO_4$) se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, EtOAc/Hexanos 1:1→1:0) para dar

525 528

43 (42 mg) como un sólido incoloro. ^{1}**H RMN** (DMSO, 500 MHz) δ 8,71 (t, 1 H, *J*=6,0 Hz), 8,36 (d, 1 H, *J*=9,0 Hz), 6,22 (d, 1 H, *J*=8,5 Hz), 5,88 (s, 1 H), 5,29 (dt, 1 H, *J*=9,5 & 2,5 Hz), 4,34 (s, 1 H), 4,23 (t, 1 H, *J*=9,0 Hz), 3,86 (d, 1 H, *J*=10,5 Hz), 3,76 (dd, 1 H, *J*=5,0 & 5,5 Hz), 3,60 (d, 1 H, *J*=13,5 Hz), 3,41 (d, 1 H, *J*=13,5 Hz), 3,13-3,04 (m, 2 H), 2,23-2,15 (m, 2 H), 1,67-0,9 (bm, 30 H), 1,25 (s, 9 H), 0,99 (s, 3 H), 0,88 (s, 3 H), 0,83 (t, 3 H, *J*=7,0 Hz). ^{13}C RMN (DMSO, 125 MHz) δ 198,5, 172,1, 171,3, 162,1, 157,3, 60,5, 60,1, 55,8, 54,3, 52,8, 51,0, 47,6, 35,4, 35,1, 32,3, 31,7, 31,3, 28,3, 28,0, 27,9, 27,3, 26,9, 26,6, 26,2, 25,8, 24,6, 23,3, 22,8, 21,5, 19,5, 13,7, 12,2. MS (ES) *m/z* intensidad relativa 744 [(M+Na)$^+$, 40]; 722 [(M+1)$^+$, 100].

Ejemplo Preparativo 44: Preparación de:



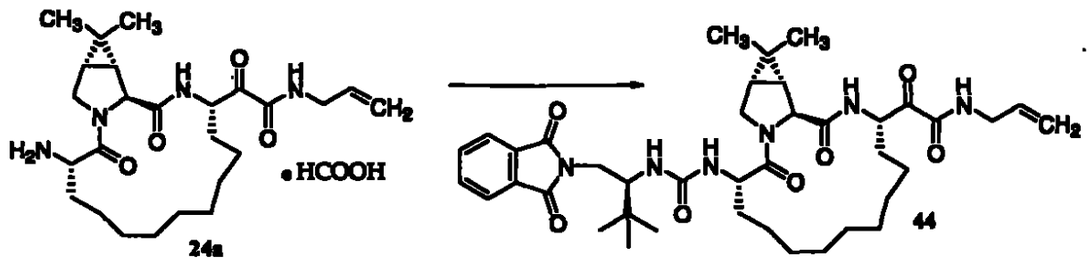
Paso A:



Se trató una solución de la amina desprotegida **44a** (Busacca, C. A.; Grossbach, D.; Spinelli, E. *Tetrahedron: Asymmetry*; **2000**, *9*, 1907) en CH_2Cl_2 (10 ml) y $NaHCO_3$ acuoso saturado (10 ml) a 0°C con fosgeno (5 ml, solución al 15% en tolueno) y se agitó a 0°C durante 2 h. La mezcla de reacción se diluyó con CH_2Cl_2 (50 ml) y la capa orgánica se lavó con $NaHCO_3$ acuoso frío. La capa orgánica se secó ($MgSO_4$), se filtró y también se diluyó con 10 ml de tolueno, se concentró la capa de cloruro de metileno y se usó como solución.

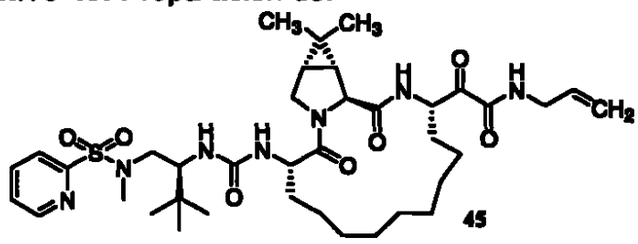
Paso B:

526

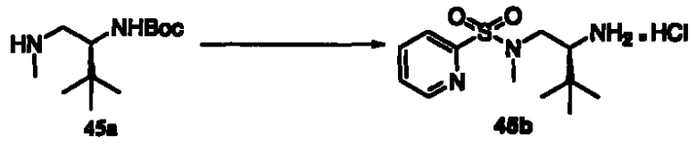


Se trató una solución de la amina **24a** (100 mg, 0,196 mmol) en cloruro de metileno (3,0 ml) con NMM (60 mg, 0,6 mmol) y se enfrió a 0°C. Se agregó una solución del isocianato **44b** (2,5 ml, 0,25 mmol,) en tolueno y la mezcla de reacción se agitó a ta. durante 2 h. La mezcla de reacción se diluyó con cloruro de metileno (100 ml) y se lavó con HCl acuoso (1 M, 50 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetato de etilo/hexanos 1:1→1:0) dando **44** (31 mg) como un sólido incoloro. MS (ES) *m/z* intensidad relativa 755 [$(M+Na)^+$, 40]; 733 [$(M+1)^+$, 100].

Ejemplo Preparativo 45: Preparación de:



Paso A:



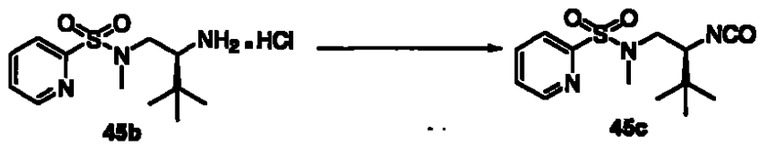
Se trató una solución de la amina **45a*** (2,00 g, 9,20 mmol) en CH_2Cl_2 a 0°C con $(C_2H_5)_3N$ (3,7 g, 37 mmol) y cloruro de 2-piridinsulfonilo (2,4 g, 11,2 y se agitó a ta. durante 12 h. La mezcla de reacción se diluyó con CH_2Cl_2 (300 ml) y se lavó con $NaHCO_3$ acuoso en exceso (1M, 500 ml). La capa orgánica se secó ($MgSO_4$), se filtró, se concentró *in vacuo* y se purificó mediante cromatografía

527 530

(SiO_2, Acetona/Hexanos 0:1→1:1) para dar la sulfonamida (2,3 g). Se desprotegió una solución de amina protegida con Boc por disolución (2,1 g, 5,7 mmol) en solución 4M de HCl en dioxano y se agitó a ta. durante 2 h. La mezcla de reacción se concentró *in vacuo* y se usó tal cual en el siguiente paso sin otra purificación.

* obtenida por protección de *ter*-leucin-N-metilamida (TCI-Jpn) con diterbutildicarbonato y reducción posterior con BH_3•DMS en THF (reflujo, 2 h).

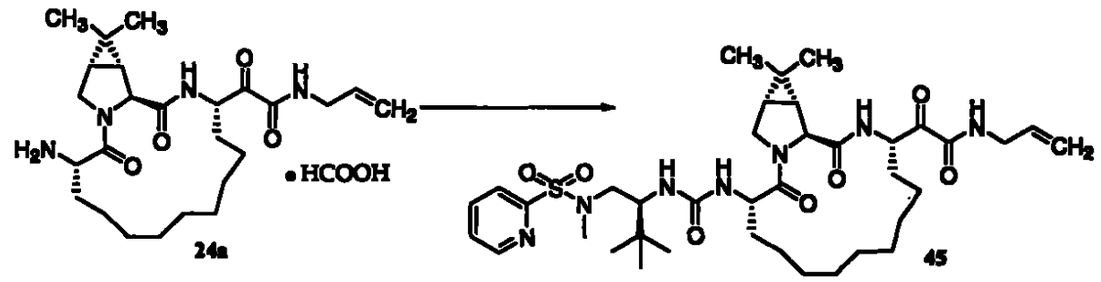
Paso B:



45b 45c

Se trató una solución de la amina **45b** (300 mg, 1 mmol) en CH_2Cl_2 (3 ml) y $NaHCO_3$ acuoso saturado (3 ml) a 0°C con fosgeno (2,5 ml, solución 15% en tolueno) y se agitó a 0°C durante 2 h. La mezcla de reacción se diluyó con CH_2Cl_2 (30 ml) y la capa orgánica se lavó con $NaHCO_3$ acuoso frío. La capa orgánica se secó ($MgSO_4$), se filtró y también se diluyó con 3 ml de tolueno, se concentró la capa de cloruro de metileno y se usó como una solución.

Paso C:



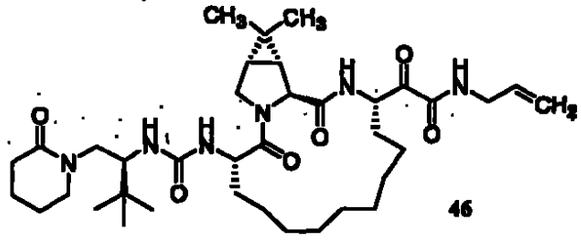
24a 45

Se trató una solución de la amina **24a** (100 mg, 0,197 mmol) en cloruro de metileno (3,0 ml) con NMM (60 mg, 0,6 mmol) y se enfrió a 0°C. Se agregó una solución del isocianato **45c** (2,5 ml, 0,25 mmol) en tolueno y la mezcla de reacción se agitó a ta. durante 2 h. La mezcla de reacción se diluyó con cloruro de metileno (100 ml) y se lavó con HCl acuoso (1 M, 50 ml). Las capas orgánicas se secaron con ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante

528 831

cromatografía (SiO_2, acetato de etilo/hexanos 1:1→1:0) para dar el producto **45** como un sólido incoloro. La mezcla bruta también se purificó usando HPLC para dar el producto puro **45** (27 mg). ^{1}H RMN (DMSO, 500 MHz) δ 8,89 (t, 1 H, *J*=7,0 Hz), 8,72 (d, 1 H, *J*=6,0 Hz), 8,37 (d, 1 H, *J*=10,5 Hz), 8,07 (t, 1 H, *J*=9,0 Hz), 7,88 (d, 1 H, *J*=9,0 Hz), 7,66 (dd, 1 H, *J*=6,5 &3,5 Hz), 6,12 (d, 1 H, *J*=11 Hz), 5,84-5,75 (m, 2 H), 4,27 (s, 1 H), 4,22 (bt, 1 H, *J*=11,5 Hz), 3,92 (d, 1 H, *J*=13 Hz), 3,77-3,60 (m, 4 H), 3,33 (bd, 1 H), 3,06 (bt, 1 H, *J*=12,5 Hz), 2,75 (s, 3 H), 1,68-1,59 (m, 2 H), 1,44-1,12 (m, 18 H), 0,98 (s, 3 H), 0,83 (s, 3 H), 0,78 (s, 9 H). ^{13}C RMN (DMSO, 125 MHz) δ 198,3, 172,1, 171,7, 162,1, 158,3, 157,1, 151,0, 139,6, 135,0, 127,9, 123,3, 116,4, 60,5, 55,8, 52,8, 52,2, 51,5, 36,4, 35,0, 28,0, 27,1, 26,9, 26,3, 19,5, 13,7. MS (ES) *m/z* Intensidad relativa 780 [(M+Na)$^+$, 50]; 758 [(M+1)$^+$, 100].

Ejemplo Preparativo 46: Preparación de:



46

Paso A:



46a **46b**

Se trató una solución de (S)–*ter*-leucinol (5,0 g, 42,7 mmol, Aldrich) **46a** a 0°C en CH_2Cl_2 (100,0 ml) con cloroformiato de bencilo (6,7 ml, 47,0 mmol), seguido de base de Hunig (9,3 ml, 53,3 mmol). Se permitió que la mezcla de reacción se entibiara hasta la temperatura ambiente y se agitó hasta el día siguiente. La mezcla de reacción se diluyó con acetato de etilo (500 ml), se lavó con KH_2PO_4 10 %, seguido de $NaHCO_3$ saturado y salmuera. La capa orgánica se secó sobre $MgSO_4$ y se concentró para dar leucinol protegido (10,7 g, 100%) que se usó en una reacción posterior sin ninguna purificación.

A una solución de leucinol protegido (bruto) (10,7 g, 42,7 mmol) en CH_2Cl_2 (100,0 ml) se agregó a 0°C piridina (20,0 ml) y cloruro de metansulfonilo (3,63 ml, 47,0 mmol). Se permitió que la mezcla de reacción se entibiara a temperatura ambiente y se agitó hasta el día siguiente, se concentró, se redisolvió en acetato de etilo (500 ml), se lavó con $NaHCO_3$ saturado y salmuera. La capa orgánica se secó ($MgSO_4$), se concentró y se purificó mediante cromatografía flash sobre SiO_2 usando acetato de etilo/hexano (1:4) para dar **46b** (14,0 g, 100 %).

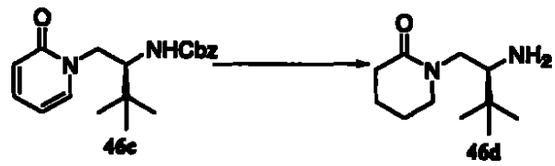
Paso B:



46b **46c**

Se trató una solución de **46b** (3,1g, 9,9 mmol) en tolueno (72 ml) que contenía agua (400 µl) con $(C_4H_9)_4NBr$ (582 mg, 1,8 mmol), K_2CO_3 (2,72 g, 1,97 mmol) y 2-hidroxipiridina (937 mg, 9,85 mmol). La mezcla de reacción se refluió hasta el día siguiente con agitación, se filtró y el filtrado se concentró *in vacuo*. El residuo se purificó mediante cromatografía flash sobre SiO_2 usando acetato de etilo/CH_2Cl_2 (1:9 a 1:1) para dar **46c** (1,15 g, 35%) como un aceite incoloro.

Paso C:

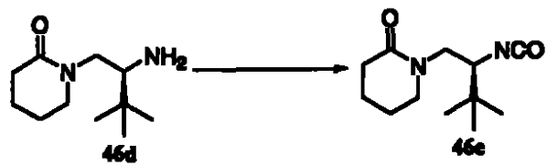


46c **46d**

Se trató una solución de la piridona **46c** (1,15 g) en MeOH (50 ml) con Pd/C (10% p/p, 450 mg) y se colocó en un agitador Parr® y se hidrogenó a 2,76 x 10^5 Pa (40 psi) durante 4 h. La mezcla de reacción se filtró a través de un tapón de Celite® y se concentró *in vacuo* para dar **46d**, que se usó en el siguiente paso sin otra purificación.

Paso D:

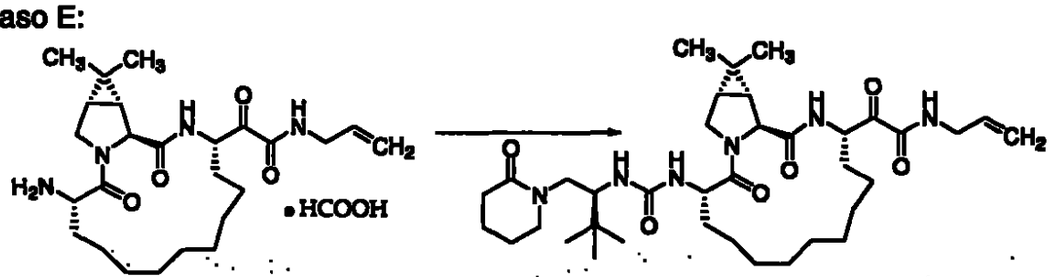
533
530



46d 46e

Se trató una solución de la amina **46d** (600 mg, 3,03 mmol) en CH_2Cl_2 (10 ml) y $NaHCO_3$ acuoso saturado (10 ml) a 0°C con fosgeno (5 ml, solución 15% en tolueno) y se agitó a 0°C durante 2 h. La mezcla de reacción se diluyó con CH_2Cl_2 (50 ml) y la capa orgánica se lavó con $NaHCO_3$ acuoso frío. La capa orgánica se secó ($MgSO_4$) se filtró y además se diluyó con 3 ml de tolueno, se concentró la capa de cloruro de metileno y se usó como una solución en tolueno.

Paso E:



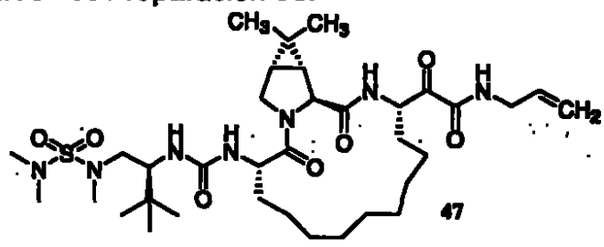
24a 46

Se trató una solución de la amina **24a** (100 mg, 0,197 mmol) en cloruro de metileno (3,0 ml) con NMM (60 mg, 0,6 mmol) y se enfrió a 0°C. Se agregó una solución del isocianato **46e** (1,5 ml, 0,25 mmol) en tolueno y la mezcla de reacción se agitó a ta. durante 2 h. La mezcla de reacción se diluyó con cloruro de metileno (100 ml) y se lavó con HCl acuoso (1 M, 50 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetato de etilo/hexanos 1:1→1:0) y 100% de acetato de etilo para dar **46** (30 mg) como un sólido incoloro. ^1H RMN (DMSO, 500 MHz) δ 8,92 (t, 1 H, *J*=6,5 Hz), 8,39 (d, 1 H, *J*=9,0 Hz), 6,17 (d, 1 H, *J*=9,0 Hz), 5,81 (m, 1 H), 5,69 (d, 1 H, *J*=10,5 Hz), 5,29 (bt, 1 H, *J*=10,0 Hz), 5,13-5,10 (m, 2 H), 4,33 (s, 1H), 4,30-4,26 (m, 1 H), 3,86-3,65 (m, 6 H), 3,50 (bt, 1 H, *J*=12 Hz), 3,15-3,08 (m, 2 H), 2,21-2,05 (m, 2 H), 1,74-1,54 (bm, 6 H), 1,46-1,11 (bm, 18 H), 0,99 (s, 3 H), 0,84 (s, 3 H), 0,82 (s, 9 H). ^{13}C RMN (DMSO, 125 MHz) δ 198,2, 172,1, 171,3,

531 534

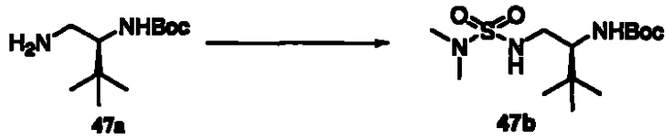
169,3, 162,1, 158,2, 135,0, 116,4, 60,5, 55,8, 55,1, 52,8, 51,5, 48,3, 47,6, 47,0, 41,7, 34,6, 33,0, 32,4, 31,5, 28,3, 28,0, 27,8, 27,2, 26,9, 26,2, 24,5, 23,7, 22,4, 21,9, 19,5, 13,7.

Ejemplo Preparativo 47: Preparación de:



47

Paso A:



47a 47b

La amina **47a** (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 a -78°C. Se agregaron 3 ml (3 equiv.) de Et_3N seguido del agregado lento de cloruro de dimetilsulfamilo (1,5 eq., Sigma-Aldrich) disuelto en DCM. La temperatura se mantuvo a -78°C hasta que se completó el agregado y luego se agitó hasta el día siguiente permitiendo que se eleve hasta temperatura ambiente. Se diluyó con cloruro de metileno y se lavó con agua, HCl 1N acuoso y por último salmuera. Las capas orgánicas se secaron sobre sulfato de sodio anhidro, se filtraron y se concentraron *in vacuo*. El producto bruto aislado se purificó mediante columna flash (EtOAc-Hexano 10→30%) para dar 1,27g (58%) de **47b.** ^{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).

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

Paso B:



47b 47c

532 525

A la sulfonilurea protegida con Boc **47b** (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 desactivó con agua. Se extrajeron las capas acuosas con EtOAc, se lavaron 4 veces con agua y salmuera. Las capas orgánicas se secaron sobre sulfato de sodio anhidro, se filtraron y se evaporó el solvente para dar 420 mg (91%) de **47c**, que se usó en la siguiente reacción sin otra 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). MS (ESI), m/z, intensidad relativa 338 [(M+1) 60], 282 (100), 238 (90).

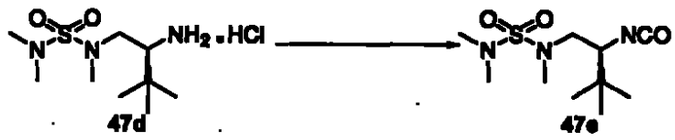
Paso C:



47c **47d**

A la sulfonilurea protegida con Boc **47c** (890 mg, 1 equiv.) se agregó solución 4 M de HCl en dioxano (25 ml) a temperatura ambiente y se agitó durante 1 hr. Después de la desaparición del material de partida (TLC), la mezcla de reacción se concentró y se destiló azeotrópicamente con hexanos y éter. El residuo se trituró con éter y el sólido que se separó se filtró y se secó al vacío para dar un sólido amarillo pálido (720 mg, ~100%). Se usó en la reacción posterior sin purificación.

Paso D:



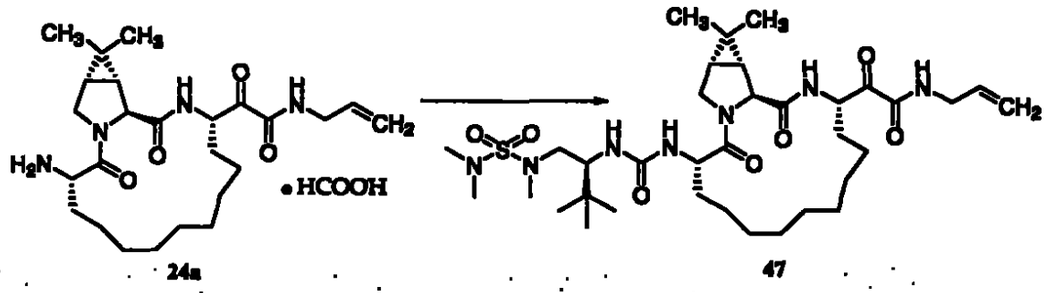
47d **47e**

Al clorhidrato de amina **47d** (720 mg, 2,63 mmol) en diclorometano (15 ml) se agregaron 15 ml de $NaHCO_3$ acuoso saturado y se agitó vigorosamente a 0°C durante 5 min. Una solución de fosgeno (2 equiv. 20% en tolueno) se extrajo con

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jeringa de la capa inferior y se reanudó la agitación vigorosa inmediatamente. Se verificó por TLC algunas veces y después de 2 hs se demostró el consumo total del material de partida. Se separó la capa de cloruro de metileno y la capa acuosa se extrajo con diclorometano (30 ml). Las capas orgánicas combinadas se secaron sobre sulfato de sodio anhidro, se filtraron y se concentraron usando evaporador rotativo a presión reducida a ta. hasta la mitad del volumen y luego se saturó con N_2 durante 15 minutos. La solución se diluyó a 130 ml con diclorometano y se usó como solución 0,02 M en posteriores reacciones.

Paso E:



24a 47

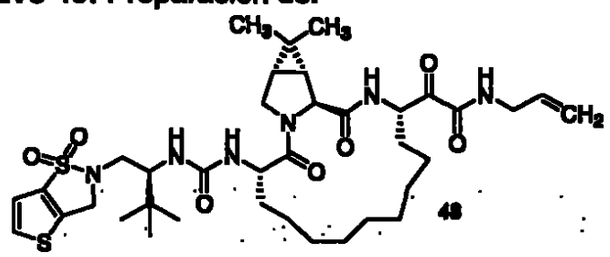
Se trató una solución de la amina **24a** (100 mg, 0,197 mmol) en cloruro de metileno (3,0 ml) con NMM (60 mg, 0,6 mmol) y se enfrió a 0°C. Se agregó una solución del isocianato **47e** (1,5 ml, 0,25 mmol) en tolueno y la mezcla de reacción se agitó a ta. durante 2 h. La mezcla de reacción se diluyó con cloruro de metileno (100 ml) y se lavó con HCl acuoso (1 M, 50 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetato de etilo/hexanos 1:1→1:0) y 100% de acetato de etilo para dar **47** (49 mg) como un sólido incoloro.

^{1}H RMN (dmso, 500 MHz) δ 8,89 (t, 1 H, *J*=6 Hz), 8,37 (d, 1 H, *J*=9,0 Hz), 6,15 (d, 1 H, *J*=9,0 Hz) 5,83-5,76 (m, 2 H), 5,31-5,27 (m, 2 H), 4,33 (s, 1 H), 4,30-4,28 (m, 1 H), 3,91 (d, 1 H, *J*=10,5 Hz), 3,80-3,70 (m, 4 H), 3,63-3,59 (m, 1 H), 2,93 (dd, 1 H), 2,7 (s, 3 H), 2,69 (s, 6 H), 1,73-1,65 (m, 2 H), 1,51-1,02 (m, 18 H), 0,99 (s, 3 H), 0,84 (s, 3 H), 0,81 (m, 9 H). ^{13}C RMN (dmso, 125 MHz) δ, 198,3, 172,1, 171,7, 162,1, 158,2, 135,0, 116,5, 60,5, 55,8, 52,8, 51,7, 1,3, 47,6, 41,1, 38,5, 36,0, 34,9,

534

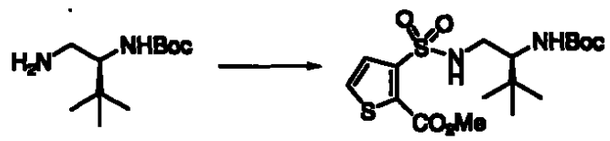
32,3, 31,6, 31,3, 28,5, 28,4, 27,9, 27,4, 27,4, 27,1. MS (ES) *m/z* intensidad relativa 746 [(M+Na)$^+$, 40]; 724 [(M+1)$^+$, 100].

Ejemplo Preparativo 48: Preparación de:



48

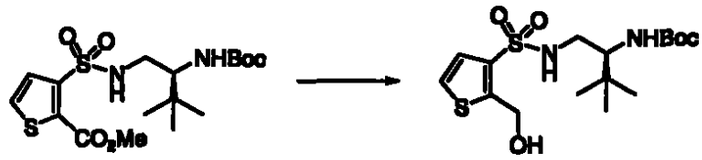
Paso A:



48a 48b

Se preparó el compuesto **48b** a partir de **48a** y cloruro de 2-carbometoxi-3-tiofensulfonilo de acuerdo con los procedimientos descriptos para la preparación del compuesto **45b**.

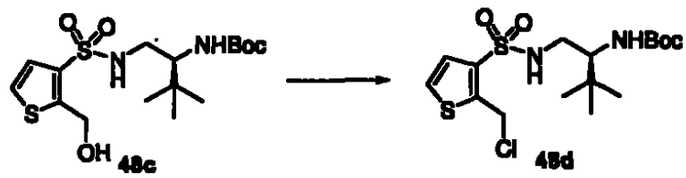
Paso B:



45b 48c

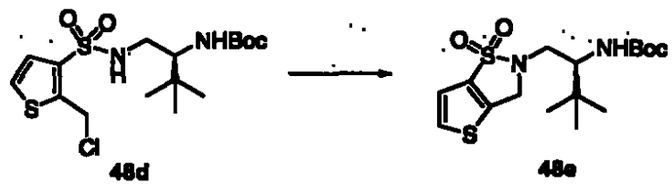
A la solución del éster **48b** (4,65 g, 11,1 mmol) en tolueno anhidro (40 ml) a -78°C se agregó una solución de DIBAL-H en tolueno (23,0 ml, 34,5 mmol). La mezcla se agitó a -78°C durante 20 min. y a ta. durante 2 h. Se agregó metanol (20 ml) seguido de solución acuosa de ácido cítrico 10% (100 ml). Después se agitó durante 5 min, se agregó EtOAc (200 ml) y se separaron las capas. La solución acuosa se extrajo con EtOAc (2 x100 ml). Las soluciones orgánicas se combinaron, se secaron ($MgSO_4$), se filtraron y se concentraron. El residuo se purificó mediante cromatografía flash en columna usando acetona/hexanos 10-50% para dar 4,6 g (cuant.) de **48c**.

Paso C:



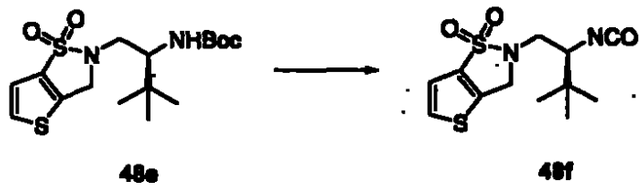
A una solución de **48c** (1,04 g, 2,65 mmol) en CH_2Cl_2 I (50 ml) a 0°C se agregó cloruro de metansulfonilo (0,23 ml, 2,97 mmol) y trietilamina (0,80 ml, 5,74 mmol). La mezcla se entibió hasta t.a. junto con el baño de hielo y se agitó durante 18 h. Se agregó EtOAc (200 ml) y solución de H_3PO_4 5% (100 ml) y las capas se separaron. Las soluciones orgánicas se lavaron con solución de carbonato de sodio 1 N (100 ml) antes de secarse ($MgSO_4$), se filtraron y se concentraron. El residuo se purificó mediante cromatografía flash en columna usando 10-50% acetona/hexanos para dar 0,80 g (73%) de **48d**.

Paso D:



Se agitó una suspensión de **48d** (1,17 g, 2,85 mmol) y carbonato de cesio (1,40 g, 4,30 mmol) en DMF anhidro (100 ml) a ta. durante 18 h. Se agregó agua (50 ml), salmuera (50 ml) y EtOAc (300 ml) y las capas se separaron. Se lavó la solución orgánica con agua (3 x 150 ml) antes de secar, se filtró y se concentró para dar 0,99 g del producto deseado **48e** (93%).

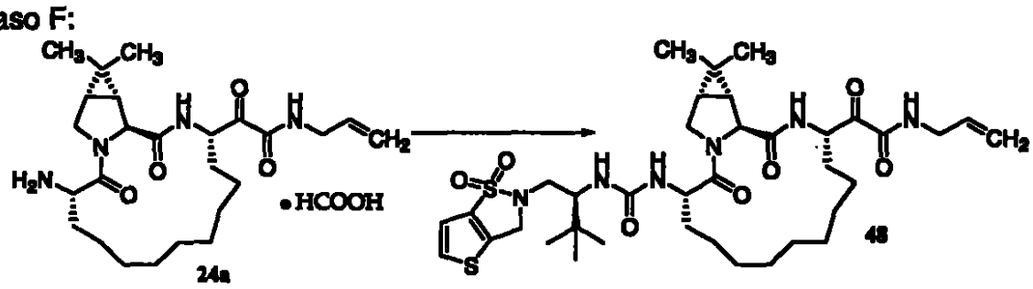
Paso E:



Se preparó el compuesto **48f** a partir de **48e** de acuerdo con los procedimientos descriptos para la preparación de los compuestos **45b** y **45c**.

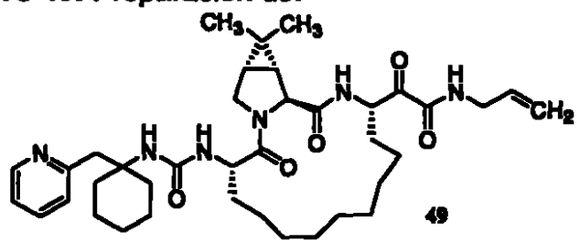
939
536

Paso F:

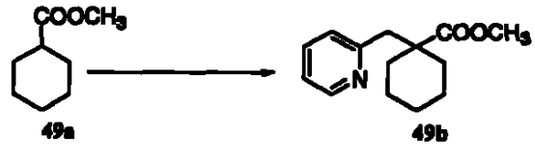


Se trató una solución de la amina **24a** (100 mg, 0,197 mmol) en cloruro de metileno (3,0 ml) con NMM (60 mg, 0,6 mmol) y se enfrió a 0°C. Se agregó una solución del isocianato **48f** (2 ml, 0,25 mmol) en tolueno y la mezcla de reacción se agitó a ta. durante 2 h. La mezcla de reacción se diluyó con cloruro de metileno (100 ml) y se lavó con HCl acuoso (1 M, 50 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2, acetato de etilo/hexanos 1:1→1:0) y 100% de acetato de etilo para dar **48** como un sólido incoloro.

Ejemplo Preparativo 49: Preparación de:



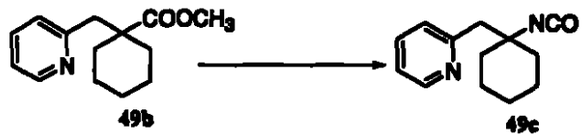
Paso A:



Se enfrió una solución de LDA/THF-heptano 2 M (Acros Chemical Co.) en 50 ml de THF a -70°C, se agregó ciclohexancarboxilato de metilo **49a** gota a gota a <-60°C. Después de agitar durante 0,5 hr adicionales a –70°C, se agregó cloruro de 2-picolilo en 40 ml de éter gota a gota a <-60°C. Luego se permitió que se eleve la temperatura lentamente a temperatura ambiente durante 2 hr, y se

agitó 2 hr adicionales. La reacción se desactivó en una mezcla fría de 200 ml de KH_2PO_4 acuoso 20% y 5 ml de HCl 12 N, la mezcla se extrajo con EtOAc, el extracto se lavó con salmuera, y luego se secó con $MgSO_4$. La mezcla se filtró, el filtrado se evaporó, el residuo se evaporó dos veces de xileno, y el residuo final se sometió a cromatografía sobre gel de sílice (Et_2O-CH_2Cl_2 1:3 a acetona-CH_2Cl_2 1:1) para obtener **49b**.

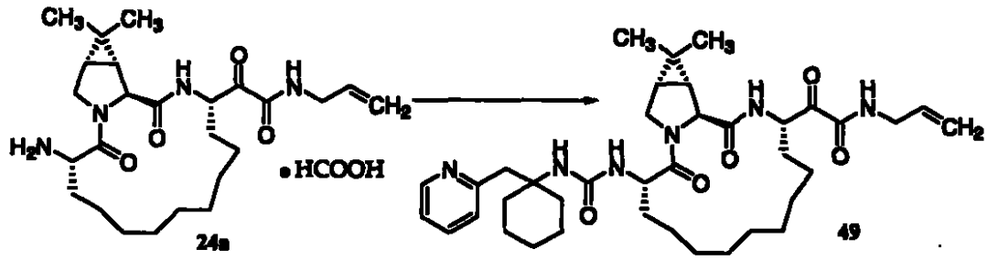
Paso B:



49b 49c

Se trató una solución del éster **49b** en 20 ml de dioxano con 30 ml de LiOH 1 N acuoso, y la mezcla se agitó a 100ºC durante 6 hr. La mezcla se desactivó en hielo-agua, se extrajo con éter, y la fase acuosa fría se acidificó lentamente hasta pH ~4 con HCl 3 N. El precipitado se filtró, se lavó con agua, y se secó para dejar ácido el producto, que se usó en el siguiente paso sin otra purificación. La conversión del ácido al isocianato **49c** fue idéntica a la síntesis de **27b** en el Ejemplo Preparativo **27**.

Paso C:



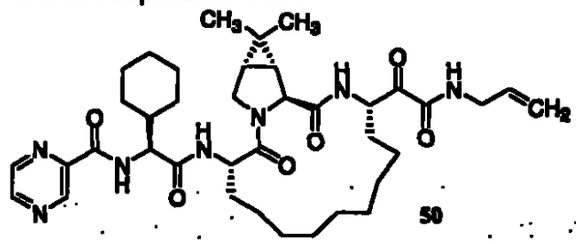
24a 49

Se trató una solución de la amina **24a** (100 mg, 0,197 mmol) en cloruro de metileno (3,0 ml) con NMM (60 mg, 0,6 mmol) y se enfrió a 0°C. Se agregó una solución del isocianato **49c** (2,9 ml, 0,25 mmol) en tolueno y la mezcla de reacción se agitó a ta. durante 2 h. La mezcla de reacción se diluyó con cloruro de metileno (100 ml) y se lavó con HCl acuoso (1 M, 50 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante

341
538

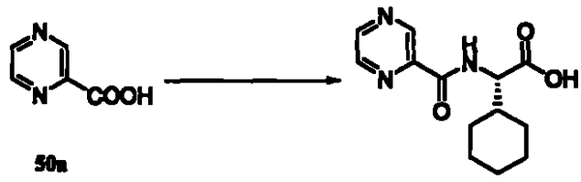
cromatografía (SiO_2, acetato de etilo/hexanos 1:1→1:0) y 100% de acetato de etilo para dar **49** como un sólido incoloro.

Ejemplo Preparativo 50: Preparación de:



50

Paso A:



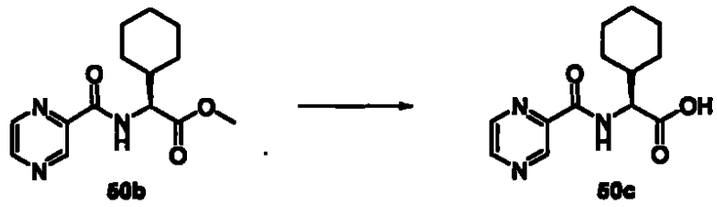
50a **50b**

Se agitó una solución de ácido pirazincarboxílico **50a** (Aldrich, 3 g) en 150 ml de diclorometano seco y 150 ml de DMF seco a 0ºC y se trató con HATU (1,4 eq, 6,03 g). Se agregó clorhidrato del L-ciclohexilglicin-metil éster (1,2 eq, 6,03 g) en pequeñas cantidades. Luego, se agregó N-metilmorfolina (4 eq, 10 ml, d 0,920) gota a gota. La mezcla de reacción se calentó gradualmente hasta temperatura ambiente y se agitó durante 20 h. Se eliminaron todos los volátiles al vacío y el residuo se disolvió en 500 ml de acetato de etilo. La capa orgánica se lavó con agua (100 ml), HCl acuoso 1N (100 ml), solución acuosa saturada de bicarbonato de sodio (100 ml), y salmuera (100 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 5:95 a 3:7) para dar el producto **50b** (6,5 g, 95%) como un sólido blanco.

Paso B:

542

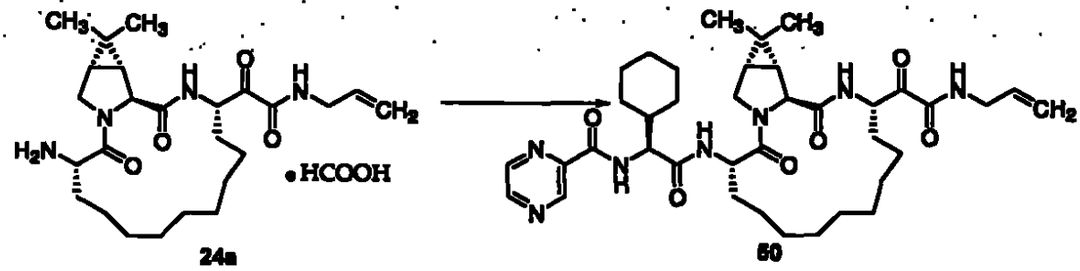
539



50b 50c

Se enfrió una solución del metil éster **50b** (6,5 g) en 270 ml de una mezcla 1:1:1 de THF/MeOH/H_2O a 0ºC y se trató con monohidrato de hidróxido de litio (2,5 eq, 2,45 g). La mezcla se agitó y se monitoreó mediante TLC (acetona/hexanos; 2:8). Una vez que se consumió todo el material de partida, la mezcla de reacción se trató con 100 ml de HCl acuoso 1N y la mezcla se concentró *in vacuo*. Se agregó diclorometano (250 ml) y las capas se separaron. La capa acuosa se extrajo con diclorometano (3 x 80 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron para dar el ácido **50c**.

Paso C:



24a 50

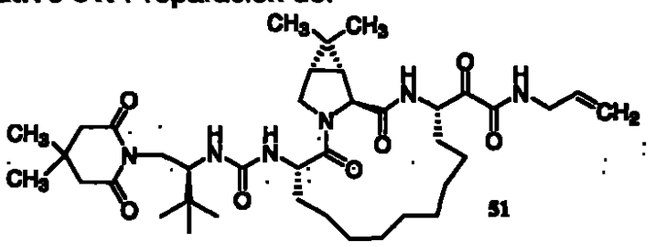
Se enfrió una solución del ácido **24a** (100 mg, 0,197 mmol) en CH_2Cl_2 seco (2 ml) y DMF (2 ml) a 0°C y se trató con el ácido **50c** (51,8 mg, 0,197 mmol), HATU (94 mg, 0,25 mmol) y NMM (45 mg, 0,45 mmol). La reacción se agitó a 0°C durante 12 h y se concentró *in vacuo*. El residuo se disolvió en CH_2Cl_2 (100 ml) y se lavó con HCl acuoso (1 M, 2x30 ml), $NaHCO_3$ acuoso saturado (2x30 ml), salmuera (30 ml), se secó ($MgSO_4$), se filtró, se concentró *in vacuo*. El dipéptido bruto se purificó mediante cromatografía (SiO_2, acetona/Hexanos 0:1→1:1) para dar **50**, ^{1}H RMN (dmso, 400 MHz) δ *J*=12 Hz), 8,89 (d, 1 H, *J*=2,4 Hz), 8,74 (s, 1 H), 8,59 (d, 1 H, *J*=7,4 Hz), 8,43-8,38 (m, 2 H), 5,81-5,75 (m, 1 H), 5,28 (t, 1 H,

843

540

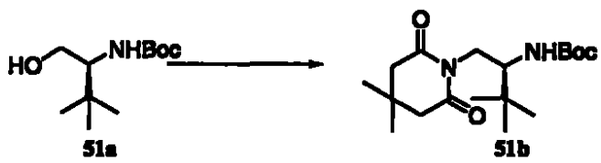
J=10,8 Hz), 5,11-5,03 (m, 2 H), 4,45-4,31 (m, 3 H), 3,88-3,70 (m, 5 H), 1,65-1,22 (m, 31 H), 0,97 (s, 3 H), 0,83 (s, 3 H).MS (ES) *m/z* intensidad relativa 728 [$(M+Na)^+$, 4]; 706 [$(M+1)^+$, 80].

Ejemplo Preparativo 51: Preparación de:



51

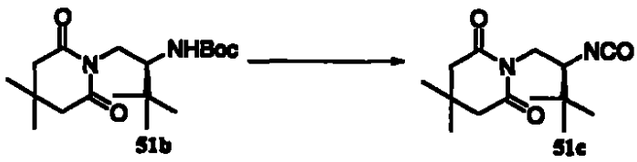
Paso A:



51a 51b

Se trató una solución del alcohol **51a** (1,00 g, 4,6 mmol) en CH_2Cl_2 anhídrido (30 ml) en una atmósfera inerte con trifenilfosfina (1,52 g, 5,75 mmol) y dimetilglutarimida (780 mg, 5,52 mmol). La mezcla de reacción se enfrió a 0°C y se trató con DIAD (930 mg, 4,60 mmol, en 4 ml de CH_2Cl_2) gota a gota y se calentó hasta ta. Esta se agitó a ta. durante 5 h y se concentró *in vacuo*. El residuo se purificó mediante cromatografía (SiO_2, Hexanos/acetona 1:0→1:1) para obtener **51b** (600 mg) como un sólido incoloro.

Paso B:

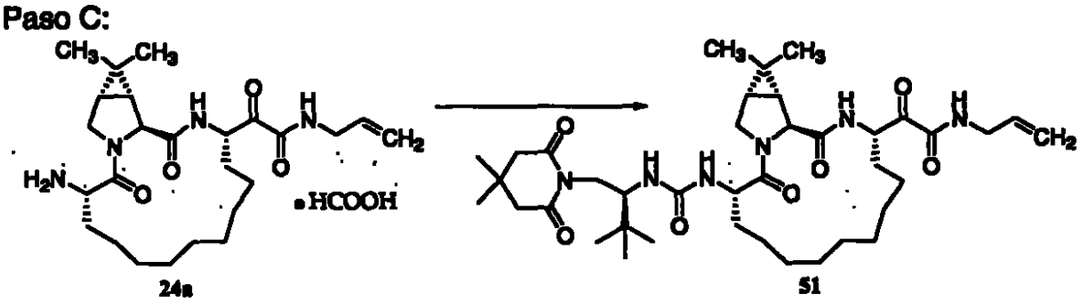


51b 51c

Se agitó una solución de **51b** (500 mg, 1,5 mmol) en HCl (15 ml, solución 4M en dioxano) a ta. durante 1 h y se concentró *in vacuo*. El residuo se usó en la siguiente reacción sin purificación. Se trató una solución de la amina desprotegida en CH_2Cl_2 (10 ml) y $NaHCO_3$ acuoso saturado (10 ml) a 0°C con fosgeno (5 ml, solución 15% en tolueno) y se agitó a 0°C durante 2 h. La mezcla de reacción se

diluyó con CH_2Cl_2 (50 ml) y la capa orgánica se lavó con $NaHCO_3$ acuoso frío. La capa orgánica se secó ($MgSO_4$), se filtró y se diluyó también con 3 ml de tolueno, se concentró la capa de cloruro de metileno y se usó como una solución.

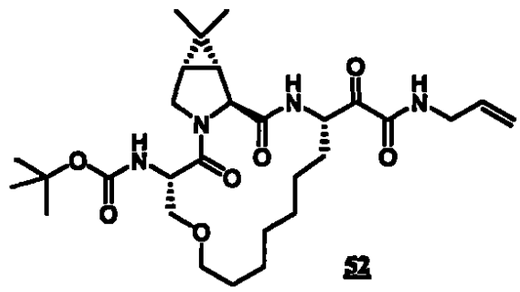
Paso C:



Una solución de la amina **24a** (100 mg, 0,196 mmol) en cloruro de metileno (3,0 ml) se trató con NMM (60 mg, 0,6 mmol) y se enfrió a 0°C. Una solución del isocianato **51c** (2 ml, 0,5 mmol) en tolueno se agregó y la mezcla de reacción se agitó a ta. durante 2 h. La mezcla de reacción se diluyó con cloruro de metileno (100 ml) y se lavó con HCl acuoso (1 M, 50 ml). Las capas orgánicas se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo* y se purificaron mediante cromatografía (SiO_2 Acetona/hexanos 0:1→1:1), dando **51** como un sólido incoloro. ^{1}H RMN (dmso, 500 MHz) δ 8,91 (d, 1H), 6,19 (d, 1 H, *J*=8,5 Hz), 5,84-5,57 (m, 1 H), 5,58 (d, 1 H, *J*=10,5 Hz), 5,28 (t, 1 H, *J*=7,0 Hz), 5,10-5,05 (m, 2 H), 4,31 (s, 1 H), 4,18 (t, 1 H, *J*=8,5 Hz), 3,83-3,57 (m, 7 H), 2,44-2,38 (AB, 4 H), 1,66-1,62 (m, 2 H), 1,44-1,03 (m, 18 H), 0,98 & 0,96 (2s, 9 H), 0,84 & 0,81 (2s, 12 H). ^{13}C RMN (dmso, 125 MHz) δ 198,2, 172,7, 172,1, 171,3, 162,1, 158,1, 135,0, 116,4, 60,5, 55,5, 52,9, 51,3, 47,5, 46,4, 41,7, 39,6, 35,0, 32,4, 31,5, 31,3, 29,3, 28,3, 27,9, 27,0, 26,9, 26,6, 26,1, 24,5, 22,4, 19,5, 13,7,MS (ES) *m/z* intensidad relativa 749 [$(M+Na)^+$, 20]; 727 [$(M+1)^+$, 100].

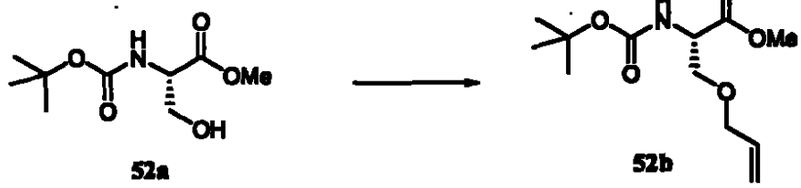
Ejemplo Preparativo 52: Preparación de:

542



52

Paso A:



52a 52b

Se desgasificó una solución de N-Boc-L-Ser-OMe (3,6 g, Aldrich) en 150 ml de THF seco (vacío/N2-saturación) y se trató con carbonato de alilmetilo (1,4 eq, 2,6 ml, d 1,022). Se agregó una cantidad catalítica de tetrakis(trifenilfosfina)-paladio (0,02 mol%, 379 mg). La mezcla levemente amarilla se desgasificó nuevamente y se calentó a 60ºC durante alrededor de 3 h hasta que el análisis por TLC (acetona/hexanos; 2:8) mostró que ya no quedaba material de partida (la mezcla de reacción se tornó marrón). El THF se eliminó a presión reducida y el residuo se diluyó con 300 ml de acetato de etilo y se lavó con 80 ml de solución acuosa saturada de bicarbonato de sodio y 80 ml de salmuera. La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 5:95 to 2:8) para dar el producto 52b como un aceite claro (2,7 g, 64%).

Paso B



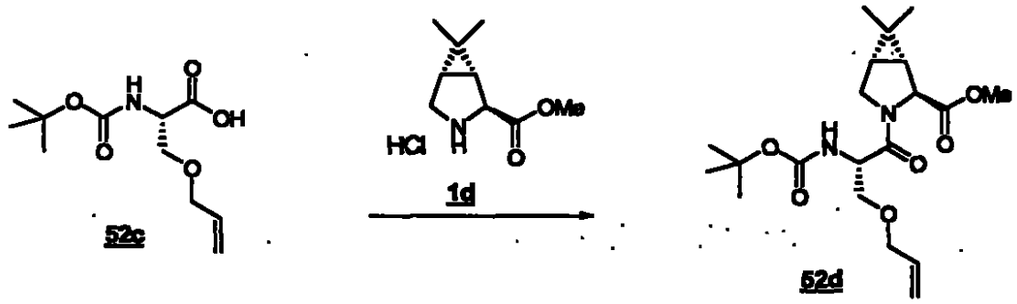
52b 52c

546

543

Se trató una solución del metil éster **52b** (1,5 g) en 90 ml de una mezcla de THF/MeOH/H_2O (1:1:1) con monohidrato de hidróxido de litio (2,5 eq, 630 mg). La reacción se agitó a temperatura ambiente y se monitoreó mediante TLC (acetona/hexanos; 1:9). Después de 45 min, se eliminaron todos los volátiles a presión reducida. El residuo se dividió entre 80 ml de HCl acuoso 1N y 200 ml de diclorometano. La capa acuosa se extrajo con diclorometano (2 x 80 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida para dar el producto **52c** como un aceite claro (1,4 g, 95%).

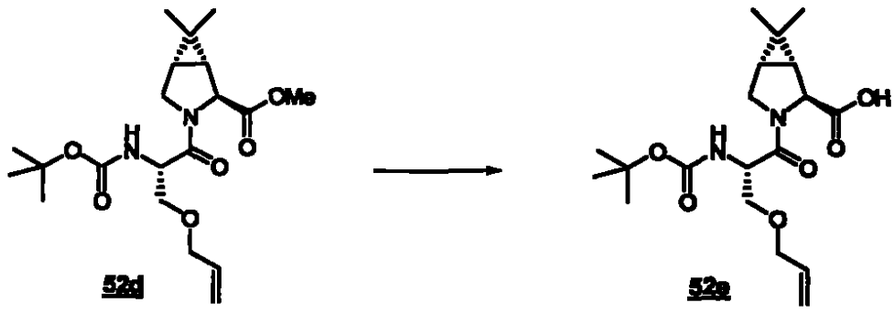
Paso C



52c 52d

Se agitó una solución del ácido **52c** (6 mmol) en 40 ml de diclorometano seco y 40 ml de DMF seco a 0ºC y se trató con HATU (1,4 eq, 3,2 g). Se agregaron sucesivamente clorhidrato de amina **1d** (1,3 eq, 1,6 g) y N-metilmorfolina (4 eq, 2,6 ml, d 0,920). La mezcla de reacción se calentó gradualmente hasta temperatura ambiente y se agitó hasta el día siguiente. Se eliminaron todos los volátiles al vacío y el residuo se tomó en 300 ml de acetato de etilo. La capa orgánica se lavó con HCl acuoso 1N (50 ml), bicarbonato de sodio acuoso saturado (50 ml), y salmuera (50 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 5:95 a 2:8) para dar el producto deseado **52d** (2,23 g, 93%) como un aceite claro.

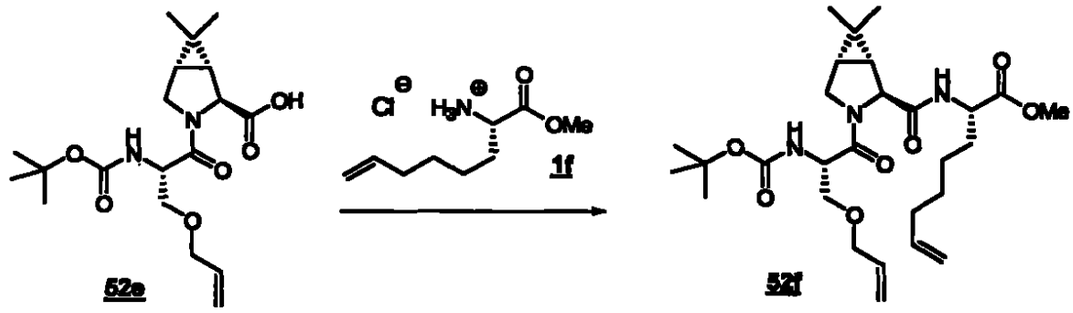
Paso D



52d 52e

Una solución del metil éster 52d (2,23 g) en 45 ml de una mezcla de THF/MeOH/H_2O (1:1:1) se trató con monohidrato de hidróxido de litio (2,5 eq, 300 mg) a 0ºC. El baño de enfriamiento se retiró y la mezcla de reacción se agitó a temperatura ambiente y se monitoreó mediante TLC (acetona/hexanos; 2:8). Después de 1 h, se agregaron 10 ml de HCl acuoso 1N y se eliminaron todos los volátiles a presión reducida. El residuo se dividió entre 30 ml de HCl acuoso 1N y 100 ml de diclorometano. La capa acuosa se extrajo con diclorometano (2 x 50 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida para dar el producto 52e (1,88 g, 88%) como un aceite claro.

Paso E

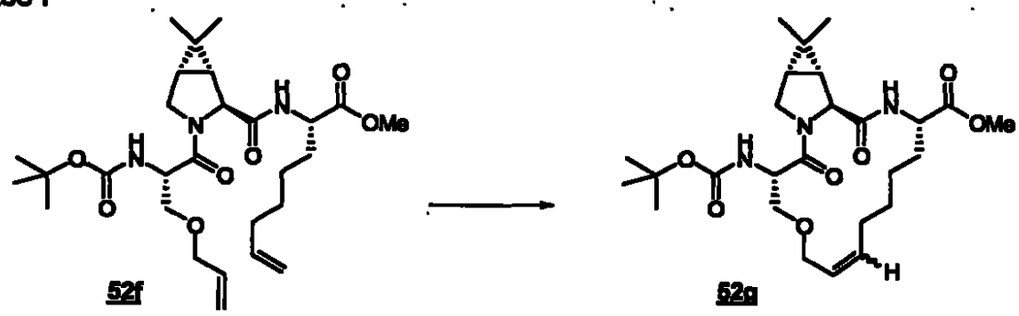


52e 1f 52f

Una solución del ácido 52e (830 mg) en 20 ml de diclorometano seco y 20 ml de DMF seco se agitó a 0ºC y se trató con HATU (1,4 eq, 1,15 g). Se agregó clorhidrato de amina 1f (1,1 eq, 227 mg) en 10 ml de diclorometano seguido de N-metilmorfolina (4 eq, 0,95 ml, d 0,920). La mezcla de reacción se mantuvo en el congelador (-20°C) durante 48 h. Se eliminaron todos los volátiles al vacío y el residuo se disolvió en 200 ml de acetato de etilo. La capa orgánica se lavó con

agua (50 ml), HCl acuoso 1N (50 ml), solución acuosa saturada de bicarbonato de sodio (50 ml) y salmuera (50 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 5:95 a 3:7) para dar el producto **52f** (680 mg) como un sólido blanco junto con un producto diastereomérico menor (130 mg) para un rendimiento combinado del 70%.

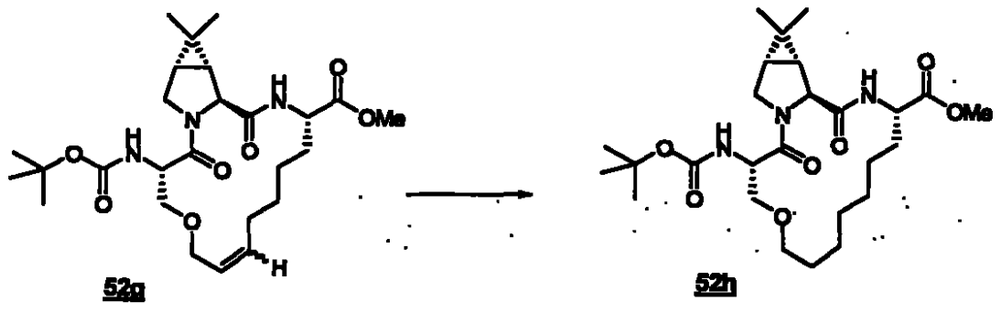
Paso F



52f **52g**

Se desgasificó una solución 0,01M del dieno **52f** (670 mg) en tolueno durante 30 min. (burbujeo bajo argón) y se trató con catalizador de Grubb (0,2 eq, 205 mg). La solución rosada se calentó a 60ºC durante 16 h (la solución se volvió oscura después de calentar durante 10 min). El solvente se eliminó a presión reducida y el residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetato de etilo/hexanos; 2:8 a 1:1) para dar el producto alqueno **52g** (570 mg, 90%) como una mezcla de isómeros E y Z (aprox 4:1).

Paso G

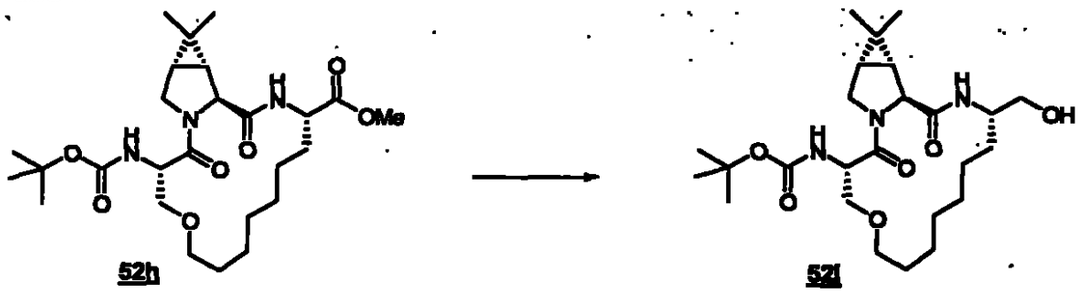


52g **52h**

Se trató una solución del alqueno **52g** (570 mg) en 20 ml de metanol con dihidróxido de paladio sobre carbono (0,1 mol%, 78 mg de Pd(OH)2/C 20%). La

mezcla se hidrogenó a 3,45 x 10^5 Pa (50 psi) hasta que se consumió todo el material de partida. La mezcla de reacción se diluyó con 100 ml de diclorometano y se filtró a través de un taco corto de Celite. El filtrado se concentró y el residuo se sometió a cromatografía sobre gel de sílice para dar el producto **52h** (590 mg, 70%) como un aceite claro.

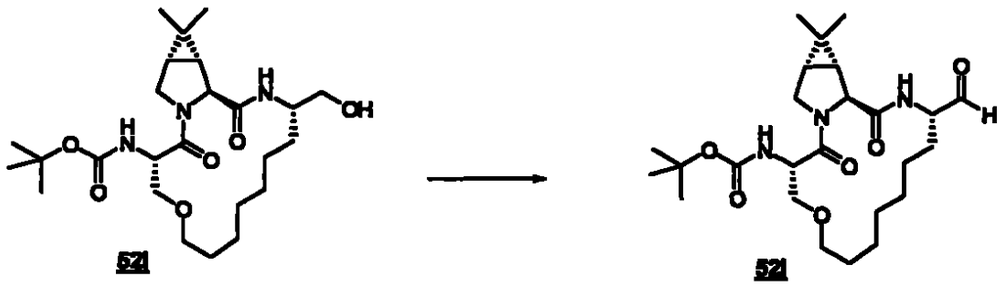
Paso H



52h **52i**

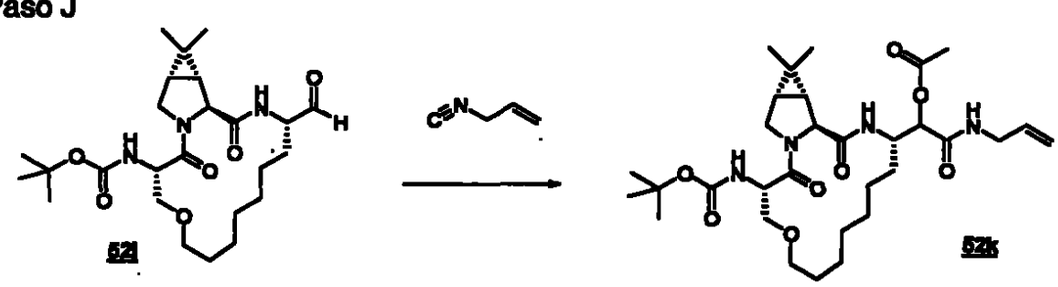
Una solución del metil éster **52h** (580 mg) en 20 ml de THF seco se trató con borohidruro de litio (2,1 eq, 1,2 ml de una solución 2M en THF). La mezcla de reacción se agitó a temperatura ambiente y se monitoreó mediante TLC (acetona/hexanos; 3:7) para verificar la desaparición del material de partida. Después de 5 h, el borohidruro de litio en exceso se desactivó por agregado de solución de cloruro de amonio acuoso saturado (3 ml). La mezcla se dividió entre acetato de etilo (100 ml) y solución acuosa saturada de bicarbonato de sodio (50 ml). La capa acuosa se extrajo con acetato de etilo (2 x 30 ml) y diclorometano (2 x 30 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 1:9 a 5:5) para dar el producto **52i** (360 mg, 68%) como un sólido blanco.

Paso I



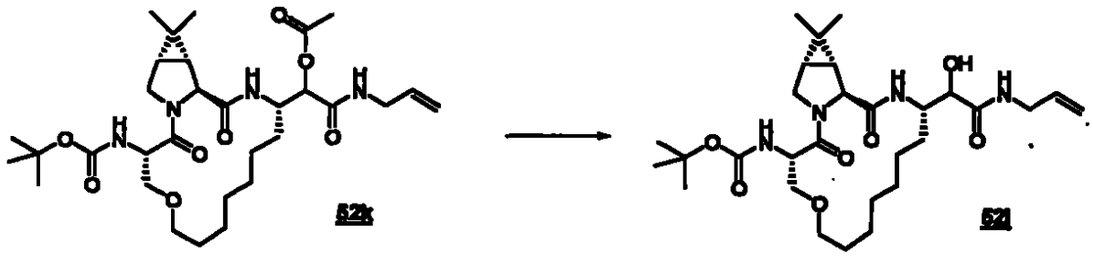
Una solución del alcohol **52l** (350 mg) en 20 ml de diclorometano seco se trató con periodinano de Dess-Martin (3 eq, 925 mg). La mezcla de reacción se agitó a temperatura ambiente durante 45 min. La mezcla se trató con solución de tiosulfato de sodio acuoso 1M (15 ml) y solución acuosa saturada de bicarbonato de sodio (15 ml) y se agitó durante 15 min. La mezcla se extrajo con diclorometano (3 x 50 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 1:9 a 4:6) para dar el producto **52j** (285 mg, 83%) como un sólido incoloro.

Paso J



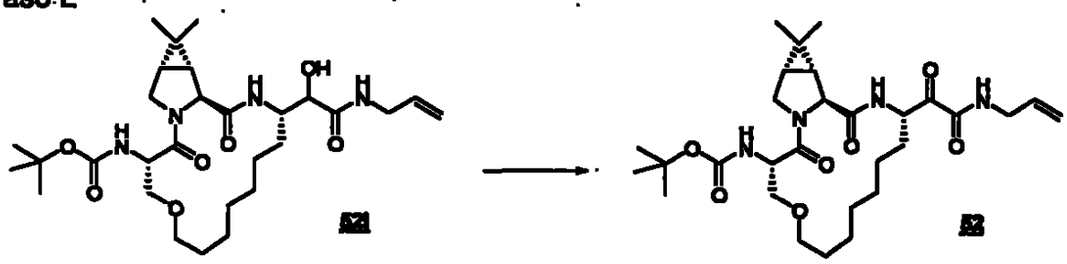
Una solución del aldehído **52j** (270 mg) en 10 ml de diclorometano seco se trató con isocianuro de alilo (2 eq, 77 mg) y ácido acético (2 eq, 0,064 ml, d 1,049). La mezcla se agitó durante alrededor de 5 h. Se eliminaron todos los volátiles al vacío y el residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 1:9 a 1:1) para dar el producto **52k** (303 mg, 90%) como un sólido blanco.

Paso K



El acetato **52k** (300 mg) se disolvió en 15 ml de una mezcla 1:1:1 de THF/MeOH/H_2O y se trató con monohidrato de hidróxido de litio (2,5 eq, 51 mg). El avance de la reacción se siguió mediante TLC (acetona/hexanos; 4:6). Después de 15 min. la mezcla de reacción se concentró en el evaporador rotativo y el residuo se dividió entre diclorometano (80 ml) y solución acuosa saturada de bicarbonato de sodio (20 ml). La capa acuosa se extrajo con diclorometano (3 x 50 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El producto bruto **52l** (276 mg, 98%) se usó sin otra purificación.

Paso L



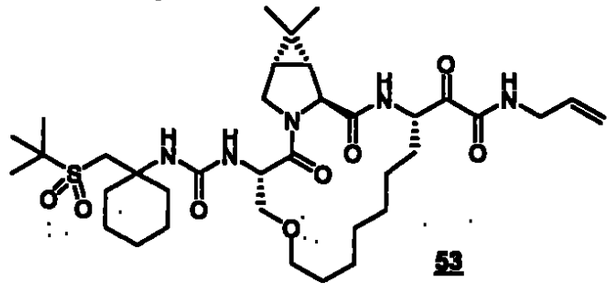
Se trató una solución de la hidroxiamida **52l** (276 mg) en 20 ml de diclorometano seco con periodinano de Dess-Martin (3 eq, 424 mg). La mezcla de reacción se agitó a temperatura ambiente durante 30 min. La mezcla se trató con solución de tiosulfato de sodio acuoso 1M (20 ml) y solución acuosa saturada de bicarbonato de sodio (10 ml) y se agitó durante 10 min. La mezcla se extrajo con diclorometano (3 x 20 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 1:9 a 4:6) para dar el producto **52** (236 mg, 86%) como un sólido blanco. ^1H RMN (500 MHz, $CDCl_3$):

852

549

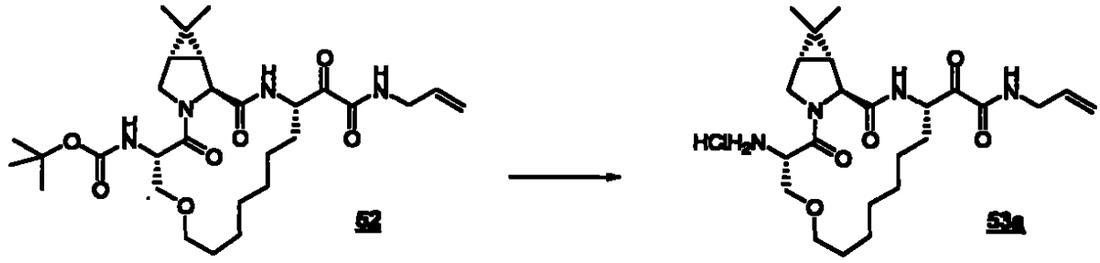
δ 7,47 (d, 1H, *J* = 7,56 Hz), 7,03 (dd, 1H, *J* = 5,68, 5,99 Hz), 5,88 (ddt, 1H, *J* = 5,6, 10,0, 17,0 Hz), 5,50 (d, 1H, *J* = 8,83 Hz), 5,46 (m, 1H), 5,28 (dd, 1H, *J* = 0,9, 17,0 Hz), 5,25 (dd, 1H, *J* = 0,9, 10,0 Hz), 4,61 (m, 1H), 4,51 (s, 1H), 3,99 (dt, 2H, *J* = 1,2, 5,6 Hz), 3,88 (dd, 1H, *J* = 5,0, 10,8 Hz), 3,83 (d, 1H, *J* = 11,0 Hz), 3,66 (m, 2H), 3,48 (dd, 2H, *J* = 4,7, 5,6 Hz), 1,95 (m, 1H), 1,81 (d, 1H, *J* = 7,56 Hz), 1,47 (s, 9H), 1,27-1,63 (m, 12H), 1,09 (s, 3H), 0,93 (s, 3H); ^{13}C RMN ($CDCl_3$, 125 MHz): δ 196,7, 170,9, 170,7, 159,3, 155,6, 133,2, 117,9, 80,4, 71,0, 70,8, 61,2, 54,5; 52,9, 48,2, 42,1, 31,4, 29,3, 28,7, 27,8, 26,8, 26,6, 26,4, 23,6, 23,4, 19,2, 13,2 ppm; HRMS calculado para $C_{29}H_{47}N_4O_7$ $[M+H]^+$: 563,3445, experimental 563,3457.

Ejemplo Preparativo 53: Preparación de:



53

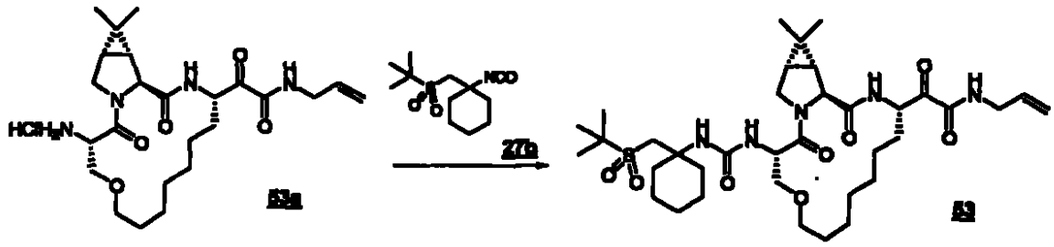
Paso A



52 53a

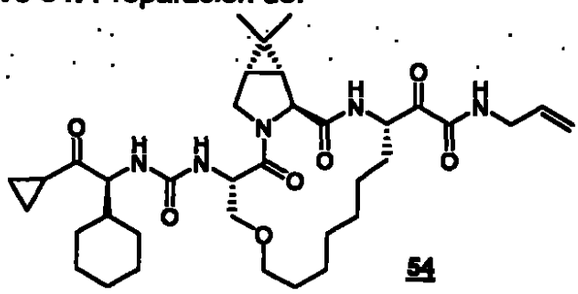
La amina protegida N-Boc 52 (60 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos y se agitó a temperatura ambiente durante 1 h. Se eliminaron todos los volátiles a presión reducida y el producto se colocó en alto vacío durante 3 h. No se realizó otra purificación para el producto 53a (99%).

Paso B



La sal de amina **53a** (31 mg) se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregaron 10 gotas de solución acuosa saturada de bicarbonato de sodio. Después de 10 min, se agregó una solución del isocianato **27b** (2,5 eq, 0,8 ml de una solución 0,2M en tolueno) y se continuó agitando durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 3 h. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 1:9 a 4:6) para dar el producto **53** (25 mg, 58%) como un sólido blanco. ^{1}H RMN (500 MHz, CDCl3): δ 7,90 (d, 1H, *J* = 8,5 Hz), 7,38 (br s, 1H), 5,9 (ddt, 1H, *J* = 5,6, 10,4, 17,0 Hz), 5,61 (ddd, 1H, *J* = 1,6, 8,8, 10,4 Hz), 5,27 (dd, 1H, *J* = 1,26, 17,3 Hz), 5,24 (dd, 1H, *J* = 1,26, 10,0 Hz), 4,9 (dd, 1H, *J* = 3,4, 8,8 Hz), 4,53 (s, 1H), 3,94-4,08 (m, 4H), 3,62 (dd, 1H, *J* = 8,5, 8,8 Hz), 3,56 (m, 1H), 3,47 (dd, 1H, *J* = 4,0, 7,9 Hz), 3,37 (ddd, 1H, *J* = 2,2, 7,2, 9,4), 3,15 (d, 1H, *J* = 13,5 Hz), 2,4 (m, 1H), 2,24 (m, 1H), 1,95 (m, 1H), 1,85 (m, 1H), 1,27-1,70 (m, 20H), 1,4 (s, 9H), 1,2 (m, 1H), 1,07 (s, 3H), 0,94 (s, 3H), 0,92 (m, 1H); ^{13}C RMN ($CDCl_3$, 125 MHz): δ 198,0, 172,1, 171,0, 159,5, 157,0, 133,3, 117,7, 70,8, 70,5, 61,0, 60,8, 54,9, 53,8, 51,0, 48,4, 42,2, 36,2, 32,0, 30,5, 28,7, 27,9, 27,2, 27,0, 26,8, 25,9, 24,1, 23,9,23,5, 21,9, 21,8, 19,3, 13,4 ppm; HRMS calculado para $C_{36}H_{60}N_5O_6S$ $[M+H]^+$: 722,4163, experimental 722,4193.

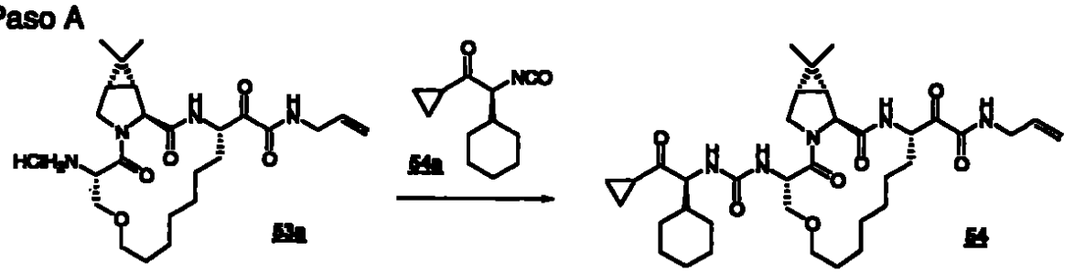
Ejemplo Preparativo 54: Preparación de:



854

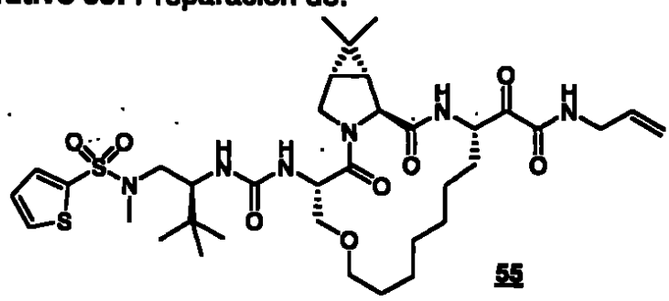
551

Paso A



Una solución de la sal de amina **53a** (17 mg) en 2 ml de diclorometano seco se trató con bicarbonato de sodio sólido (3 eq, 8 mg) seguido del agregado del isocianato **54a** (2,5 eq, 0,26 ml de una solución 0,307M en tolueno). La mezcla heterogénea resultante se agitó a temperatura ambiente durante aproximadamente 3 h. La mezcla se diluyó con 50 ml de acetato de etilo y se lavó con HCl acuoso 1M (10 ml) y salmuera (10 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 2:8 a 1:1) para dar el producto **54** (8 mg, 34%) como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$): δ 7,91 (br s, 1H), 7,40 (m, 1H), 6,37 (br s, 1H), 5,91 (ddt, 1H, *J* = 5,6, 10,4, 17,3 Hz), 5,88 (br s, 1H), 5,62 (dt, 1H, *J* = 1,26, 9,45 Hz), 5,28 (dd, 1H, *J* = 1,26, 17,3 Hz), 5,23 (dd, 1H, *J* = 1,26, 10,4 Hz), 4,92 (ddd, 1H, *J* = 3,46, 8,5, 8,5 Hz), 4,77 (dd, 1H, *J* = 4,7, 8,8 Hz), 4,55 (s, 1H), 3,94-4,06 (m, 4H), 3,63 (t, 1H, *J* = 8,2 Hz), 3,54 (ddd, 1H, *J* = 3,4, 6,6, 9,7 Hz), 3,47 (m, 1H), 3,38 (m, 1H), 2,09 (ddd, 1H, *J* = 4,4, 7,8, 12,3 Hz), 1,91 (m, 2H), 0,91-1,83 (m, 27H), 1,07 (s, 3H), 0,94 (s, 3H); HRMS calculado para $C_{38}H_{58}N_5O_7$ $[M+H]^+$: 670,4180, experimental 670,4177,

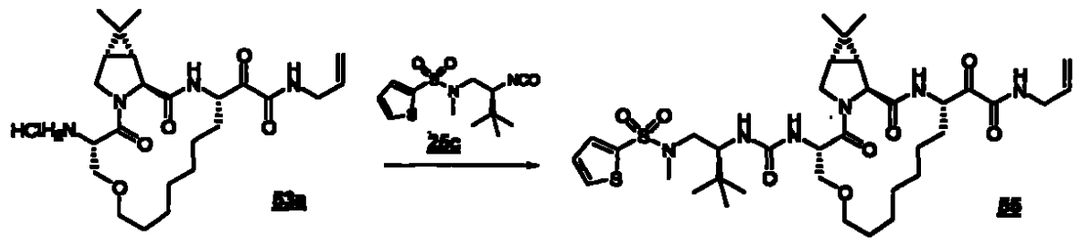
Ejemplo Preparativo 55: Preparación de:



655

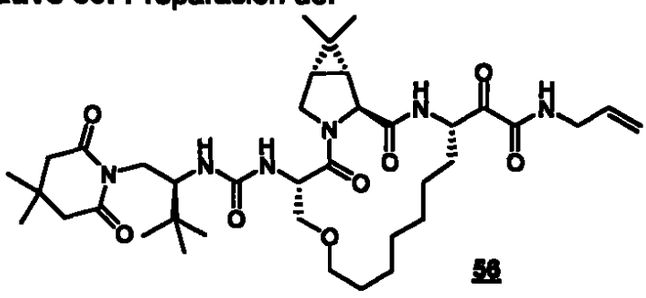
552

Paso A

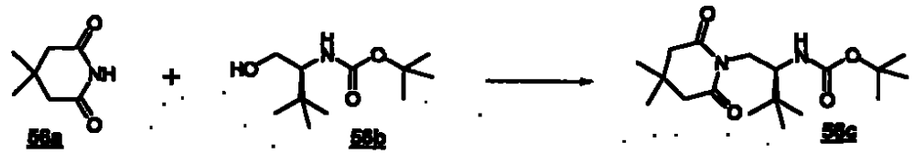


Se trató una solución de la sal de amina **53a** (17 mg) en 2 ml de diclorometano seco con bicarbonato de sodio sólido (3 eq, 8 mg) seguido del agregado del isocianato **25c** (2,5 eq, 0,45 ml de una solución 0,18M en tolueno). La mezcla heterogénea resultante se agitó a temperatura ambiente durante aproximadamente 3 h. La mezcla se diluyó con 50 ml de acetato de etilo y se lavó con HCl acuoso 1M (10 ml) y salmuera (10 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 2:8 a 1:1) para dar el producto **55** (8 mg, 30%) como un sólido blanco. HRMS calculado para $C_{38}H_{57}N_8O_8S_2$ $[M+H]^+$: 765,3679, experimental 765,3687.

Ejemplo Preparativo 56: Preparación de:



Paso A



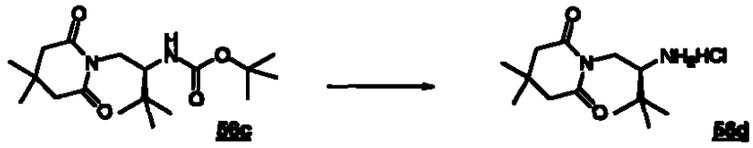
Se enfrió una solución de 4,4-dimetilglutarimida **56a** (Aldrich, 1,5 eq, 4,86 g) en 200 ml de THF seco a 0°C y se trató con trifenilfosfina (3 eq, 18,07 g) y S-Boc-ter-butilglicinol **56b** (Aldrich, 5 g).

556

553

Se agregó diisopropilazodicarboxilato (2,5 eq, 11,3 ml, d 1,027) gota a gota y la solución resultante se agitó a 0°C. Después de 10 min, la mezcla se tornó una suspensión y se continuó agitando hasta el día siguiente (0 a 25°C). La mezcla se concentró a presión reducida y el residuo se disolvió en 80 ml de éter. Se agregaron hexanos (100 ml) y los sólidos precipitados se filtraron. El filtrado se concentró a la mitad de su volumen y se agregaron hexanos (100 ml) nuevamente. Los sólidos se filtraron. El filtrado se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (acetato de etilo/hexanos; 2:8) para dar el producto **56c** (4,0 g, 51%) como un sólido blanco.

Paso B



56c **56d**

La amina protegida N-Boc **56c** (4,0 g) se disolvió en 200 ml de solución HCl 4M en dioxanos. La mezcla se agitó a temperatura ambiente y precipitó un sólido blanco después de 10 min. La mezcla también se agitó durante 2 h. Se eliminaron todos los volátiles a presión reducida para dar el producto **56d** (3,24 g, 98%) como un sólido blanco.

Paso C



56d **56e**

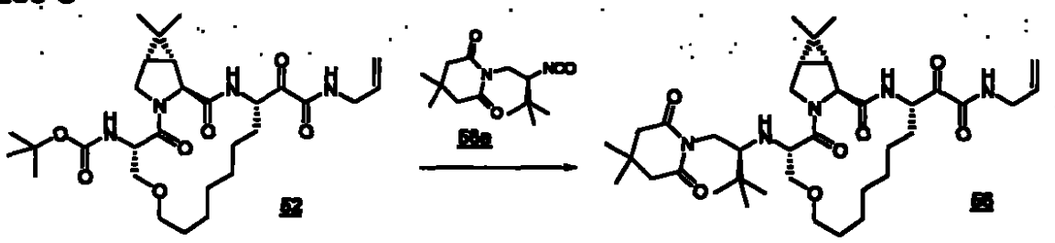
Se trató una solución del clorhidrato de amina **56d** (1,5 g) en 60 ml de diclorometano con 50 ml de solución acuosa saturada de bicarbonato de sodio y se agitó vigorosamente durante 10 min. a 0°C. La agitación se detuvo y se permitió que las capas se separaran. Se agregó fosgeno (15 ml de solución 20% en tolueno) a través de una aguja a la capa orgánica (capa inferior) en una porción. La mezcla se agitó vigorosamente inmediatamente después de la adición durante 10 min. a 0°C y se agitó además a temperatura ambiente durante 2,5 h.

857

559

La mezcla se diluyó con 100 ml de diclorometano y las capas se separaron. La capa orgánica se lavó con 40 ml de solución acuosa saturada de bicarbonato de sodio fría y se secó sobre sulfato de magnesio. La capa orgánica se filtró y se diluyó con 50 ml de tolueno. El producto **56e** (1,44 g, 98%) se mantuvo como una solución 0,216M en tolueno.

Paso C

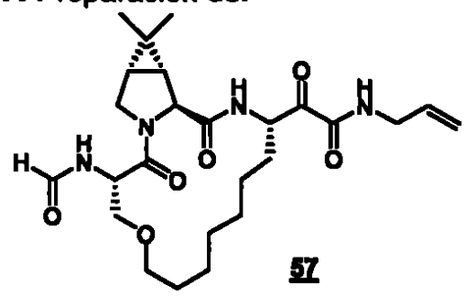


La N-Boc amina **52** (200 mg) se disolvió en 20 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregaron 10 gotas de solución acuosa saturada de bicarbonato de sodio. Después de 10 min, se agregó una solución del isocianato **56e** gota a gota (1,2 eq, 1,97 ml de una solución 0,216M en tolueno) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con diclorometano (70 ml) y se lavó con solución acuosa saturada de bicarbonato de sodio (20 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 15:85 a 55:45) para dar el producto **56** (172 mg, 66%) como un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$): δ 7,95 (d, 1H, J = 8,8 Hz), 7,59 (br s, 1H), 5,91 (br s, 1H), 5,84 (ddt, 1H, J = 5,8, 10,2, 16,8 Hz), 5,61 (ddd, 1H, J = 1,5, 8,7, 10,2 Hz), 5,21 (dd, 1H, J = 1,4, 17,5 Hz), 5,17 (dd, 1H, J = 1,4, 10,2 Hz), 5,13 (br s, 1H), 4,86 (br s, 1H), 4,52 (s,

555

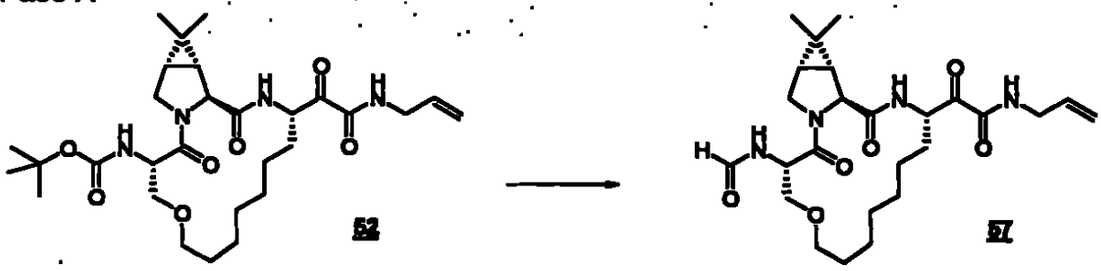
1H), 4,05 (d, 1H, J = 10,2 Hz), 3,80-3,99 (m, 6H), 3,50 (m, 2H), 3,27 (m, 2H), 2,51 (d, 2H, J = 16,8 Hz), 2,43 (d, 2H, J = 16,8 Hz), 1,88 (m, 1H), 1,77 (m, 1H), 0,84-1,58 (m, 12H), 1,05 (s, 6H), 0,97 (s, 3H), 0,92 (s, 9H), 0,81 (s, 3H); ^{13}C RMN (CDCl3, 125 MHz): δ 198,6, 172,8, 172,0, 171,2, 159,3, 157,8, 133,4, 117,7, 71,4, 70,8, 60,7, 57,0, 53,5, 48,5, 46,8, 42,2, 40,0, 34,9, 32,1, 30,9, 29,4, 28,7, 28,1, 27,7, 27,4, 26,9, 24,3, 19,3, 13,5 ppm; HRMS calculado para $C_{38}H_{61}N_6O_8$ $[M+H]^+$: 729,4551, experimental 729,4529.

Ejemplo Preparativo 57: Preparación de:



57

Paso A



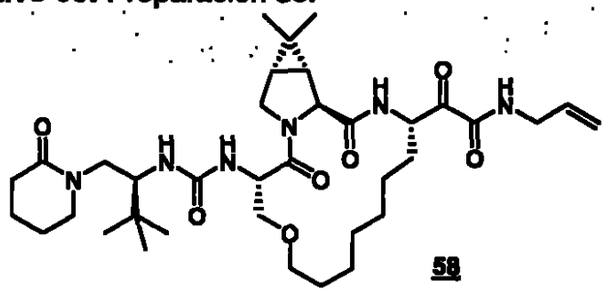
52 57

La amina protegida con N-Boc **52** (101 mg) se disolvió en 10 ml de ácido fórmico y se agitó a temperatura ambiente durante 1 h. Se eliminaron todos los volátiles en evaporador rotativo y el residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 2:8 a 6:4) para dar el producto formilado **57** (35 mg, 40%) como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$) δ 8,24 (s, 1H), 7,35 (d, 1H, J = 7,8 Hz), 7,07 (br s, 1H), 6,83 (d, 1H, J = 6,9 Hz), 5,89 (ddt, 1H, J = 5,6, 10,0, 17,0 Hz), 5,47 (m, 1H), 5,28 (dd, 1H, J = 1,2, 17,3 Hz), 5,25 (dd, 1H, J = 1,2, 10,4 Hz), 4,95 (ddd, 1H, J = 3,1, 5,9, 8,5 Hz), 4,51 (s, 1H), 3,99 (m, 2H), 3,92 (dd, 1H, J = 5,3, 11,0 Hz), 3,75 (d, 1H, J = 11,0 Hz), 3,74 (m, 1H), 3,70 (dd, 1H, J

559
556

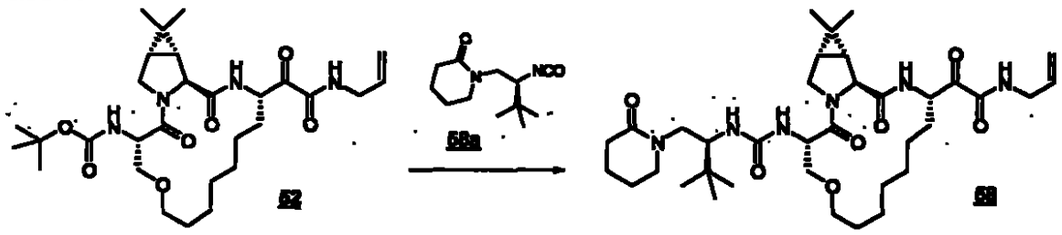
= 5,6, 9,1 Hz), 3,48 (m, 2H), 1,96 (m, 1H), 1,77 (d, 1H, J = 7,8 Hz), 1,76 (m, 1H), 1,27-1,63 (m, 11H), 1,10 (s, 3H), 0,92 (s, 3H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 196,8, 170,5, 169,4, 160,8, 159,3, 133,1, 117,9, 71,3, 70,0, 61,5, 54,4, 50,8, 48,2, 42,1, 32,0, 31,5, 29,4, 28,6, 27,8, 26,7, 26,6, 23,6, 23,5, 19,3, 14,5, 13,2 ppm; HRMS calculado para $C_{25}H_{39}N_4O_6$ $[M+H]^+$: 491,2870, experimental 491,2882.

Ejemplo Preparativo 58: Preparación de:



58

Paso A



52 58a 58

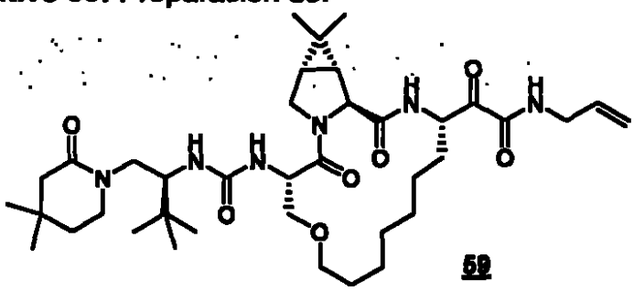
La amina protegida con N-Boc **52** (80 mg) se disolvió en 5 ml de solución de HCl 4M en dioxanos y se agitó a temperatura ambiente durante 45 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 3 ml de diclorometano seco y se trató con N-metilmorfolina (3 eq, 0,05 ml, d 0,920). Se agregó el isocianato **58a** en solución (2 eq, 3,8 ml de una solución 0,075M en tolueno). La mezcla de reacción se agitó a temperatura ambiente durante alrededor de 3 h. La mezcla se diluyó con acetato de etilo (50 ml) y se lavó con HCl acuoso 1M (10 ml), bicarbonato de sodio acuoso saturado (10 ml) y salmuera (10 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 3:7 a 7:3) para dar el producto **58** (16 mg, 16%) como un sólido

560

557

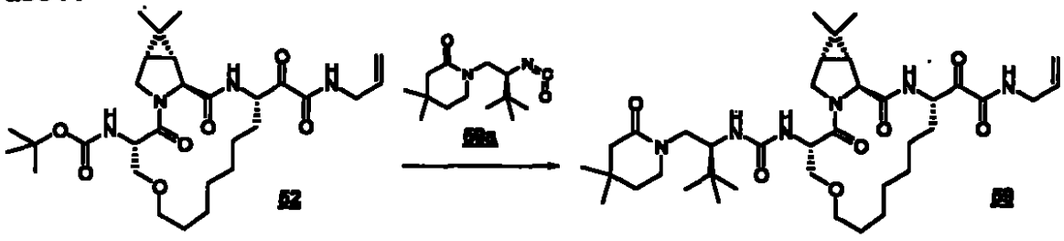
blanco. ^{1}H RMN (500 MHz, $CDCl_3$) δ 8,19-8,39 (br s, 1H), 8,05 (d, 1H, *J* = 8,5 Hz), 6,22 (br s, 1H), 5,91 (ddt, 1H, *J* = 5,6, 10,0, 17,0 Hz), 5,71 (dd, 1H, *J* = 9,4, 10,0 Hz), 5,33 (d, 1H, *J* = 9,4 Hz), 5,28 (m, 1H), 5,26 (dd, 1H, *J* = 1,2, 17,0 Hz), 5,20 (dd, 1H, *J* = 1,2, 10,4 Hz), 4,96 (ddd, 1H, *J* = 4,0, 9,4, 9,4 Hz), 4,60 (s, 1H), 4,32 (t, 1H, *J* = 12,6 Hz), 4,12 (d, 1H, *J* = 10,7 Hz), 3,86-4,07 (m, 4H), 3,49-3,63 (m, 3H), 3,38 (dd, 1H, *J* = 4,1, 7,9 Hz), 3,31 (m, 1H), 3,16 (m, 1H), 2,66 (dd, 1H, *J* = 2,8, 13,8 Hz), 2,39 (dt, 1H, *J* = 5,6, 17,3 Hz), 2,27 (dt, 1H, *J* = 6,6, 17,3 Hz), 1,89-2,04 (m, 2H), 1,71-1,87 (m, 4H), 0,88-1,64 (m, 11H), 1,03 (s, 3H), 0,93 (s, 9H), 0,90 (s, 3H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 196,2, 171,8, 171,3, 159,5, 158,2, 133,7, 117,3, 71,4, 70,8, 60,6, 55,7, 53,5, 51,0, 48,3, 48,1, 46,5, 42,2, 34,3, 32,7, 31,8, 31,0, 28,7, 27,8, 27,6, 27,0, 26,9, 24,6, 24,4, 23,5, 21,7, 19,2, 13,5 ppm; HRMS calculado para $C_{38}H_{59}N_6O_7$ $[M+H]^+$: 687,4445, experimental 687,4434.

Ejemplo Preparativo 59: Preparación de:



59

Paso A

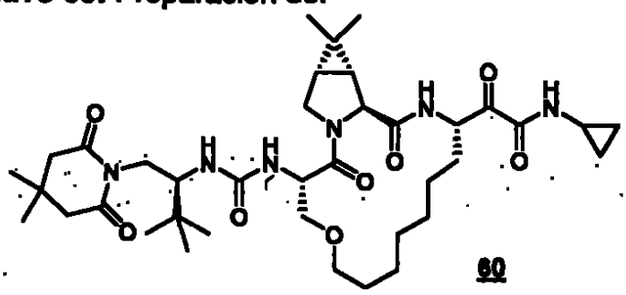


La N-Boc amina 52 (56 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó bajo alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregaron 15 gotas de solución

561
558

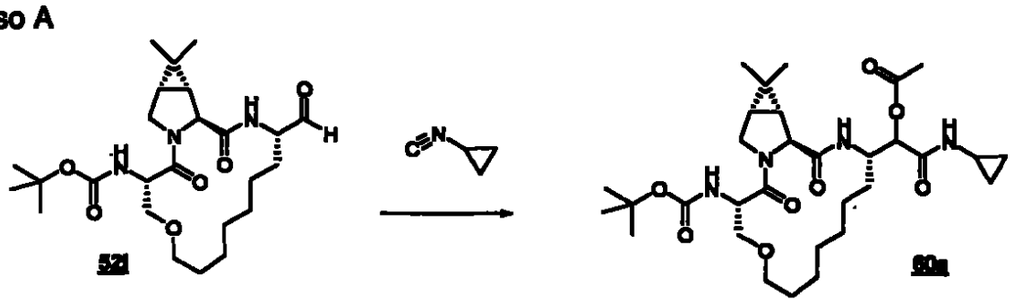
acuosa saturada de bicarbonato de sodio. Después de 10 min, se agregó una solución del isocianato **59a** gota a gota (1,0 eq) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con acetato de etilo (50 ml) y se lavó con HCl acuoso 1M (10 ml) y salmuera (10 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 2:8 a 6:4) para dar el producto **59** (35 mg, 50%) como un sólido blanco. HRMS calculado para $C_{38}H_{63}N_8O_7$ $[M+H]^+$: 715,4758, experimental 715,4739,

Ejemplo Preparativo 60: Preparación de:



60

Paso A

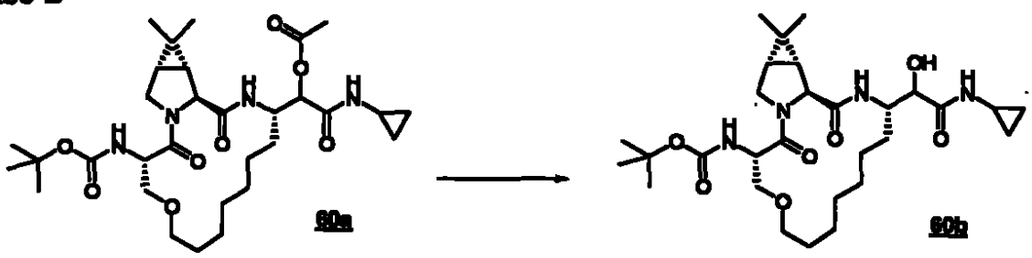


52I **60a**

Una solución del aldehído **52J** (405 mg) en 15 ml de diclorometano seco se trató con isocianuro de ciclopropilo (Oakwood Prod., 2 eq, 117 mg) y ácido acético (2 eq, 0,1 ml, d 1,049). La mezcla se agitó a temperatura ambiente hasta el día siguiente. Se eliminaron todos los volátiles a presión reducida y el residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 1:9 a 1:1) para dar el producto **60a** (500 mg, 98%) como un sólido blanco.

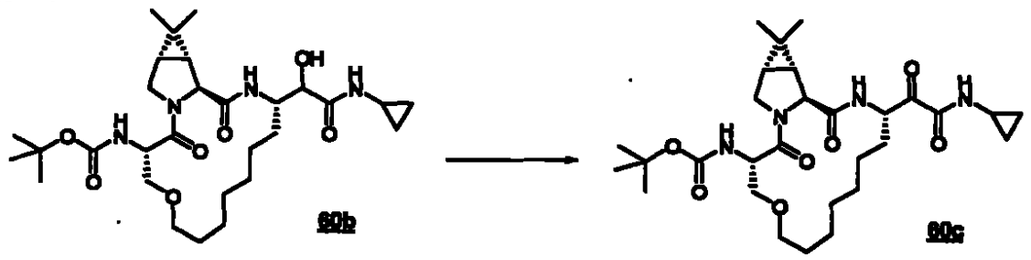
559

Paso B



Se trató una solución del acetato **60a** (500 mg) en 15 ml de una mezcla 1:1:1 de THF/MeOH/agua con monohidrato de hidróxido de litio (2,5 eq, 86 mg) y se agitó durante aprox. 30 min. hasta que el material de partida se había consumido según lo determinado mediante análisis por TLC (acetato de etilo/hexanos; 6:4). La mezcla de reacción se diluyó con 30 ml de solución acuosa saturada de bicarbonato de sodio y se extrajo con diclorometano (3 x 50 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron para dar el producto bruto **60b** (464 mg, 98%) como un semi-sólido incoloro que se usó sin otra purificación.

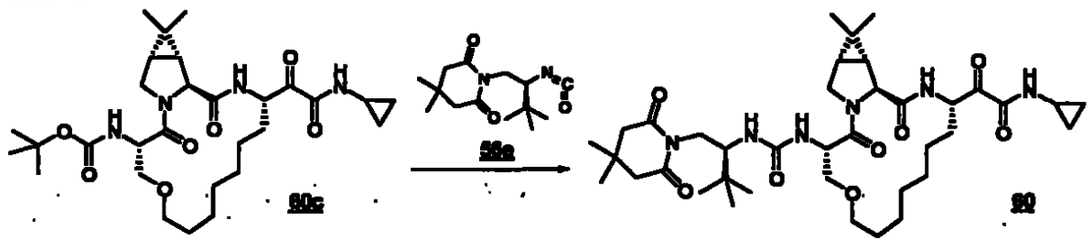
Paso C



Se trató una solución de la hidroxiamida **60b** (0,824 mmol) en 20 ml de diclorometano seco con periodinano de Dess-Martin (2,0 eq, 698 mg). La mezcla de reacción se agitó a temperatura ambiente durante 30 min. La mezcla se trató con solución de tiosulfato de sodio acuoso 1M (15 ml) y se agitó durante 5 min. También se agregó solución acuosa saturada de bicarbonato de sodio (20 ml) y la agitación se continuó durante otros 10 min. La mezcla se extrajo con diclorometano (3 x 50 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se sometió a

cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 5:95 a 35:65) para dar el producto **60c** (333 mg, 72%) como sólido blanco.

Paso D

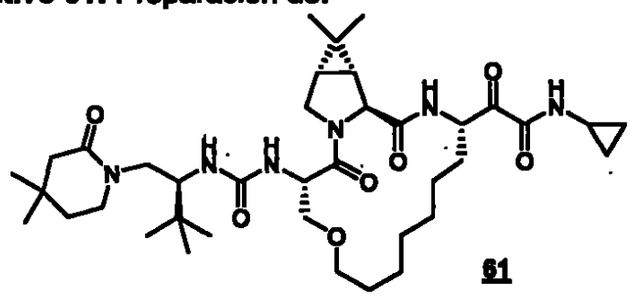


La N-Boc amina **60c** (70 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío hasta el día siguiente. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregaron 20 gotas de solución del bicarbonato de sodio acuoso saturado seguido de una solución del isocianato **56e** (1,3 eq, 0,7 ml de una solución 0,241M en tolueno) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con diclorometano (50 ml) y se lavó con solución acuosa saturada de bicarbonato de sodio (10 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 2:8 a 55:45) para dar el producto **60** (70 mg, 77%) como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$): δ 7,95 (br s, 1H), 7,56 (br s, 1H), 5,86 (br s, 1H), 5,65 (t, 1H, *J* = 8,8 Hz), 5,09 (br s, 1H), 4,91 (br s, 1H), 4,56 (s, 1H), 4,07 (d, 1H, *J* = 10,4 Hz), 3,98 (dd, 1H, *J* = 5,0, 10,7 Hz), 3,91 (m, 3H), 3,54 (m, 2H), 3,34 (m, 2H), 2,88 (ddd, 1H, *J* = 3,7, 7,5, 15,1 Hz), 2,56 (d, 2H, *J* = 16,7 Hz), 2,50 (d, 2H, *J* = 16,7 Hz), 1,94 (m, 1H), 0,87-1,76 (m, 15H), 1,11 (s, 6H), 1,03 (s, 3H), 0,97 (s, 9H), 0,86 (s, 3H), 0,70 (m, 2H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 198,0, 172,9, 172,0, 171,2, 160,8, 157,7, 71,5, 70,8, 60,7, 56,9, 53,4, 51,1,

564
561

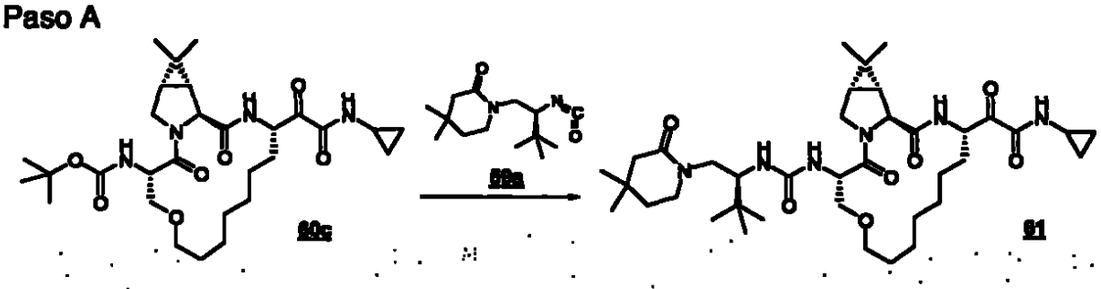
48,4, 46,8, 39,9, 34,9, 32,1, 30,8, 29,4, 28,7, 28,1, 27,7, 27,5, 26,9, 26,8, 24,4, 23,0, 19,2, 13,5, 6,8, 6,7 ppm. HRMS calculado para $C_{36}H_{61}N_6O_8$ $[M+H]^+$: 729,4551, experimental 729,4558.

Ejemplo Preparativo 61: Preparación de:



61

Paso A



60c 59a 61

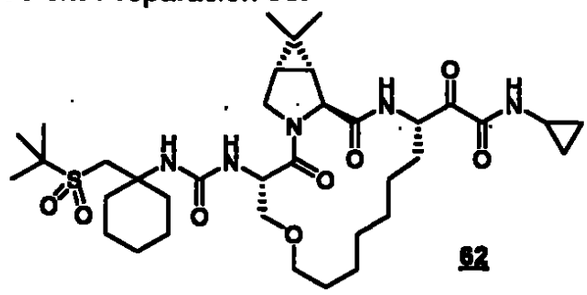
La N-Boc amina **60c** (56 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregaron 20 gotas de solución del bicarbonato de sodio acuoso saturado seguido de una solución del isocianato **59a** en tolueno (1,3 eq) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con diclorometano (60 ml) y se lavó con solución acuosa saturada de bicarbonato de sodio (20 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 2:8 a 6:4) para dar el producto **61** (52 mg, 73%) como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$): δ 8,30-8,53 (br s, 1H), 8,15 (d, 1H, J = 8,8 Hz), 6,13 (br s, 1H), 5,74

865

862

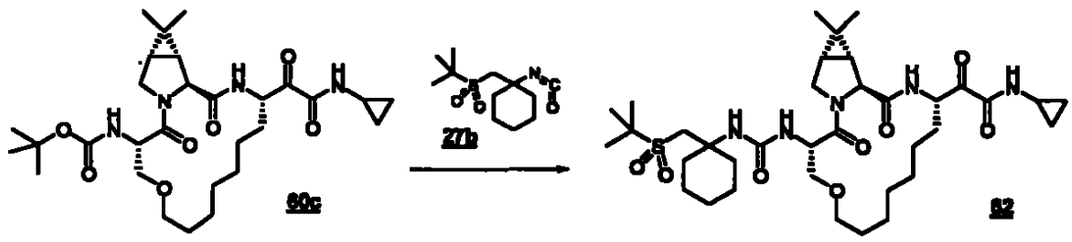
(dd, 1H, *J* = 8,8, 9,7 Hz), 5,38 (d, 1H, *J* = 9,1 Hz), 4,96 (br s, 1H), 4,59 (s, 1H), 4,35 (dd, 1H, *J* = 12,9, 12,9 Hz), 4,10 (d, 1H, *J* = 10,4 Hz), 4,01 (dd, 1H, *J* = 5,0, 10,4 Hz), 3,94 (m, 1H), 3,56 (m, 2H), 3,50 (dd, 1H, *J* = 8,5, 8,8 Hz), 3,31 (m, 2H), 3,17 (ddd, 1H, *J* = 5,6, 6,0, 12,3 Hz), 2,91 (ddd, 1H, *J* = 4,0, 7,8, 15,4 Hz), 2,67 (dd, 1H, *J* = 3,4, 13,5 Hz), 2,17 (d, 1H, *J* = 17,0 Hz), 2,10 (d, 1H, *J* = 17,0 Hz), 1,94 (m, 3H), 1,24-1,70 (m, 12H), 1,14 (m, 1H), 1,04 (s, 3H), 1,02 (s, 3H), 1,00 (s, 3H), 0,91 (s, 9H), 0,89 (s, 3H), 0,84 (m, 2H), 0,73 (m, 2H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 199,9, 171,9, 171,3, 171,0, 160,9, 158,0, 71,4, 70,9, 60,4, 55,4, 53,2, 48,2, 46,3, 45,0, 35,8, 34,6, 31,7, 30,3, 28,8, 28,7, 27,8, 27,7, 27,6, 27,1, 26,9, 26,8, 24,8, 24,7, 23,2, 19,1, 13,4, 6,4 ppm. HRMS calculado para $C_{38}H_{63}N_6O_7$ $[M+H]^+$: 715,4758, experimental 715,4768.

Ejemplo Preparativo 62: Preparación de:



62

Paso A

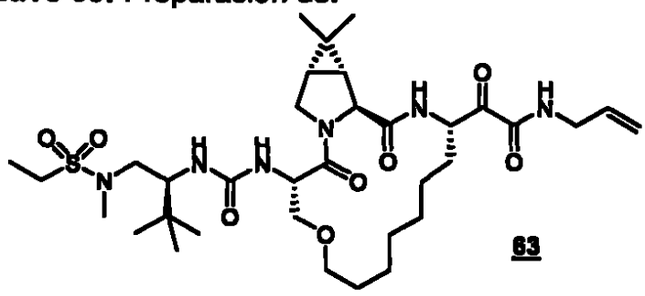


60c 27b 62

La N-Boc amina **60c** (60 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregaron 20 gotas de solución del bicarbonato de sodio acuoso saturado seguido de una solución del isocianato

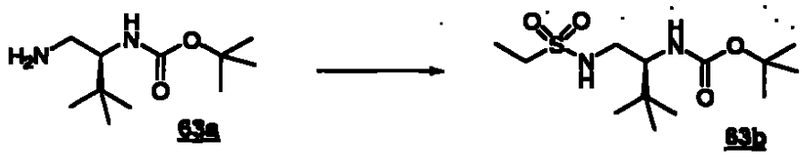
27b en tolueno (1,2 eq) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con diclorometano (60 ml) y se lavó con solución acuosa saturada de bicarbonato de sodio (20 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 2:8 a 6:4) para dar el producto **62** (65 mg, 85%) como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$): δ 7,84 (d, 1H, *J* = 8,2 Hz), 7,28 (br s, 1H), 5,73-6,02 (br s, 1H), 5,57 (ddd, 1H, *J* = 1,9, 8,2, 8,5 Hz), 5,22 (br s, 1H), 4,88 (dd, 1H, *J* = 3,4, 8,5 Hz), 4,51 (s, 1H), 4,01 (m, 3H), 3,62 (dd, 1H, *J* = 8,5, 8,5 Hz), 3,55 (ddd, 1H, *J* = 3,7, 6,3, 9,7 Hz), 3,48 (dd, 1H, *J* = 4,0, 8,1 Hz), 3,38 (m, 1H), 3,18 (d, 1H, *J* = 13,5 Hz), 2,86 (ddd, 1H, *J* = 3,8, 7,2, 14,8 Hz), 2,41 (d, 1H, *J* = 11,6 Hz), 2,24 (d, 1H, *J* = 11,6 Hz), 1,93 (m, 1H), 1,72-1,89 (m, 4H), 1,40 (s, 9H), 1,28-1,70 (m, 16H), 1,21 (m, 1H), 1,06 (s, 3H), 0,93 (s, 3H), 0,91 (m, 2H), 0,70 (m, 2H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 197,9, 172,0, 171,0, 160,9, 157,0, 70,8, 70,6, 61,0, 60,8, 54,9, 53,7, 51,1, 48,4, 36,2, 32,0, 30,5, 28,7, 27,9, 27,2, 26,9, 26,8, 25,9, 24,1, 23,8, 23,5, 23,0, 21,9, 21,8, 19,3, 13,4, 6,9, 6,8 ppm.

Ejemplo Preparativo 63: Preparación de:



63

Paso A



63a **63b**

567

564

Se enfrió una solución de la amina **63a** (2,0 g) en 100 ml de diclorometano seco a 0°C y se trató con piridina (3,0 eq, 2,24 ml, d 0,978) y cloruro de etansulfonilo (1,2 eq, 1,05 ml, d 1,357). La solución homogénea amarilla resultante se agitó hasta el día siguiente (temperatura de 0 a 25°C). La mezcla se diluyó con 200 ml de éter y se lavó con HCl acuoso 1M (100 ml) y salmuera (100 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: diclorometano a acetato de etilo/diclorometano 3:7) para dar el producto **63b** (850 mg, 30%) como un sólido blanco.

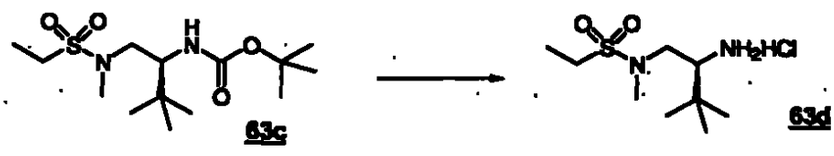
Paso B



63b **63c**

Se trató una solución de la etilsulfonamida **63b** (850 mg) en DMF seco (30 ml) con carbonato de cesio (3,0 eq, 2,74 g) y yodometano (3,0 eq, 0,51 ml, d 2,280). La mezcla de reacción se agitó durante aproximadamente 4 h. El análisis por TLC (acetona/hexanos; 2:8) demostró que todo el material de partida se había consumido. La mezcla se diluyó con acetato de etilo (300 ml) y se lavó con agua (3 x 50 ml) y salmuera (1 x 50 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida para dar el producto **63c** (860 mg, 97%) como un sólido blanco. No se realizó otra purificación para el producto.

Paso C



63c **63d**

La amina protegida con N-Boc **63c** (850 mg) se disolvió en 100 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura

568
565

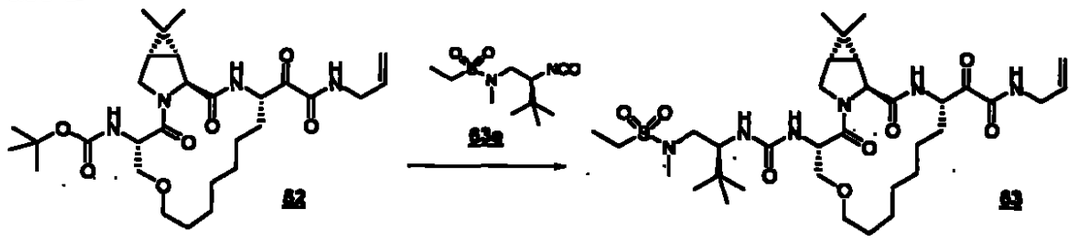
ambiente hasta que todo el material se había consumido según lo determinado mediante TLC (acetona/hexanos 2:8). Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío para dar el producto **63d** (680 mg, 98%).

Paso D



Se trató una solución del clorhidrato de amina **63d** (2,636 mmol) en 40 ml de diclorometano con 40 ml de solución acuosa saturada de bicarbonato de sodio y se agitó vigorosamente durante 10 min. a 0°C. Se detuvo la agitación y se permitió que las capas se separen. Se agregó fosgeno (10 ml de solución de 20% en tolueno) por medio de una aguja a la capa orgánica (capa inferior) en una porción. La mezcla se agitó vigorosamente inmediatamente después de la adición durante 10 min. a 0°C y también se agitó a temperatura ambiente durante 2,5 h. La mezcla se diluyó con 100 ml de diclorometano y las capas se separaron. La capa orgánica se lavó con 30 ml de solución acuosa saturada de bicarbonato de sodio frío y se secó sobre sulfato de magnesio. La capa orgánica se filtró y el filtrado se diluyó con 50 ml de tolueno. El producto **63e** (654 mg, 98%) se concentró y se mantuvo como una solución 0,131M en tolueno (la solución contiene alrededor de 2 ml de diclorometano).

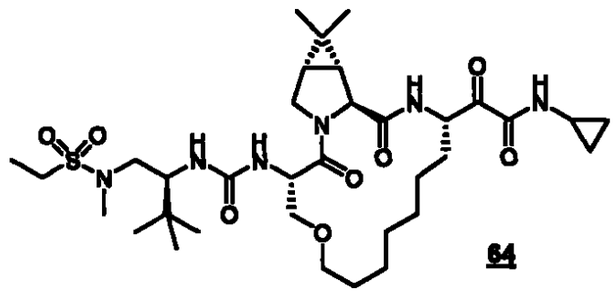
Paso E



La N-Boc amina **52** (60 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min.

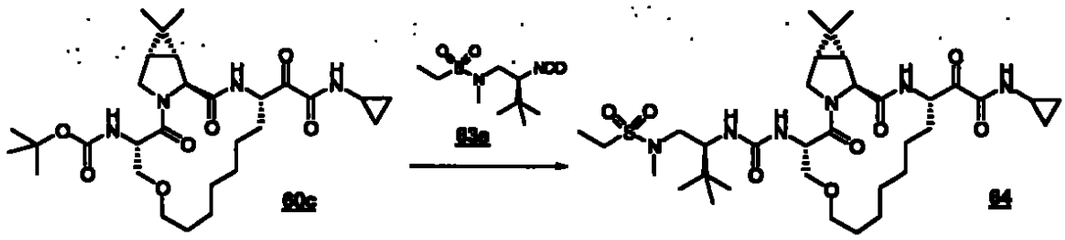
Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregaron 10 gotas de solución acuosa saturada de bicarbonato de sodio. Después de 10 min, se agregó una solución del isocianato **63e** gota a gota (1,2 eq, 0,97 ml de una solución 0,131M en tolueno) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con diclorometano (70 ml) y se lavó con solución acuosa saturada de bicarbonato de sodio (20 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 2:8 a 6:4) para dar el producto **63** (49 mg, 65%) como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$): δ 8,04 (d, 1H, *J* = 8,5 Hz), 7,52 (br s, 1H), 6,04 (br s, 1H), 5,89 (ddt, 1H, *J* = 5,6, 10,4, 17,0 Hz), 5,65 (dd, 1H, *J* = 8,8, 10,4 Hz), 5,26 (dd, 1H, *J* = 1,2, 17,0 Hz), 5,22 (dd, 1H, *J* = 1,2, 10,0 Hz), 5,17 (d, 1H, *J* = 10,0 Hz), 4,99 (br s, 1H), 4,61 (s, 1H), 4,19 (d, 1H, *J* = 10,7 Hz), 4,02 (m, 2H), 3,95 (m, 2H), 3,60 (dd, 1H, *J* = 8,1, 9,1 Hz), 3,54 (m, 1H), 3,49 (d, 1H, 1,9 Hz), 3,44 (m, 1H), 3,32 (m, 1H), 3,07 (m, 3H), 2,94 (s, 3H), 1,93 (m, 1H), 1,35 (t, 3H, *J* = 7,5 Hz), 1,27-1,62 (m, 15H), 1,16 (m, 1H), 1,03 (s, 3H), 0,92 (s, 9H), 0,91 (s, 3H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 198,6, 172,3, 171,3, 159,4, 158,0, 133,4, 117,6, 71,1, 70,6, 60,7, 54,7, 53,5, 51,0, 50,6, 48,4, 45,8, 42,2, 34,8, 34,5, 32,0, 30,9, 28,7, 27,8, 27,3, 27,0, 26,9, 24,3, 24,2, 19,2, 13,5, 8,6 ppm; HRMS calculado para $C_{34}H_{59}N_6O_6S$ $[M+H]^+$: 711,4115, experimental 711,4133.

Ejemplo Preparativo 64: Preparación de:



64

Paso A

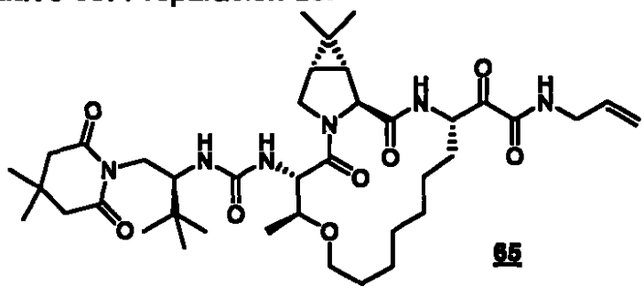


60c 63e 64

La N-Boc amina **60c** (60 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregaron 10 gotas de solución acuosa saturada de bicarbonato de sodio. Después de 10 min, se agregó una solución del isocianato **63e** gota a gota (1,2 eq, 0,97 ml de una solución 0,131M en tolueno) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con diclorometano (70 ml) y se lavó con solución acuosa saturada de bicarbonato de sodio (20 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 2:8 a 6:4) para dar el producto **64** (62 mg, 82%) como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$): δ 8,10 (br s, 1H), 7,47 (br s, 1H), 5,94-6,19 (br s, 1H), 5,65 (dd, 1H, *J* = 8,8, 10,7 Hz), 5,21 (d, 1H, *J* = 7,8 Hz), 5,00 (dd, 1H, *J* = 3,7, 9,4 Hz), 4,59 (s, 1H), 4,21 (d, 1H, *J* = 10,7 Hz), 4,02 (dd, 1H, *J* = 5,0, 10,7 Hz), 3,93 (dd, 1H, *J* = 9,1, 9,7 Hz), 3,55 (m, 2H), 3,48 (d, 1H, *J* = 12,6 Hz), 3,40 (m, 1H), 3,29 (m, 1H), 3,07 (q, 2H, *J*

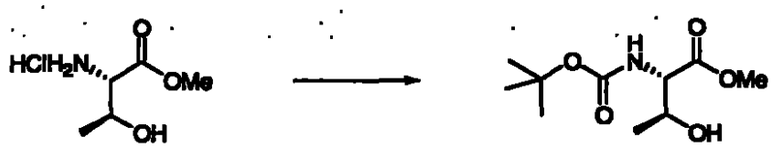
= 7,2 Hz), 3,06 (m, 1H), 2,93 (s, 3H), 2,85 (dddd, 1H, *J* = 1,8, 4,0, 7,5, 15,1 Hz), 1,91 (m, 1H), 1,34 (t, 3H, *J* = 7,2 Hz), 1,25-1,61 (m, 12H), 1,13 (m, 1H), 1,01 (s, 3H), 0,90 (s, 9H), 0,89 (s, 3H), 0,87 (m, 2H), 0,69 (m, 2H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 198,9, 172,3, 171,4, 160,9, 158,0, 71,0, 70,6, 60,6, 53,2, 50,9, 50,6, 48,4, 45,9, 34,8, 34,5, 32,1, 31,1, 28,7, 27,8, 27,5, 27,0, 26,9, 24,4, 23,0, 19,2, 13,6, 8,6, 6,7 ppm; HRMS calculado para $C_{34}H_{59}N_6O_6S$ $[M+1]^+$: 711,4115, experimental 711,4133.

Ejemplo Preparativo 65: Preparación de:



65

Paso A



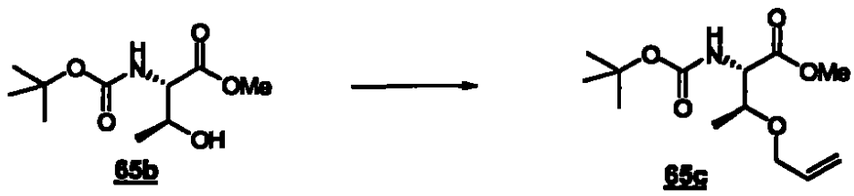
65a **65b**

Una solución del clorhidrato de (S)-alo-treonina-OMe **65a** (Chem-Impex, 5 g) en diclorometano seco (150 ml) se enfrió a 0°C y se trató con di-ter-butildicarbonato (1,1 eq, 7,0 g) en 50 ml de diclorometano seco. Se agregó N-metilmorfolina (2,5 eq, 8,1 ml, d 0,920) gota a gota y la mezcla se agitó durante 30 min. El baño de enfriamiento se retiró y la mezcla se agitó durante otras 3 h. La mezcla se concentró a un tercio de su volumen y luego se diluyó con acetato de etilo (300 ml) y se lavó con HCl acuoso 1M (100 ml), bicarbonato de sodio acuoso saturado (80 ml) y salmuera (80 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida para dar el producto **65b** (6,78 g, 98%) como un aceite incoloro.

Paso B

572

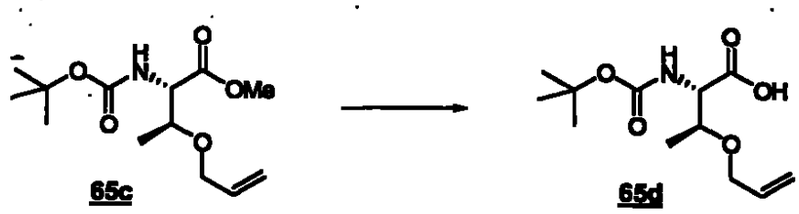
569



65b 65c

Se desgasificó una solución de Boc-L-alo-Thr-OMe **65b** (6,8 g) en 250 ml de THF seco (vacío/N2-saturación) y se trató con carbonato de allilmetilo (1,3 eq, 4,3 ml, d 1,022). Se agregó una cantidad catalítica de tetrakis(trifenilfosfina)-paladio (0,02 mol%, 673 mg). la mezcla levemente amarilla se desgasificó nuevamente y se calentó a 60ºC durante alrededor de 3 h hasta que el análisis por TLC (acetona/hexanos; 2:8) demostró que no quedaba material de partida (la mezcla de reacción se tornó marrón). La mezcla se concentró a presión reducida y el residuo se sometió a cromatografía sobre gel de sílice (acetato de etilo/hexanos; 1:9) para dar el producto **65c** (5,72 g, 72%) como un aceite incoloro.

Paso C

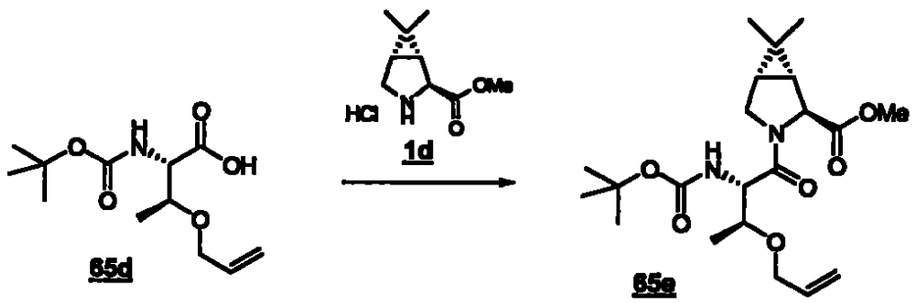


65c 65d

Se enfrió una solución del metil éster **65c** (1,45 g) en 250 ml de una mezcla 4:2:1 de THF/agua/MeOH a 0°C y se trató con monohidrato de hidróxido de litio (2,5 eq, 2,19 mg). El baño de enfriamiento se retiró después de 30 min. y la mezcla se agitó a temperatura ambiente durante otras 4 h hasta que todo el material se había consumido según lo determinado mediante análisis por TLC (acetona/hexanos 15:85). La mezcla de reacción se trató con 200 ml de HCl acuoso 1M (pH de mezcla = 1) y el producto se tomó en diclorometano (4 x 100 ml). Los extractos orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida para dar el producto. No se realizó otra purificación para el producto **65d** (5,42 g, 98%).

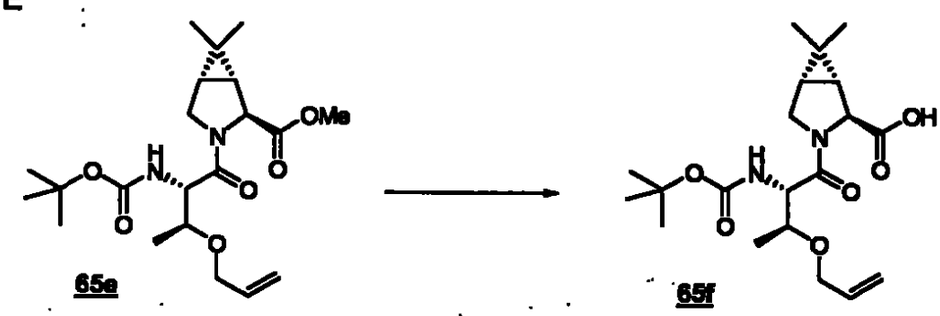
570

Paso D



Se agitó una solución del ácido **65d** (20,92 mmol) en 200 ml de diclorometano seco y 100 ml de DMF seco a 0ºC y se trató con HATU (1,4 eq, 11,16 g). La sal de amina **1d** (1,2 eq, 5,16 g) se agregó seguida de N-metilmorfolina (4 eq, 9,19 ml, d 0,920). La mezcla de reacción se agitó hasta el día siguiente. Se eliminaron todos los volátiles al vacío y el residuo se disolvió en 500 ml de acetato de etilo. La capa orgánica se lavó con agua (200 ml), HCl acuoso 1M (100 ml), solución acuosa saturada de bicarbonato de sodio (100 ml), y salmuera (100 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (acetato de etilo/hexanos; 2:8) para dar el producto **65e** (7,6 g, 88%) como un aceite incoloro junto con una pequeña cantidad de su producto diastereomérico correspondiente.

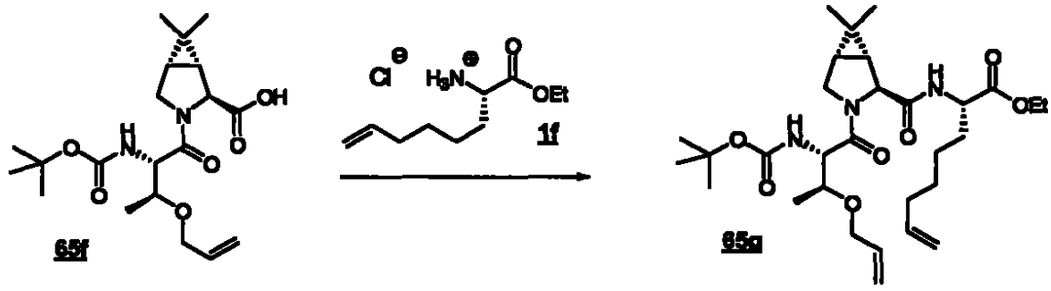
Paso E



Se enfrió una solución del metiléster **65e** (7,6 g) en 300 ml de una mezcla 2:1 de THF/agua a 0°C y se trató con monohidrato de hidróxido de litio (2,5 eq, 1,93 mg). El baño de enfriamiento se retiró después de 30 min. y la mezcla se

agitó a temperatura ambiente durante otras 4 h hasta que todo el material se había consumido según lo determinado mediante análisis por TLC (acetato de etilo/hexanos 25:75). La mezcla de reacción se trató con 200 ml de HCl acuoso 1M (pH de mezcla = 1) y el producto se tomó en diclorometano (4 x 100 ml). Los extractos orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida para dar el producto **65f** (6,86 g, 93%) como un sólido incoloro.

Paso F

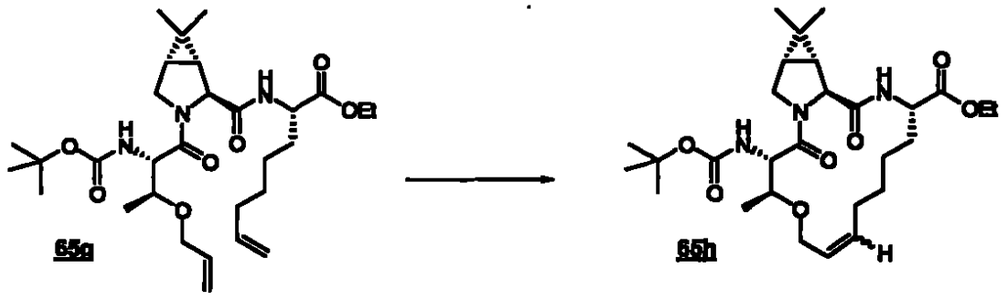


Se agitó una solución del ácido **65f** (6,86 g) en 100 ml de diclorometano seco y 100 ml de DMF seco a 0ºC y se trató con HATU (1,4 eq, 9,23 g). La sal de amina **1f** (1,1 eq, 4,21 g) se agregó en 100 ml de diclorometano seguido del agregado de N-metilmorfolina (4 eq, 7,6 ml, d 0,920). La mezcla de reacción se agitó a 0°C hasta el día siguiente. Se eliminaron todos los volátiles al vacío y el residuo se disolvió en 500 ml de acetato de etilo. La capa orgánica se lavó con agua (2 x 100 ml), HCl acuoso 1M (100 ml), solución acuosa saturada de bicarbonato de sodio (100 ml), y salmuera (100 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (acetato de etilo/hexanos; 3:7) para dar el producto **65g** (8,17 g, 84%) como un aceite incoloro.

Paso G

575

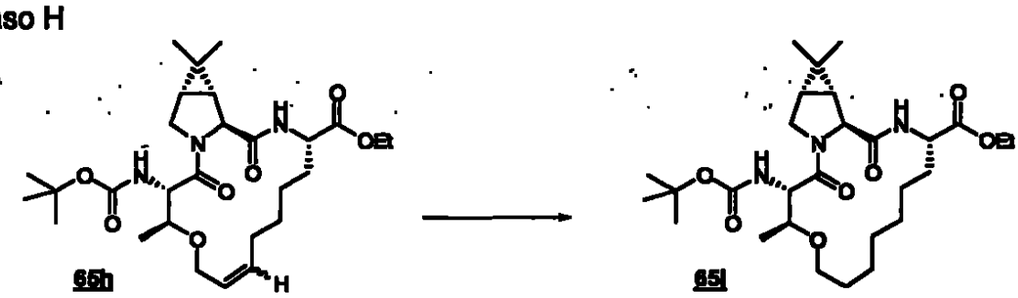
572



65g 65h

Se desgasificó una solución del dieno **65g** (8,17 g) en 1,5 l de tolueno durante 30 min. (burbujeo de argón) y se trató con catalizador de Grubb (0,2 eq, 2,38 g). La solución rosada se calentó a 60ºC durante 18 h (la solución se tornó oscura después de 10 min. de calentamiento). El solvente se eliminó a presión reducida y el residuo se sometió a cromatografía sobre gel de sílice (acetato de etilo/hexanos 3:7) para dar el producto alqueno **65h** (7,0 g, 90%) como una mezcla de isómeros E y Z (aproximadamente 4:1).

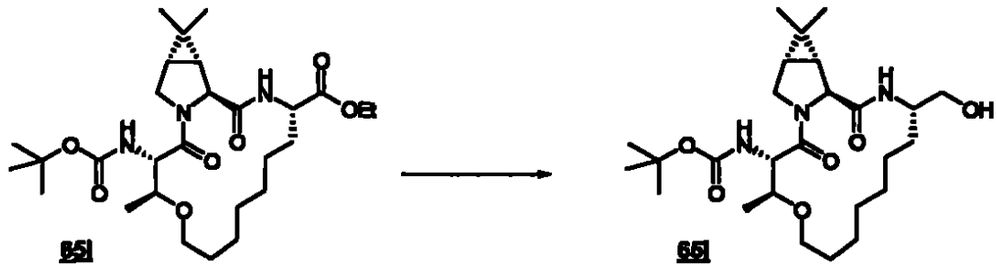
Paso H



65h 65i

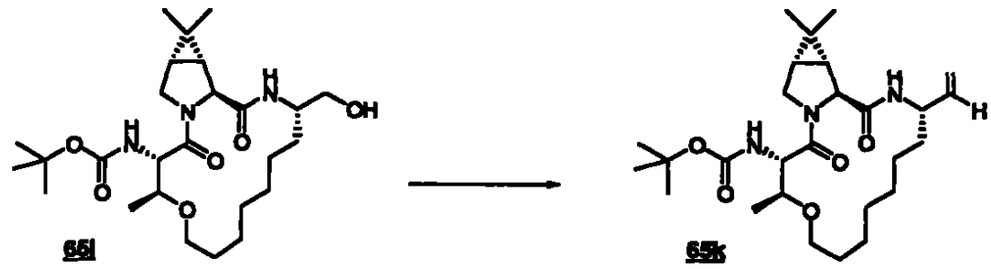
Se trató una solución del alqueno **65h** (7,0 g) en 300 ml de metanol con paladio sobre carbono (0,1 mol%, 1,37 g de Pd/C 10%). La mezcla se hidrogenó a 2,4 x 10^5 Pa (35 psi) hasta que todo el material de partida se había consumido (aproximadamente 3 h). La mezcla de reacción se diluyó con 300 ml de diclorometano y se filtró a través de un taco de Celite. El filtrado se concentró y el residuo se sometió a cromatografía sobre gel de sílice (acetato de etilo/hexanos; 3:7) para dar el producto **65i** (5,33 g, 76%) como un sólido blanco.

Paso I



Se trató una solución del etil éster **65I** (5,33 g) en 100 ml de THF seco con borohidruro de litio (2,1 eq, 10,4 ml de una solución de 2M en THF). La mezcla de reacción se agitó a temperatura ambiente y se monitoreó mediante TLC (acetona/hexanos; 3:7) para verificar la desaparición del material de partida. Después de 2 h, se agregó más solución de borohidruro de litio (1 eq) y la agitación se continuó durante 1h. El borohidruro de litio en exceso se desactivó mediante la adición de solución de cloruro de amonio acuoso saturado. La mezcla se dividió entre acetato de etilo (300 ml) y solución acuosa saturada de bicarbonato de sodio (100 ml). La capa acuosa se extrajo con acetato de etilo (2 x 100 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (acetona/hexanos; 3:7) para dar el producto **65J** (3,93 g, 80%) como un sólido blanco.

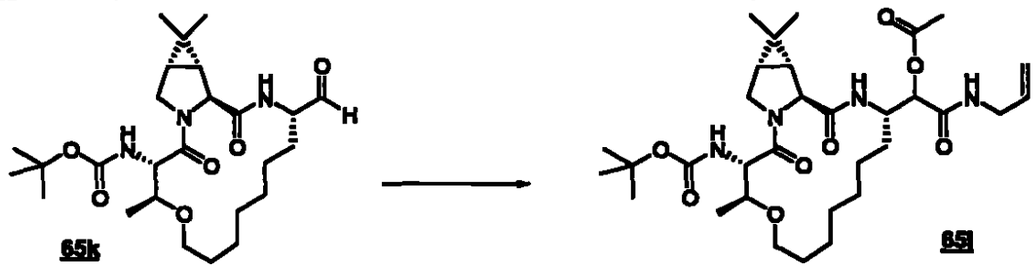
Paso J



Se trató una solución del alcohol **65J** (1,0 g) en 40 ml de diclorometano seco con periodinano de Dess-Martin (1,5 eq, 1,28 g). La mezcla de reacción se agitó a temperatura ambiente durante 3 h. La mezcla se trató con solución de tiosulfato de sodio acuoso 1M (10 ml) y se agitó durante 5 min. También se

agregó solución acuosa saturada de bicarbonato de sodio (30 ml) y la agitación se continuó durante otros 10 min. La mezcla se extrajo con diclorometano (3 x 80 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetato de etilo/hexanos; 4:6 a 8:2) para dar el producto 65k (750 mg, 75%) como un sólido incoloro.

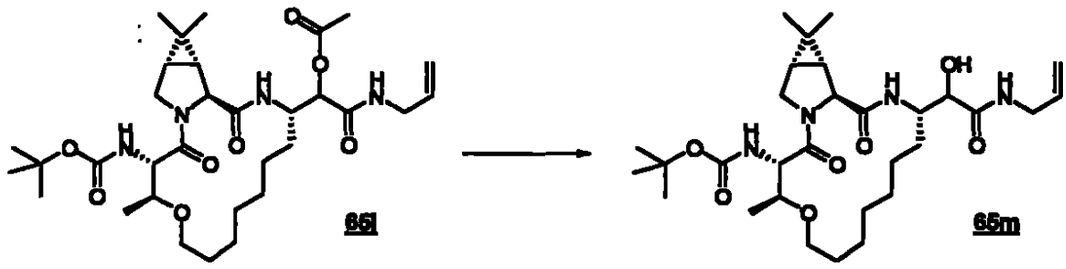
Paso K



65k 65l

Se trató una solución del aldehído 65k (750 mg) en 20 ml de diclorometano seco con isocianuro de alilo (2 eq, 0,26 ml, d 0,8) y ácido acético (2 eq, 0,17 ml, d 1,049). La mezcla se agitó a temperatura ambiente durante alrededor de 5 h. Se eliminaron todos los volátiles al vacío y el residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 1:9 a 45:55) para dar el producto 65l (700 mg, 74%) como un sólido blanco.

Paso L

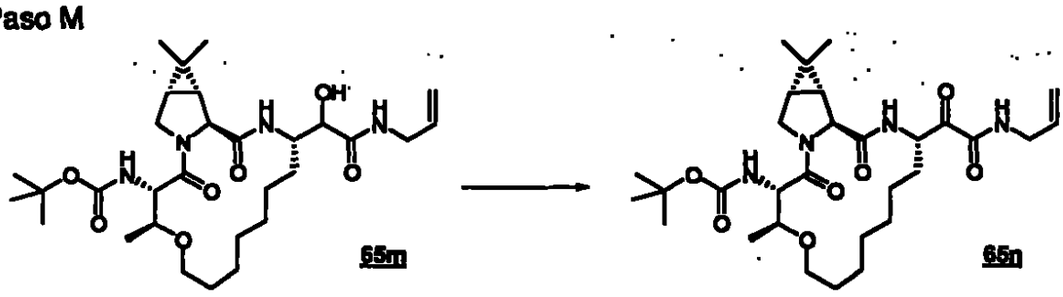


65l 65m

Se trató una solución del acetato 65l (700 mg) en 20 ml de una mezcla 2:1 de THF/agua con monohidrato de hidróxido de litio (2,5 eq, 118 mg) y se agitó durante aproximadamente 30 min. hasta que todo el material se había consumido según lo determinado mediante análisis por TLC (acetato de etilo/hexanos 8:2).

La mezcla de reacción se diluyó con 50 ml de solución acuosa saturada de bicarbonato de sodio y se extrajo con diclorometano (3 x 80 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron para dar el producto **65m** (651 mg, 98%) como un semi-sólido incoloro que se usó sin otra purificación.

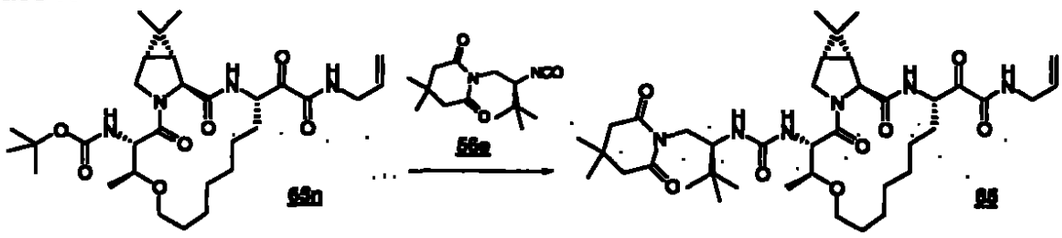
Paso M



65m **65n**

Se trató una solución de la hidroxiamida **65m** (1,127 mmol) en 25 ml de diclorometano seco con periodinano de Dess-Martin (2,0 eq, 956 mg). La mezcla de reacción se agitó a temperatura ambiente durante 30 min. La mezcla se trató con solución de tiosulfato de sodio acuoso 1M (20 ml) y se agitó durante 5 min. También se agregó solución acuosa saturada de bicarbonato de sodio (30 ml) y la agitación se continuó durante otros 10 min. La mezcla se extrajo con diclorometano (3 x 80 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 1:9 a 45:55) para dar el producto **65n** (585 mg, 90%) como sólido blanco.

Paso N

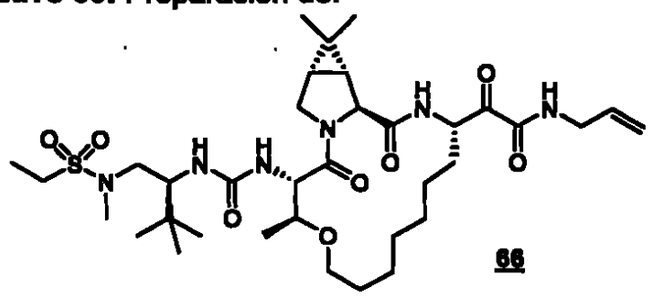


65n **56a** **66**

La N-Boc amina **65n** (60 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30

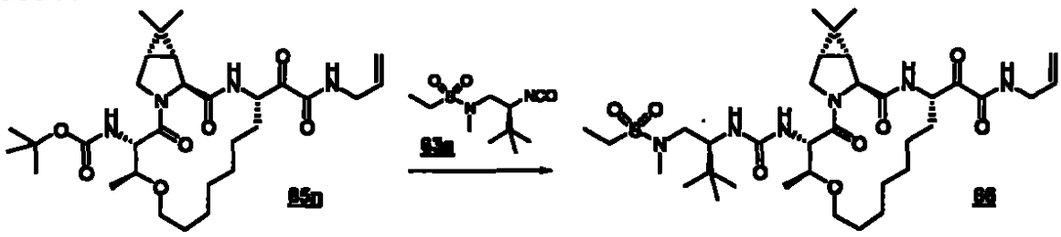
min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregaron 10 gotas de solución acuosa saturada de bicarbonato de sodio. Después de 10 min, se agregó una solución del isocianato **56e** gota a gota (1,2 eq, 0,57 ml de una solución de 0,216M en tolueno) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con diclorometano (70 ml) y se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 15:85 a 5:5) para dar el producto **65** (50 mg, 65%) como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$): δ 8,13 (br s, 1H), 7,42-7,82 (br s, 1H), 6,30 (br s, 1H), 5,90 (ddt, 1H, *J* = 5,6, 10,4, 17,0 Hz), 5,71 (br s, 1H), 5,38 (br s, 1H), 5,27 (dd, 1H, *J* = 1,2, 17,0 Hz), 5,23 (dd, 1H, *J* = 1,2, 10,4 Hz), 4,63 (dd, 1H, *J* = 7,8, 8,1 Hz), 4,50 (br s, 1H), 4,23 (d, 1H, *J* = 10,4 Hz), 4,05 (m, 2H), 3,98 (dd, 1H, *J* = 5,6, 5,9 Hz), 3,95 (d, 1H, *J* = 11,0 Hz), 3,88 (dd, 1H, *J* = 10,7, 10,8 Hz), 3,82 (q, 1H, *J* = 11,6 Hz), 3,71 (m, 1H), 3,62 (ddd, 1H, *J* = 5,0, 5,3, 9,4 Hz), 3,20 (m, 1H), 2,55 (d, 2H, *J* = 16,7 Hz), 2,47 (d, 2H, *J* = 16,7 Hz), 1,73-1,97 (m, 4H), 1,14 (d, 3H, *J* = 6,0 Hz), 1,10 (s, 6H), 1,00 (s, 3H), 0,99 (s, 9H), 0,83 (s, 3H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 198,0, 172,8, 171,5, 159,4, 157,8, 117,7, 75,5, 68,1, 60,8, 57,2, 55,9, 48,7, 46,8, 42,3, 35,2, 29,3, 28,7, 28,3, 27,8, 27,6, 26,9, 26,8, 24,7, 24,4, 19,4, 16,3, 13,6 ppm; HRMS calculado para $C_{39}H_{63}N_6O_8$ $[M+H]^+$: 743,4707, experimental 743,4717.

Ejemplo Preparativo 66: Preparación de:



66

Paso A

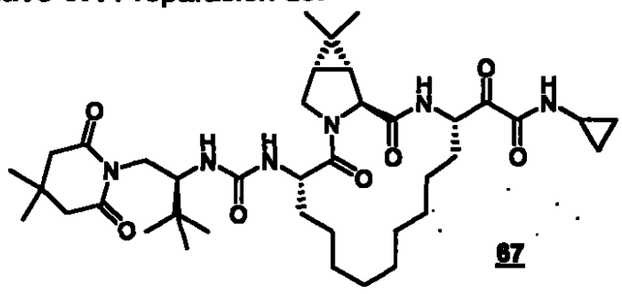


Se disolvió la N-Boc amina **65n** (60 mg) en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío hasta el día siguiente. La sal de amina resultante se disolvió en 5 ml de diclorometano y se enfrió a 0°C. Luego, se agregaron 10 gotas de solución acuosa saturada de bicarbonato de sodio. Después de 10 min, se agregó una solución del isocianato **63e** gota a gota (1,2 eq, 0,95 ml de una solución 0,131M en tolueno) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se diluyó con diclorometano (70 ml) y se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 2:8 a 6:4) para dar el producto **66** (55 mg, 73%) como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$): δ 8,20 (d, 1H, *J* = 6,6 Hz), 7,58-7,77 (br s, 1H), 6,13 (br s, 1H), 5,90 (ddt, 1H, *J* = 5,6, 10,0, 17,0 Hz), 5,76 (br s, 1H), 5,27 (dd, 1H, *J* = 1,2, 17,0 Hz), 5,22 (dd, 1H, *J* = 1,2, 10,0 Hz), 5,15 (d, 1H, *J* = 9,1 Hz), 4,69 (dd, 1H, *J* = 8,8, 8,8 Hz), 4,57 (s, 1H), 4,29 (d, 1H, *J* = 10,7 Hz), 3,91-4,09 (m, 4H), 3,61 (m, 2H), 3,47 (dd, 1H, *J* = 11,9, 13,5 Hz), 3,19 (m, 1H), 3,07 (m, 3H), 2,94 (s, 3H), 1,95 (m, 1H), 1,35 (t, 3H, *J* = 7,5 Hz), 1,27-1,69 (m, 12H), 1,22 (d, 3H, *J* = 6,3 Hz), 1,14 (m, 1H), 1,02 (s, 3H), 0,93 (s, 9H), 0,89 (s, 3H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 199,0, 172,8, 171,5, 159,3, 158,1, 133,5, 117,5, 75,8, 68,4, 60,7, 56,2, 50,4, 48,6, 45,6, 42,2, 34,7, 34,5, 32,0, 31,6, 28,6, 27,7, 27,0, 26,9, 26,7, 24,8, 24,6, 19,3, 16,2, 14,5, 13,5, 8,5

578

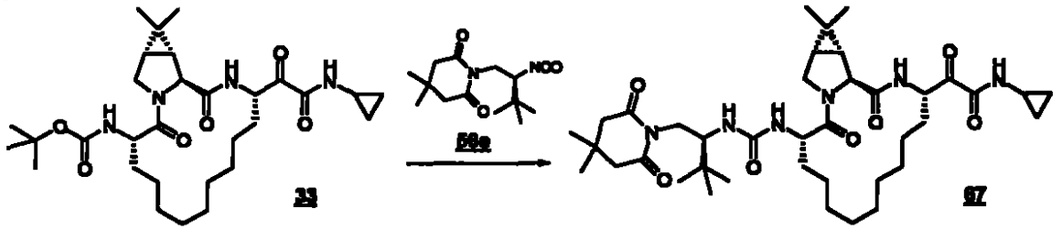
ppm; HRMS calculado para $C_{35}H_{61}N_6O_6S$ $[M+H]^+$: 725,4272, experimental 725,4285.

Ejemplo Preparativo 67: Preparación de:



67

Paso A

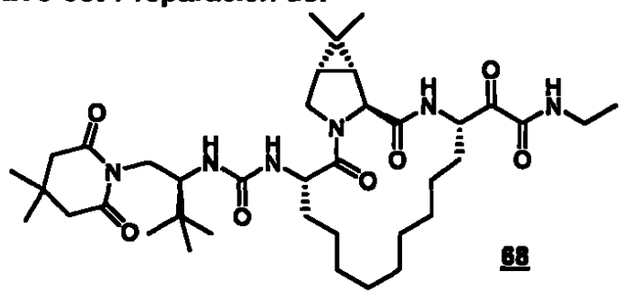


33 56e 67

La N-Boc amina **33** (60 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío hasta el día siguiente. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregó N-metilmorfolina (2 eq, 0,03 ml, d 0,920). Después de 10 min, se agregó una solución del isocianato **56e** gota a gota (1,5 eq, 0,8 ml de una solución 0,2M en tolueno) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con acetato de etilo (50 ml) y se lavó con HCl acuoso 1M (10 ml) y salmuera (10 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 2:8 a 1:1) para dar el producto **67** (50 mg, 64%) como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$): δ 8,14 (d, 1H, J = 6,9 Hz), 7,66-7,82 (br s, 1H), 6,11 (br s, 1H), 5,70 (br s, 1H), 5,32 (br s, 1H), 4,63 (br s, 1H), 4,60 (s, 1H), 4,19

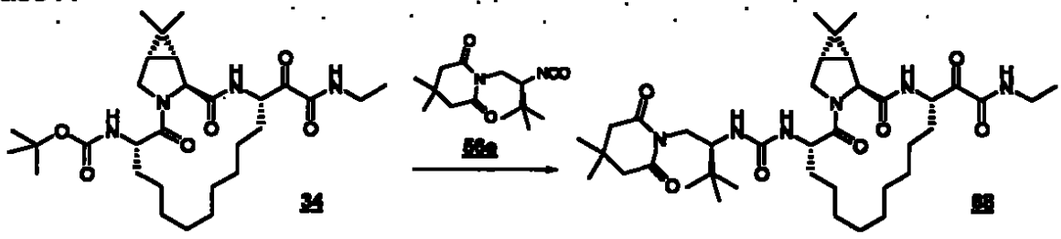
(d, 1H, J = 10,0 Hz), 3,96 (dd, 1H, J 5,0, 10,0 Hz), 3,91 (m, 3H), 2,91 (ddd, 1H, J = 3,7, 7,8, 15,1 Hz), 2,57 (d, 2H, J = 16,7 Hz), 2,50 (d, 2H, J = 16,7 Hz), 1,86 (m, 3H), 1,69 (m, 1H), 1,18-1,61 (m, 16H), 1,10 (s, 6H), 1,01 (s, 3H), 0,95 (s, 9H), 0,89 (m, 2H), 0,87 (s, 3H), 0,71 (m, 2H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 199,2, 173,5, 172,9, 171,9, 160,7, 158,0, 60,5, 56,6, 51,5, 48,5, 46,8, 39,9, 35,0, 34,2, 31,4, 29,4, 28,1, 27,8, 27,6, 27,4, 27,3, 27,0, 26,9, 26,5, 26,1, 23,4, 23,1, 19,4, 13,6, 6,8, 6,7 ppm.

Ejemplo Preparativo 68: Preparación de:



68

Paso A

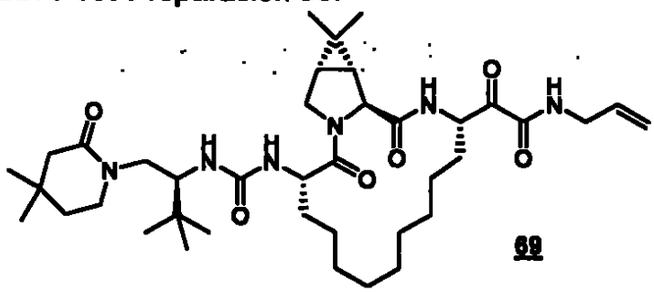


La N-Boc amina **34** (60 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregó N-metilmorfolina (2 eq, 0,02 ml, d 0,920). Después de 10 min, se agregó una solución del isocianato **56e** gota a gota (1,4 eq, 0,6 ml de una solución 0,241M en tolueno) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con acetato de etilo (50 ml) y se lavó con HCl 1M acuoso (10 ml) y salmuera (10 ml). La capa orgánica se

583
580

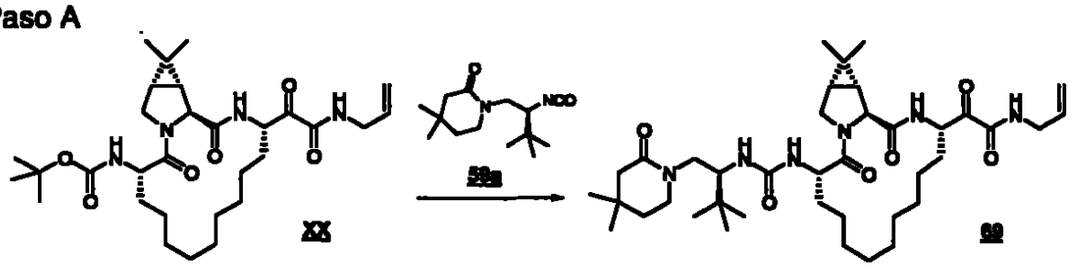
secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos 1:9 a 45:55) para dar el producto **68** (44 mg, 56%) como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$): δ 8,08 (br s, 1H), 7,52-7,77 (br s, 1H), 6,06 (br s, 1H), 5,70 (br s, 1H), 5,26 (br s, 1H), 4,63 (m, 2H), 4,20 (d, 1H, *J* = 10,0 Hz), 3,97 (dd, 1H, *J* = 5,0, 10,0 Hz), 3,92 (m, 3H), 3,43 (m, 2H), 2,57 (d, 2H, *J* = 16,7 Hz), 2,50 (d, 2H, *J* = 16,7 Hz), 1,90 (m, 1H), 1,74 (m, 2H), 1,27 (t, 3H, *J* = 7,2 Hz), 1,20-1,62 (m, 17H), 1,11 (s, 6H), 1,02 (s, 3H), 0,96 (s, 9H), 0,88 (s, 3H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 199,1, 173,5, 172,9, 171,8, 159,3, 157,9, 60,6, 56,6, 51,5, 48,5, 46,8, 40,0, 34,9, 34,8, 34,1, 32,8, 29,4, 28,1, 27,8, 27,5, 27,4, 27,3, 27,0, 26,9, 26,5, 26,0, 25,1, 23,4, 19,4, 14,8, 13,6 ppm; HRMS calculado para $C_{38}H_{63}N_6O_7$ $[M+H]^+$: 715,4758, experimental 715,4751.

Ejemplo Preparativo 69: Preparación de:



69

Paso A



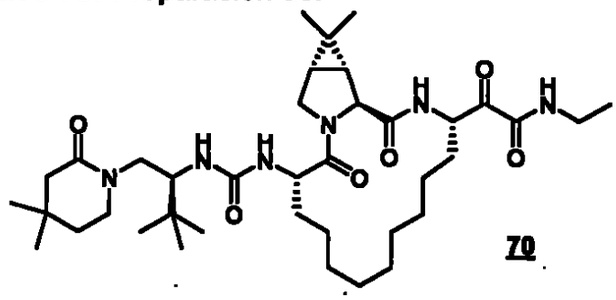
XX **69**

La N-Boc amina **XX** (93 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregó N-metilmorfolina (2 eq, 0,04 ml, d 0,920).

584
581

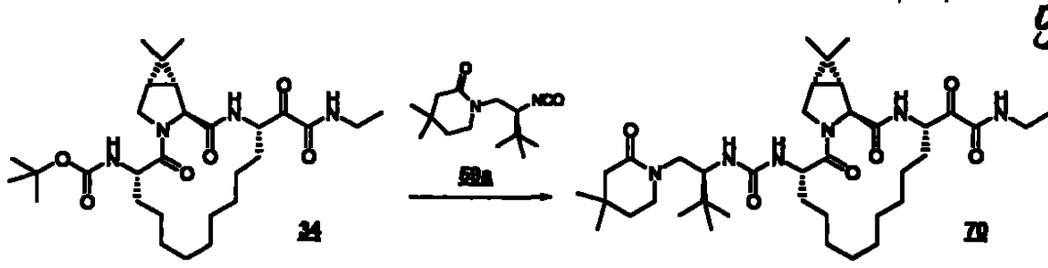
Después de 10 min, se agregó una solución del isocianato **59a** en tolueno gota a gota (1,2 eq) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con acetato de etilo (50 ml) y se lavó con HCl acuoso 1M (10 ml) y salmuera (10 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 1:9 a 45:55) para dar el producto **69** (45 mg, 38%) como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$): δ 8,26-8,67 (br s, 1H), 8,17 (br s, 1H), 6,19 (br s, 1H), 5,92 (ddt, 1H, *J* = 5,6, 10,4, 17,3 Hz), 5,74 (dd, 1H, *J* = 8,8, 9,1 Hz), 5,41 (br s, 1H), 5,26 (dd, 1H, *J* = 1,2, 17,3 Hz), 5,20 (d, 1H, *J* = 10,0 Hz), 4,67 (br s, 1H), 4,62 (s, 1H), 4,35 (dd, 1H, *J* = 1,9, 12,9 Hz), 4,20 (d, 1H, *J* = 9,8 Hz), 3,99 (m, 4H), 3,58 (ddd, 1H, *J* = 5,9, 6,9, 12,6 Hz), 3,18 (ddd, 1H, *J* = 5,9, 5,9, 11,9 Hz), 2,69 (d, 1H, *J* = 10,7 Hz), 2,18 (d, 1H, *J* = 17,0 Hz), 2,12 (d, 1H, *J* = 17,0 Hz), 1,96 (m, 1H), 1,18-1,89 (m, 20H), 1,12 (m, 1H), 1,04 (s, 3H), 1,03 (s, 3H), 1,00 (s, 3H), 0,92 (s, 9H), 0,91 (s, 3H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 199,3, 173,3, 171,8, 171,1, 159,4, 158,2, 133,7, 117,3, 60,4, 55,3, 51,5, 48,3, 46,3, 45,0, 42,3, 35,8, 34,6, 34,0, 31,2, 30,3, 28,6, 27,8, 27,7, 27,6, 27,3, 27,2, 27,0, 26,3, 25,9, 25,4, 23,2, 19,3, 13,5 ppm.

Ejemplo Preparativo 70: Preparación de:



70

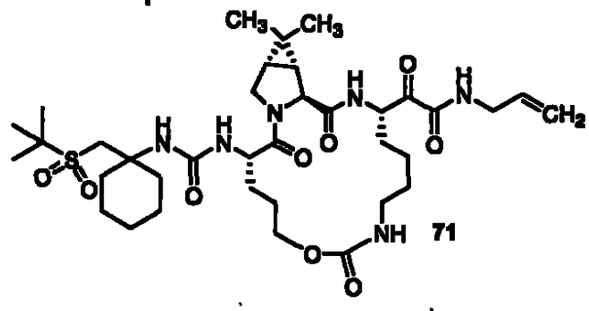
Paso A



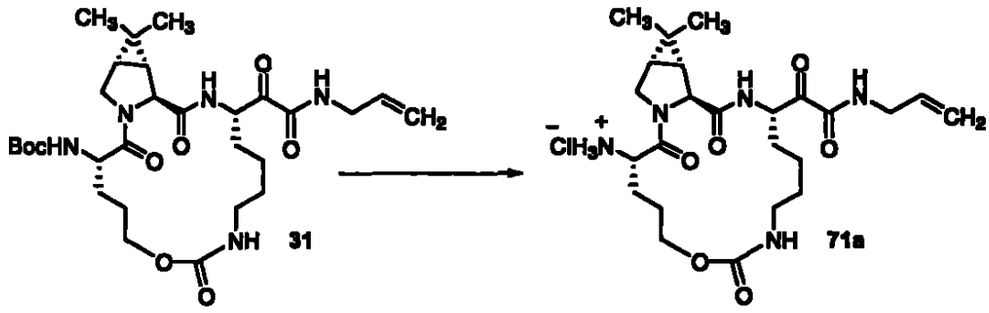
La N-Boc amina **34** (73 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregó N-metilmorfolina (2 eq, 0,03 ml, d 0,920). Después de 10 min, se agregó una solución del isocianato **59a** en tolueno gota a gota (1,2 eq) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con acetato de etilo (50 ml) y se lavó con HCl acuoso 1M (10 ml) y salmuera (10 ml). La capa orgánica se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 1:9 a 45:55) para dar el producto **70** (63 mg, 69%) como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$): δ 8,20-8,43 (br s, 1H), 8,17 (br s, 1H), 6,20 (br s, 1H), 5,75 (dd, 1H, *J* = 8,2, 9,4 Hz), 5,41 (br s, 1H), 4,66 (d, 1H, *J* = 9,1 Hz), 4,63 (s, 1H), 4,36 (dd, 1H, *J* = 12,6, 13,2 Hz), 4,18 (d, 1H, *J* = 10,4 Hz), 3,96 (m, 2H), 3,57 (m, 1H), 3,41 (m, 2H), 3,18 (ddd, 1H, *J* = 5,9, 11,9 Hz), 2,69 (d, 1H, *J* = 13,2 Hz), 2,19 (d, 1H, *J* = 17,0 Hz), 2,14 (d, 1H, 17,0 HZ), 1,76-1,99 (m, 4H), 1,25 (t, 3H, *J* = 7,2 Hz), 1,18-1,75 (m, 17H), 1,12 (m, 1H), 1,04 (s, 3H), 1,02 (s, 3H), 1,01 (s, 3H), 0,92 (s, 9H), 0,91 (s, 3H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 199,9, 173,3, 171,8, 171,1, 159,4, 158,2, 60,4, 55,2, 53,5, 51,5, 48,3, 46,3, 35,8, 34,8, 34,6, 31,3, 30,3, 28,7, 27,8, 27,7, 27,6, 27,3, 27,0, 26,4, 26,0, 23,2, 19,3, 14,8, 13,5 ppm; HRMS calculado para $C_{38}H_{65}N_8O_6$ $[M+H]^+$: 701,4966, experimental 701,4960.

583

Ejemplo Preparativo 71: Preparación de:

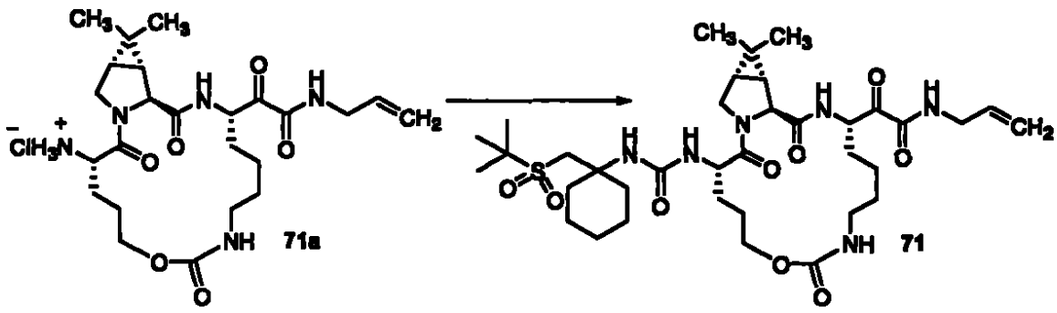


Paso A:



Se agitó una solución de **31** (100 mg, 0,169 mmol) en HCl 4 N en dioxano (5 ml) a temperatura ambiente durante 1 hora. Se eliminó el solvente hasta sequedad para dar **71a** (120 mg), que se usó sin otra purificación

Paso B:

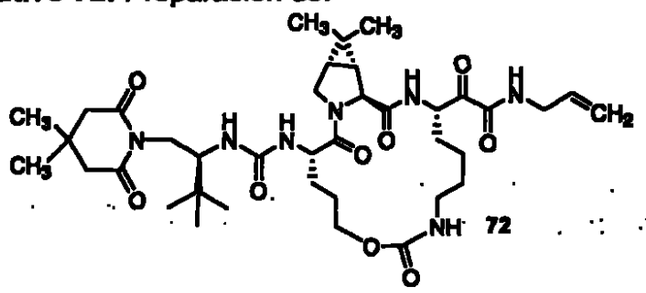


Se trató una solución de **71a** (89 mg, 0,169 mmol) en CH_2Cl_2 (10 ml) con el isocianato **27b** (3 equiv), $NaHCO_3$ saturado (3 ml) y se agitó vigorosamente durante 2 horas. Se dejó reposar la solución a 5°C durante 12 horas. La capa de CH_2Cl_2 se separó, se lavó con agua, salmuera y se filtró a través de Na_2SO_4. Se eliminó el solvente hasta sequedad y el residuo se purificó sobre columna de gel de sílice (acetona/hexanos 40% a 60%) para dar **71** (73 mg). MS (ES) *m/z*

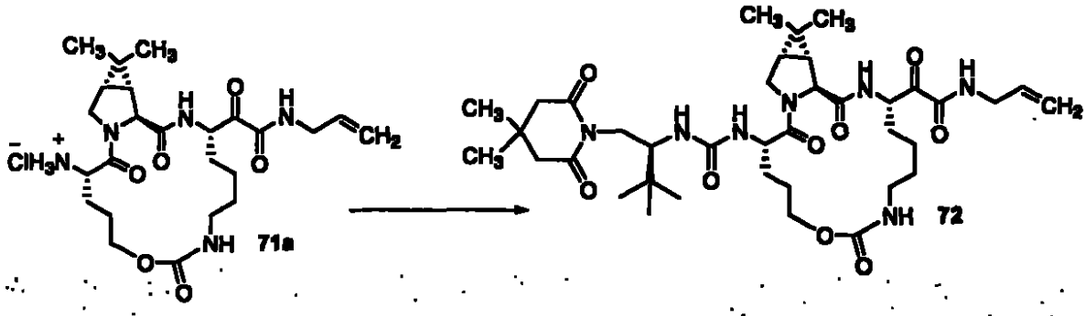
587
589

intensidad relativa 773 [(M+Na)$^+$, 20]; 751 [(M+1)$^+$, 100]. Calculado para $C_{36}H_{59}N_6O_9S$ [M+1]$^+$: 751,4064; Experimental 751,4075.

Ejemplo Preparativo 72: Preparación de:

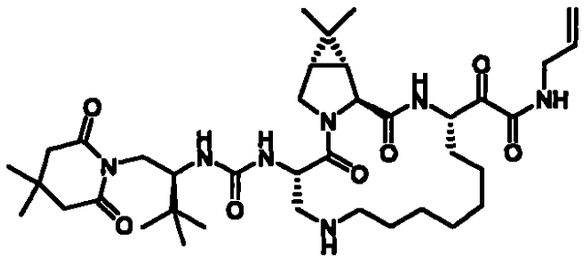


Paso A:



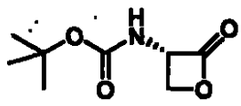
Se trató una solución de **71a** (89 mg, 0,169 mmol) en CH_2Cl_2 (10 ml) con el isocianato **51c** (1,5 equiv), $NaHCO_3$ saturado (4 ml) y se agitó vigorosamente durante 30 minutos. Se dejó reposar la solución a 5°C durante 12 horas. Se separó la capa de CH_2Cl_2, se lavó con agua, salmuera y se filtró a través de Na_2SO_4. Se eliminó el solvente hasta sequedad y el residuo se purificó sobre columna de gel de sílice (acetona/hexanos 40% a 50%) para dar **72** (95 mg). MS (ES) *m/z* intensidad relativa 790 [(M+CH_3OH+1)$^+$, 40]; 758 [(M+1)$^+$, 100]. Calculado para $C_{38}H_{59}N_7O_9$ [M+1]$^+$: 758,4453; Experimental 758,4449.

Ejemplo Preparativo 73: Preparación de:



73

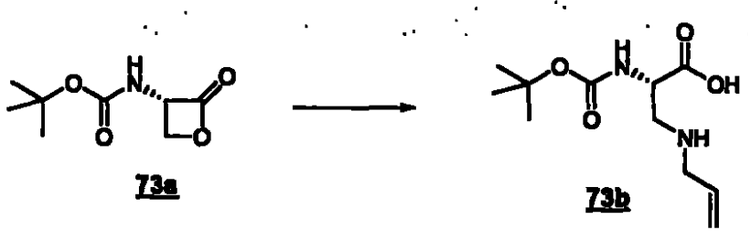
Paso A



73a

La N-(ter-butoxicarbonil)-L-serin-beta-lactona **73a** se preparará de acuerdo con el procedimiento descripto por Vederas y colaboradores (Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105-7109), comenzando por N-Boc-L-Ser-OH comercial.

Paso B

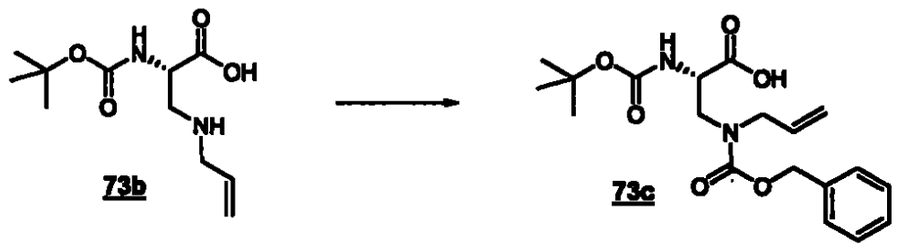


73a 73b

Se agregará una solución de N-(ter-butoxilcarbonil)-L-serin-beta-lactona **73a** (1 mmol) en 20 ml de acetonitrilo seco gota a gota a temperatura ambiente durante 1 h, a una solución agitada de alilamina (25 mmol) en 30 ml de acetonitrilo seco. Después de 2 h, la solución se concentrará a presión reducida. El residuo se suspenderá con acetonitrilo y el producto ácido **73b** se recuperará mediante filtración.

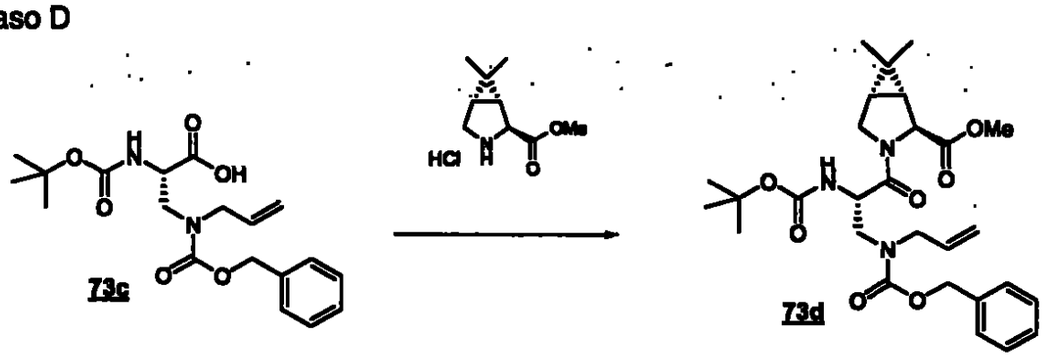
Paso C

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586



Se tratará una solución del ácido 2 (1 mmol) en solución acuosa saturada de bicarbonato de sodio (4 ml) y agua (1 ml) a temperatura ambiente con cloroformiato de bencilo (1,12 mmol) en acetona (1 ml). La mezcla de reacción se agitará durante 2 h. La mezcla se dividirá entre éter (20 ml) y agua (20 ml). La capa acuosa se enfriará en un baño de hielo-agua, se llevará a pH 2 usando HCl acuoso 5% y se extraerá con diclorometano (3 x 30 ml). Las capas orgánicas combinadas se secarán sobre sulfato de magnesio, se filtrarán y se concentrarán para dar el producto ácido **73c**.

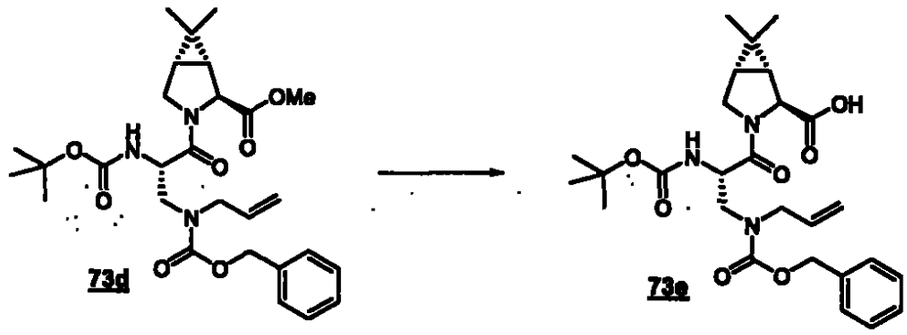
Paso D



Una solución del ácido **73c** (1 mmol) en 10 ml de diclorometano seco y 10 ml de DMF seco se agitará a 0ºC y se tratará con HATU (1,4 mmol). Sucesivamente se agregará el clorhidrato de amina (1,3 mmol) y N-metilmorfolina (4 mmol). La mezcla de reacción se calentará gradualmente hasta temperatura ambiente y se agitará hasta el día siguiente. Se eliminarán todos los volátiles al vacío y el residuo se tomará en 100 ml de acetato de etilo. La capa orgánica se lavará con agua (20 ml), HCl acuoso 1N (20 ml), solución acuosa saturada de bicarbonato de sodio (20 ml), y salmuera (20 ml). La capa orgánica se secará

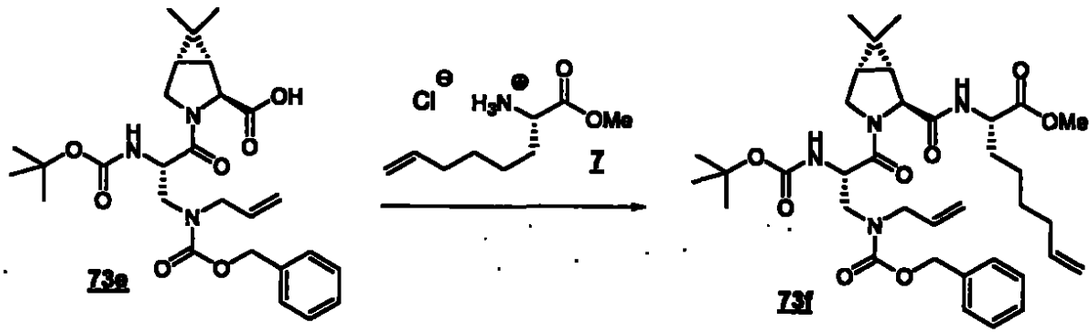
sobre sulfato de magnesio, se filtrará y se concentrará a presión reducida. El producto **73d** se purificará mediante cromatografía en columna sobre gel de sílice.

Paso E



Una solución del metil éster **73d** (1 mmol) en 15 ml de una mezcla de THF/MeOH/H2O (1:1:1) se tratará con monohidrato de hidróxido de litio (2,5 mmol) a 0ºC. El baño de enfriamiento se retirará y la mezcla de reacción se agitará a temperatura ambiente y se monitoreará mediante TLC (acetona/hexanos; 2:8). Después de 1 h, se agregarán 10 ml de HCl acuoso 1N y todos lo volátiles se eliminarán a presión reducida. El residuo se dividirá entre 30 ml de HCl acuoso 1N y 100 ml de diclorometano. La capa acuosa se extraerá con diclorometano (2 x 50 ml). Las capas orgánicas combinadas se secarán sobre sulfato de magnesio, se filtrarán y se concentrarán a presión reducida para dar el producto ácido **73e**.

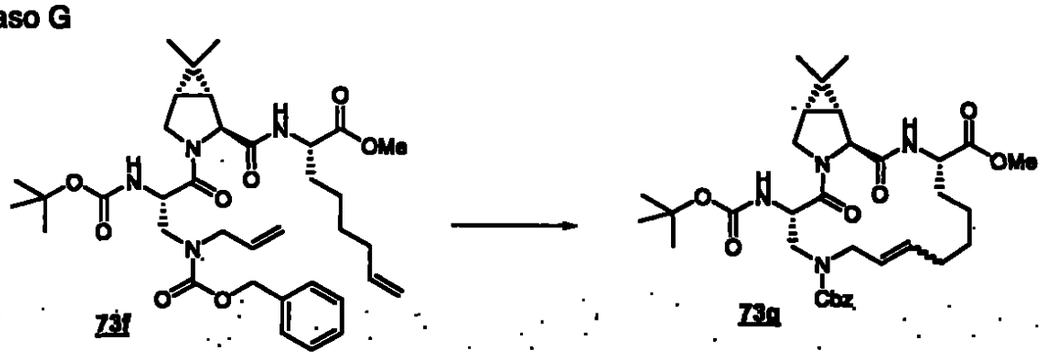
Paso F



Una solución del ácido **73e** (1 mmol) en 10 ml de diclorometano seco y 10 ml de DMF seco se agitarán a 0ºC y se tratarán con HATU (1,4 eq, 1,15 g). El

clorhidrato de amina 7 (1,2 mmol) se agregará en 10 ml de diclorometano seguido de N-metilmorfolina (4 mmol). La mezcla de reacción se agitará hasta el día siguiente (temperatura de 0 a 25°C). Todos los volátiles se eliminarán al vacío y el residuo se disolverá en 100 ml de acetato de etilo. La capa se lavará con agua (20 ml), HCl acuoso 1N (20 ml), solución acuosa saturada de bicarbonato de sodio (20 ml) y salmuera (20 ml). La capa orgánica se secará sobre sulfato de magnesio, se filtrará y se concentrará a presión reducida. El producto 73f se purificará mediante cromatografía en columna de gel de sílice.

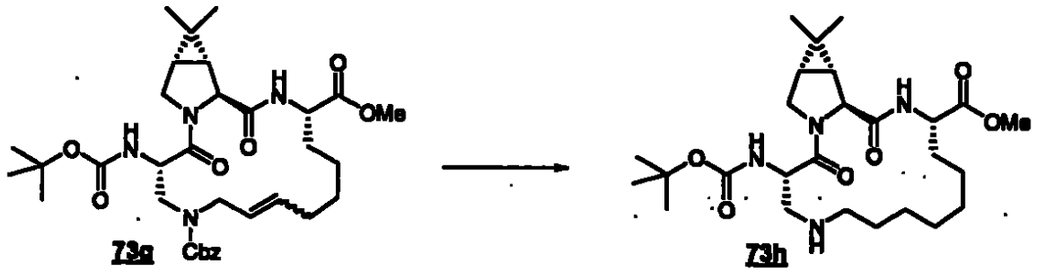
Paso G



73f 73g

Una solución 0,01M del dieno 73f (1 mmol) en tolueno se desgasificará durante 30 min. (burbujeo de argón) y se tratará con catalizador de Grubb (0,2 mmol). La solución rosada se calentará a 60ºC durante 16 h. El solvente se eliminará a presión reducida y el residuo se someterá a cromatografía sobre gel de sílice para dar el producto alqueno 73g como una mezcla de isómeros E y Z.

Paso H

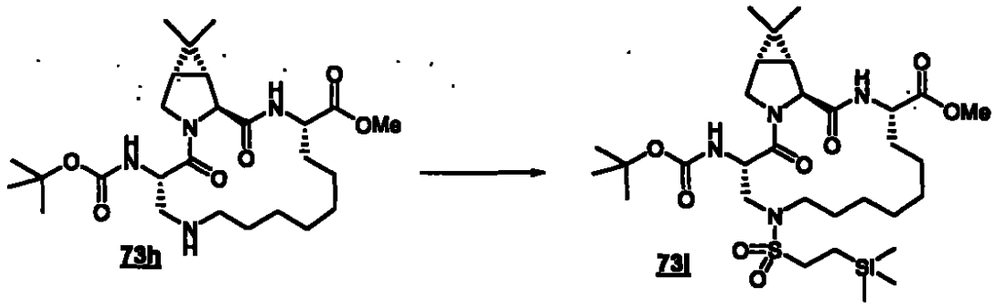


73g 73h

Se tratará una solución del alqueno 73g (1 mmol) en 20 ml de metanol con paladio 5% sobre carbono (0,1 mol%). La mezcla se hidrogenará a 3,45 x 10^5 Pa

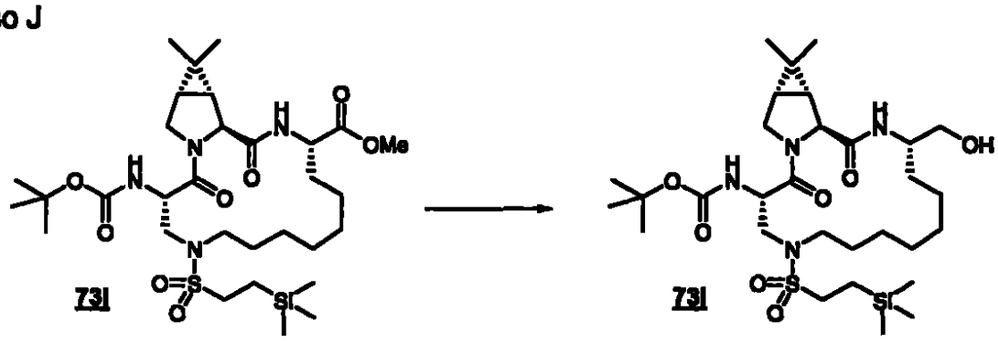
(50 psi) hasta que se haya consumido todo el material de partida. La mezcla de reacción se diluirá con 100 ml de diclorometano y se filtrará a través de un lecho de Celite. El filtrado se concentrará y el producto **73h** se purificará mediante cromatografía en columna sobre gel de sílice.

Paso I



Se tratará una solución de la amina macrocíclica **73h** (1 mmol) en 10 ml de diclorometano con carbonato de potasio (2 mmol) y cloruro de (trimetilsilil)-etansulfonilo (1 mmol). La mezcla se agita durante 1 día y el solvente se evaporará. El producto **73I** se purificará mediante cromatografía en columna sobre gel de sílice.

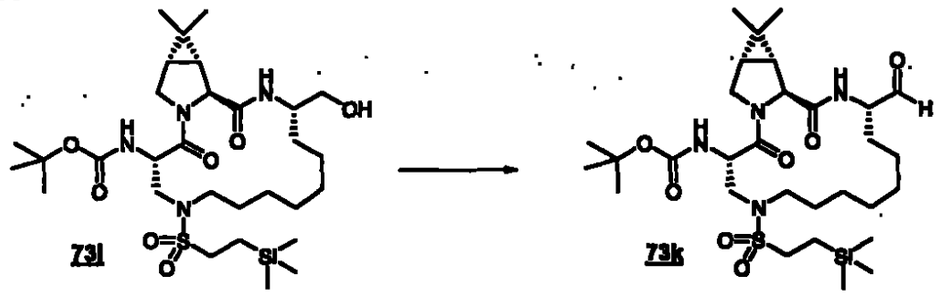
Paso J



Se tratará una solución del metil éster **73I** (1 mmol) en 10 ml de THF seco con borohidruro de litio (2,1 mmol). La mezcla de reacción se agitará a temperatura ambiente. Después de 5 h, el borohidruro de litio en exceso se desactivará por agregado de solución de cloruro de amonio acuoso saturado (3 ml). La mezcla se dividirá entre acetato de etilo (50 ml) y solución de bicarbonato de sodio acuoso saturado (30 ml). La capa acuosa se extraerá nuevamente con

acetato de etilo (2 x 30 ml) y diclorometano (2 x 30 ml). Las capas orgánicas combinadas se secarán sobre sulfato de magnesio, se filtrarán y se concentrarán a presión reducida. El residuo se someterá a cromatografía sobre gel de sílice para dar el producto **73j**.

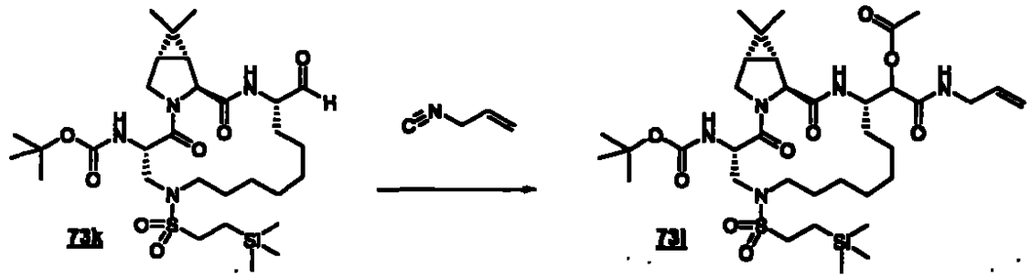
Paso K



73j **73k**

Se tratará una solución del alcohol **73j** (1 mmol) en 20 ml de diclorometano seco con periodinano de Dess-Martin (1,5 mmol). La mezcla de reacción se agitará a temperatura ambiente durante 45 min. La mezcla se tratará con solución de tiosulfato de sodio acuoso 1M (10 ml) y solución acuosa saturada de bicarbonato de sodio (20 ml) y se agitará durante 15 min. La mezcla se extraerá con diclorometano (3 x 40 ml). Las capas orgánicas combinadas se secarán sobre sulfato de magnesio, se filtrarán y se concentrarán. El residuo se someterá a cromatografía sobre gel de sílice para dar el producto aldehído **73k**.

Paso L

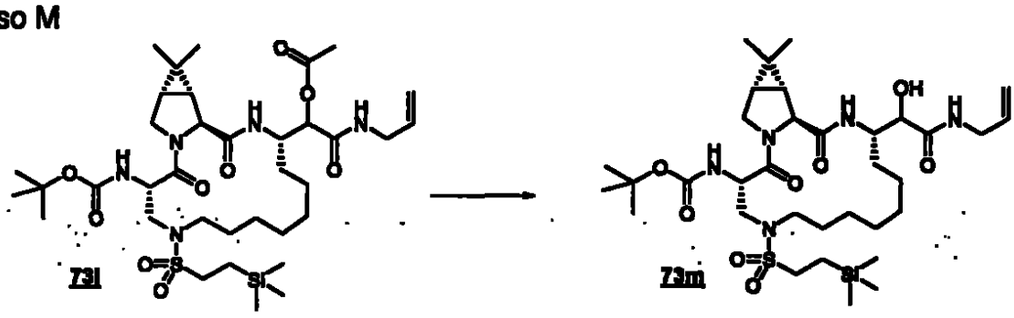


73k **73l**

Una solución del aldehído **73k** (1 mmol) en 10 ml de diclorometano seco se tratará con isocianuro de alilo (2 mmol) y ácido acético (2 mmol). La mezcla se agitará durante alrededor de 5 h. Todos lo volátiles se eliminarán en vacío y el

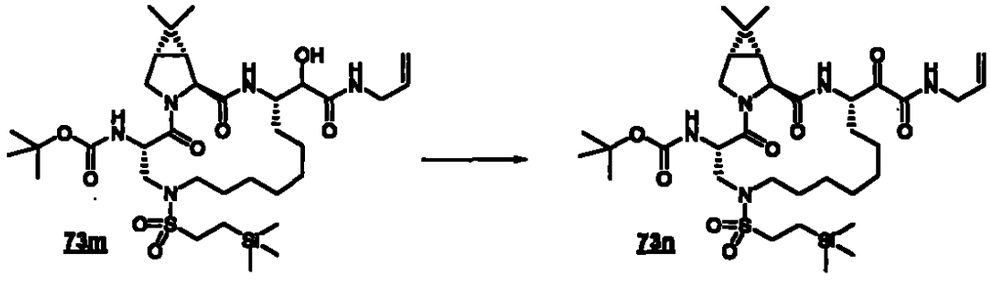
residuo se someterá a cromatografía sobre gel de sílice para dar el producto del acetato **73l**.

Paso M



El acetato **73l** (1 mmol) se disolverá en 16 ml de una mezcla 1:1 de THF/agua y se tratará con monohidrato de hidróxido de litio (2,5 mmol). Después de 30 min., la mezcla se dividirá entre diclorometano (50 ml) y solución acuosa saturada de bicarbonato de sodio (20 ml). La capa acuosa se extraerá nuevamente con diclorometano (3 x 30 ml). Las capas orgánicas combinadas se secarán sobre sulfato de magnesio, se filtrarán y se concentrarán. El producto, la hidroxiamida **73m**, se usará sin otra purificación.

Paso N

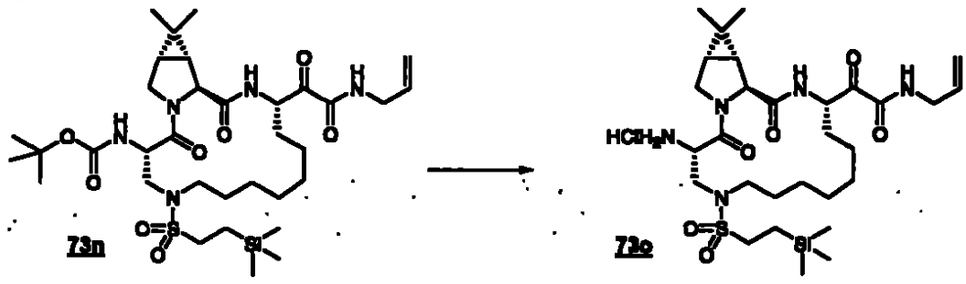


Una solución de la hidroxiamida **73m** (1 mmol) en 20 ml de diclorometano seco se tratará con periodinano de Dess-Martin (2,5 mmol). La mezcla de reacción se agitará a temperatura ambiente durante 30 min. La mezcla se tratará con solución de tiosulfato de sodio acuoso 1M (20 ml) y solución acuosa saturada de bicarbonato de sodio (10 ml) y se agitó durante 15 min. La mezcla se extraerá con diclorometano (3 x 30 ml). Las capas orgánicas combinadas se secarán sobre

595
592

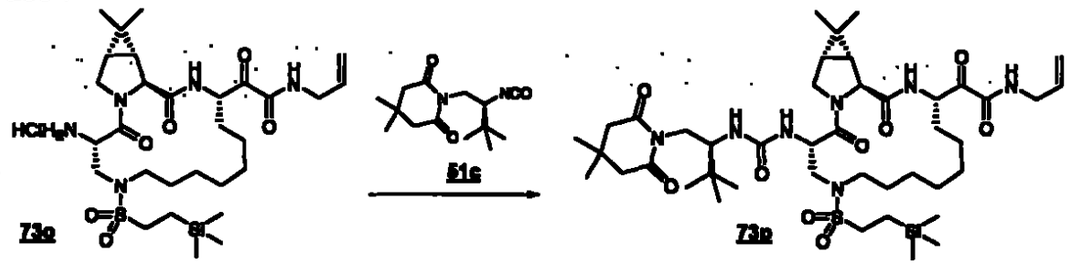
sulfato de magnesio, se filtrarán y se concentrarán. El producto, la cetoamida **73n**, se purificará mediante cromatografía en columna.

Paso O



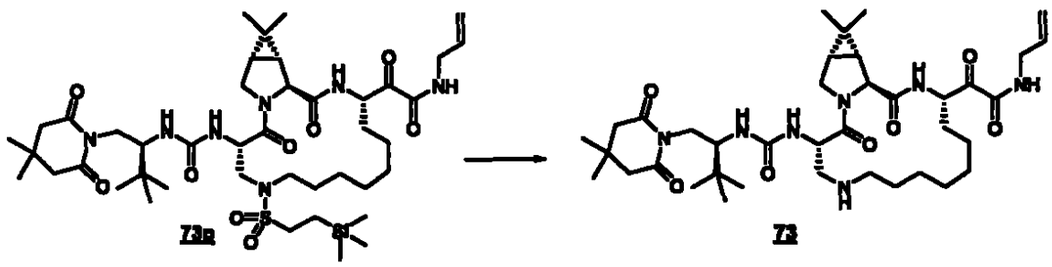
La amina protegida con N-Boc **73n** (0,1 mmol) se disolverá en 5 ml de solución 4M de HCl en dioxanos. La solución resultante se agitará durante 30 min. y luego se evaporará a presión reducida para dar el producto, el clorhidrato de amina **73o**.

Paso P



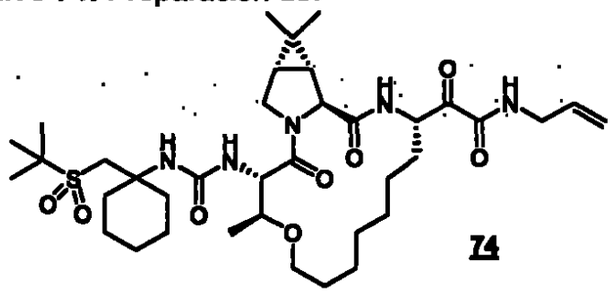
El clorhidrato de amina **73o** (0,1 mmol) se disolverá en 5 ml de diclorometano y se tratará con 20 gotas de solución de bicarbonato de sodio acuoso saturado seguido de una solución del isocianato **51c** (0,12 mmol) en tolueno. La mezcla se agitará durante 5 h y luego se diluirá con 50 ml de diclorometano y se secará sobre sulfato de magnesio. La mezcla se filtrará y se concentrará a presión reducida. El producto **73p** se purificará mediante cromatografía en columna de gel de sílice.

Paso Q

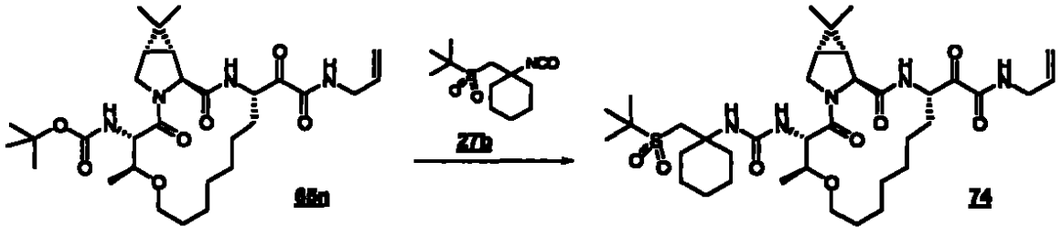


La amina protegida con SES 73p (0,1 mmol) se disolverá en 2 ml de DMF y se tratará con fluoruro de cesio (0,4 mmol). La mezcla de reacción se agitará a temperatura ambiente durante 4 h y se verterá en agua (10 ml). La mezcla se extraerá con acetato de etilo (3 x 20 ml). Las capas orgánicas combinadas se secarán sobre sulfato de magnesio, se filtrarán y se concentrarán a presión reducida. La amina macrocíclica 73 se purificará mediante cromatografía en columna de gel de sílice.

Ejemplo Preparativo 74: Preparación de:



Paso A



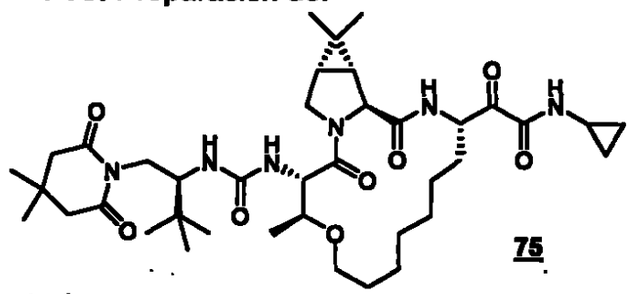
La N-Boc amina 65n (60 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregaron 20 gotas de solución

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599

del bicarbonato de sodio acuoso saturado seguido de una solución del isocianato **27b** en tolueno (1,2 eq, 0,6 ml de una solución 0,2M en tolueno) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con diclorometano (60 ml) y se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos 1:9 a 1:1) para dar el producto **74** (45 mg, 59%) como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$): δ 8,11 (br s, 1H), 7,40-7,69 (br s, 1H), 6,08-6,43 (br s, 1H), 5,91 (ddt, 1H, *J* = 5,6, 10,4, 17,3 Hz), 5,70 (br s, 1H), 5,29 (dd, 1H, *J* = 1,2, 17,3 Hz), 5,24 (dd, 1H, *J* = 1,2, 10,4 Hz), 4,66 (d, 1H, *J* = 9,4 Hz), 4,46 (br s, 1H), 4,38 (m, 1H), 4,25 (d, 1H, *J* = 10,7 Hz), 4,06 (m, 2H), 3,98 (m, 1H), 3,71 (dq, 5,6, 11,6 Hz), 3,64 (ddd, 1H, *J* = 5,0, 5,3, 9,7 Hz), 3,25 (m, 1H), 2,88 (d, 1H, *J* = 13,5 Hz), 2,47 (br s, 1H), 2,19 (d, 1H, *J* = 11,6 Hz), 1,39 (s, 9H), 1,28-1,99 (m, 22H), 1,21 (d, 3H, *J* = 5,6 Hz), 1,13 (m, 1H), 1,04 (s, 3H), 0,91 (s, 3H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 198,7, 173,0, 171,3, 159,4, 157,0, 133,4, 117,7, 75,2, 67,7, 61,2, 60,8, 55,6, 54,6, 48,7, 42,2, 36,3, 31,6, 28,9, 27,9, 27,8, 27,1, 26,8, 25,9, 24,8, 24,0, 23,6, 21,9, 21,5, 19,4, 15,8, 13,4 ppm; HRMS calculado para $C_{37}H_{62}N_5O_8S$ $[M+H]^+$: 736,4319, experimental 736,4325.

Ejemplo Preparativo 75: Preparación de:

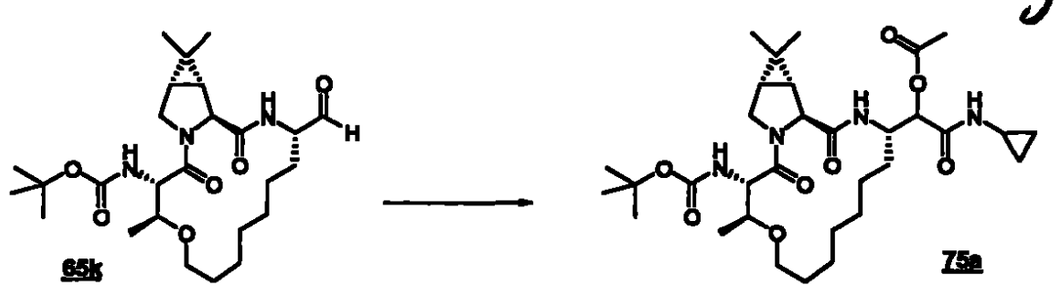


75

Paso A

595

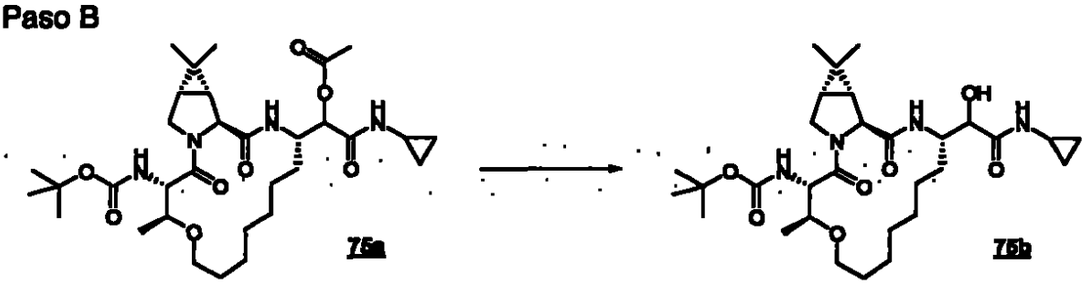
595



65k 75a

Se trató una solución del aldehído **65k** (710 mg) en 30 ml de diclorometano seco con isocianuro de ciclopropilo (Oakwood Prod., 2,0 eq, 0,25 ml, d 0,8) y ácido acético (2 eq, 0,16 ml, d 1,049). La mezcla se agitó a temperatura ambiente durante 5 h. Se eliminaron todos los volátiles a presión reducida y el residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 15:85 a 55:45) para dar el producto **75a** (740 mg, 83%) como un sólido blanco.

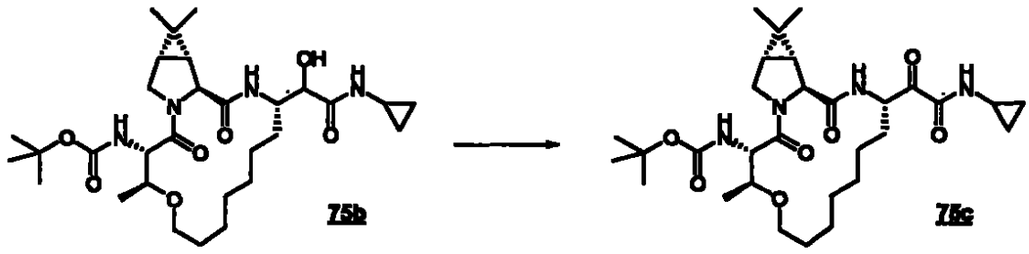
Paso B



75a 75b

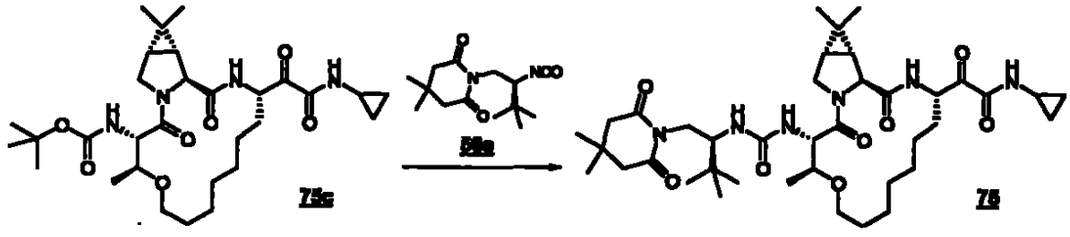
Se trató una solución del acetato **75a** (740 mg) en 20 ml de una mezcla 2:1 de THF/agua con monohidrato de hidróxido de litio (2,5 eq, 125 mg) y se agitó durante aproximadamente 30 min. hasta que todo el material se había consumido según lo determinado mediante análisis por TLC (acetato de etilo/hexanos 8:2). La mezcla de reacción se diluyó con 50 ml de solución acuosa saturada de bicarbonato de sodio y se extrajo con diclorometano (3 x 80 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron para dar el producto **75b** (688 mg, 98%) como un semi-sólido incoloro que se usó sin otra purificación.

Paso C



Una solución de la hidroxiamida **75b** (1,192 mmol) en 25 ml de diclorometano seco se trató con periodinano de Dess-Martin (2,0 eq, 1,01 g). La mezcla de reacción se agitó a temperatura ambiente durante 30 min. La mezcla se trató con solución de tiosulfato de sodio acuoso 1M (30 ml) y se agitó durante 5 min. También se agregó solución acuosa saturada de bicarbonato de sodio (30 ml) y la agitación se continuó durante otros 10 min. La mezcla se extrajo con diclorometano (3 x 80 ml). Las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 5:95 a 4:6) para dar el producto **75c** (476 mg, 69%) como sólido blanco.

Paso D



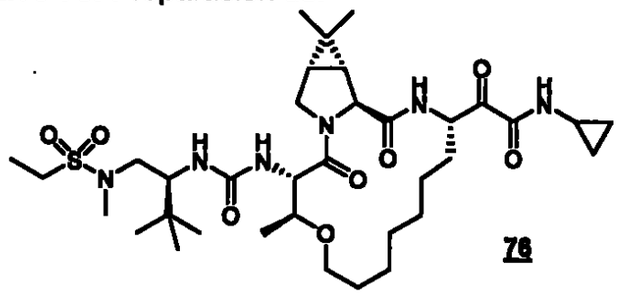
La N-Boc amina **75c** (60 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregaron 10 gotas de solución de bicarbonato de sodio acuoso saturado. Después de 10 min, se agregó una solución del isocianato **56e** gota a gota (1,2 eq, 0,59 ml de una solución de 0,216M en tolueno) y la agitación se continuó durante 10 min. El baño de

606

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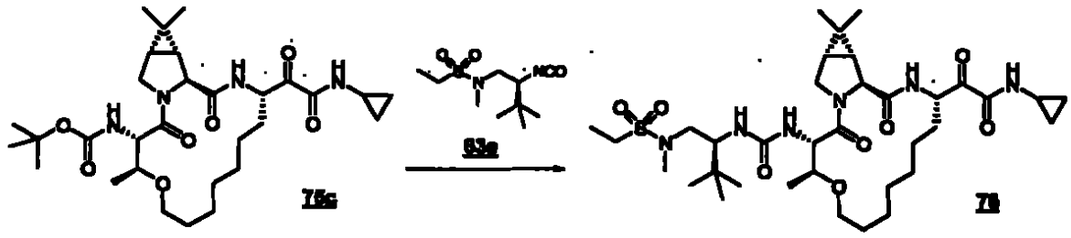
enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con diclorometano (70 ml) y se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos 1:9 a 1:1) para dar el producto 75 (41 mg, 53%) como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$): δ 8,12 (br s, 1H), 7,40-7,70 (br s, 1H), 6,28 (br s, 1H), 5,68 (br s, 1H), 5,37 (br s, 1H), 4,62 (s, 1H), 4,49 (br s, 1H), 4,22 (d, 1H, *J* = 10,7 Hz), 4,05 (dd, 1H, *J* = 5,0, 10,4 Hz), 3,94 (d, 1H, *J* = 1,6 Hz), 3,88 (dd, 1H, *J* = 10,4, 10,7 Hz), 3,82 (q, 1H, *J* = 11,0 Hz), 3,69 (m, 1H), 3,62 (ddd, 1H, *J* = 5,0, 5,6, 9,4 Hz), 3,20 (m, 1H), 2,89 (ddd, 1H, *J* = 3,4, 7,2, 14,8 Hz), 2,55 (d, 2H, *J* = 17,0 Hz), 2,48 (d, 2H, *J* = 17,0 Hz), 1,79-1,99 (m, 4H), 1,28-1,69 (m, 10H), 1,14 (d, 3H, *J* = 6,0 Hz), 1,10 (s, 6H), 1,00 (s, 3H), 0,99 (s, 9H), 0,90 (m, 2H), 0,83 (s, 3H), 0,71 (m, 2H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 198,8, 172,8, 171,5, 160,9, 157,8, 75,5, 68,1, 60,8, 57,2, 55,9, 48,7, 46,8, 35,2, 29,3, 28,6, 28,3, 27,7, 26,9, 26,8, 24,8, 24,4, 23,1, 19,3, 16,3, 13,6, 6,8 ppm; HRMS calculado para $C_{39}H_{63}N_6O_8$ $[M+H]^+$: 743,4707, experimental 743,4686.

Ejemplo Preparativo 76: Preparación de:



76

Paso A

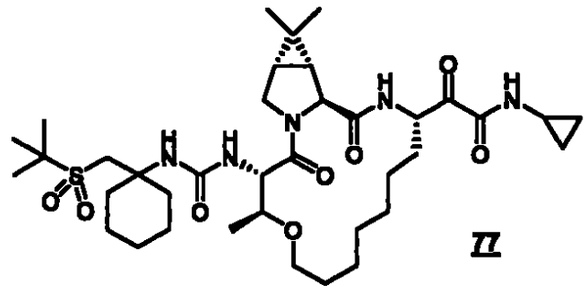


La N-Boc amina **75c** (60 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío hasta el día siguiente. La sal de amina resultante se disolvió en 5 ml de diclorometano y se enfrió a 0°C. Luego, se agregaron 10 gotas de solución acuosa saturada de bicarbonato de sodio. Después de 10 min., se agregó gota a gota una solución del Isocianato **63e** (1,2 eq, 0,95 ml de una solución 0,131M en tolueno) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se diluyó con diclorometano (70 ml) y se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 2:8 a 6:4) para dar el producto **76** (54 mg, 72%) como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$): δ 8,22 (br s, 1H), 7,58 (br s, 1H), 6,13 (br s, 1H), 5,75 (br s, 1H), 5,15 (d, 1H, *J* = 8,5 Hz), 4,68 (br s, 1H), 4,56 (s, 1H), 4,28 (d, 1H, *J* = 10,7 Hz), 4,06 (dd, 1H, *J* = 4,7, 10,4 Hz), 3,99 (dd, 1H, *J* = 9,1, 9,7 Hz), 3,60 (m, 2H), 3,47 (dd, 1H, *J* 12,2, 13,2 Hz), 3,19 (m, 1H), 3,07 (m, 3H), 2,94 (s, 3H), 2,87 (ddd, 1H, *J* = 4,0, 7,8, 15,1 Hz), 1,72-1,99 (m, 4H), 1,37 (t, 3H, *J* = 7,5 Hz), 1,27-1,68 (m, 9H), 1,21 (d, 3H, *J* = 6,0 Hz), 1,13 (m, 1H), 1,01 (s, 3H), 0,92 (s, 9H), 0,89 (s, 3H), 0,87 (m, 2H), 0,71 (m, 2H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 199,5, 172,8, 171,6, 160,8, 158,1, 75,8, 68,4, 60,6, 56,2, 54,4, 50,4, 48,5, 45,7, 34,7, 34,5, 32,1, 31,6, 28,6, 27,8, 27,7, 27,0, 26,9, 26,7, 24,9, 24,6, 23,0, 19,2, 16,2, 13,5, 8,5, 6,7 ppm; HRMS calculado para $C_{35}H_{61}N_6O_8S$ $[M+H]^+$: 725,4272, experimental 725,4292.

Ejemplo Preparativo 77: Preparación de:

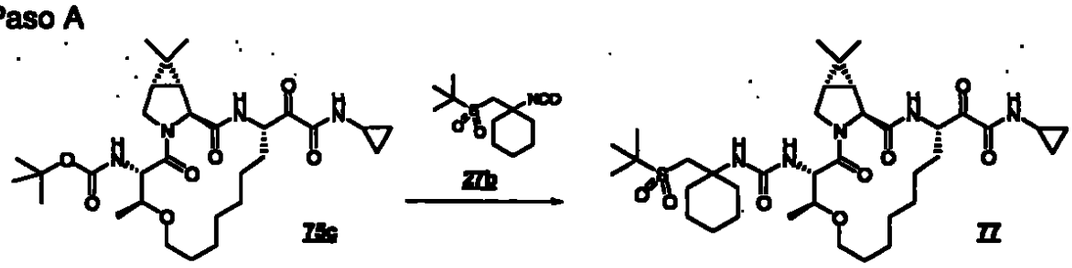
602

599



77

Paso A

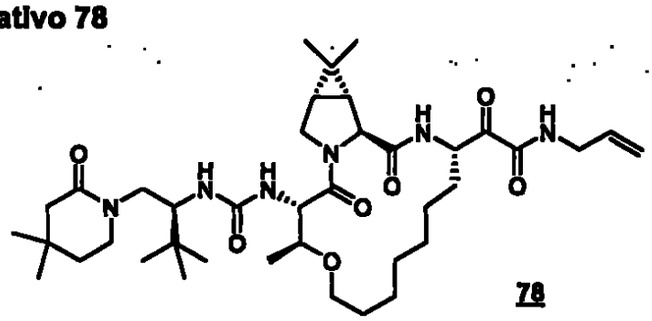


La N-Boc amina **75c** (60 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregaron 20 gotas de solución del bicarbonato de sodio acuoso saturado seguido de una solución del isocianato **27b** en tolueno (1,2 eq, 0,6 ml de una solución 0,2M en tolueno) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con diclorometano (60 ml) y se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 2:8 a 6:4) para dar el producto **77** (50 mg, 65%) como un sólido blanco. ^{1}H RMN (500 MHz, $CDCl_3$): δ 8,12 (br s, 1H), 7,33-7,63 (br s, 1H), 6,07-6,47 (br s, 1H), 5,67 (br s, 1H), 4,65 (d, 1H, *J* = 9,7 Hz), 4,45 (br s, 1H), 4,37 (m, 1H), 4,24 (d, 1H, *J* = 10,7 Hz), 4,07 (dd, 1H, *J* =5,0, 10,7 Hz), 3,70 (dq, 1H, 5,9, 9,7 Hz), 3,64 (ddd, 1H, *J* = 5,0, 5,6, 9,7 Hz), 3,24 (m, 1H), 2,89 (ddd, 1H, *J* = 3,7, 7,5, 14,5 Hz), 2,88 (m, 1H), 2,47 (br s, 1H), 2,18 (d, 1H, *J* = 12,6 Hz), 1,74-1,97 (m, 5H), 1,39 (s, 9H), 1,27-1,73 (m, 17H), 1,20 (d, 3H, *J* = 6,3 Hz),

603
600

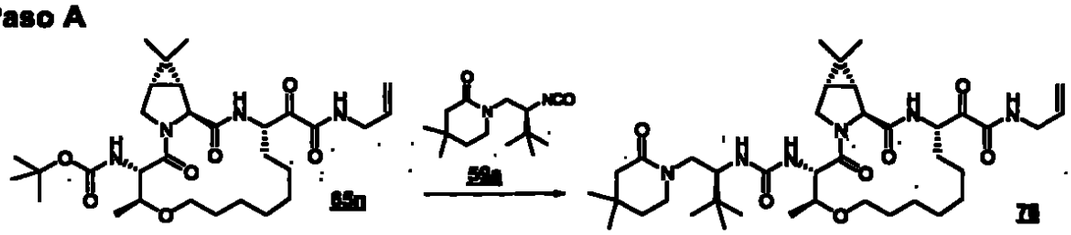
1,11 (m, 1H), 1,04 (s, 3H), 0,91 (s, 3H), 0,90 (m, 2H), 0,73 (m, 2H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 198,7, 173,0, 171,3, 161,0, 157,0, 75,2, 67,8, 61,1, 60,8, 55,5, 54,6, 50,1, 48,6, 36,3, 31,6, 28,8, 27,9, 27,0, 26,9, 25,9, 24,8, 24,0, 23,6, 23,1, 21,9, 21,5, 19,4, 15,8, 13,4, 6,9, 6,8 ppm. HRMS calculado para $C_{37}H_{62}N_5O_8S$ $[M+1]^+$: 736,4319, experimental 736,4329.

Ejemplo Preparativo 78



78

Paso A

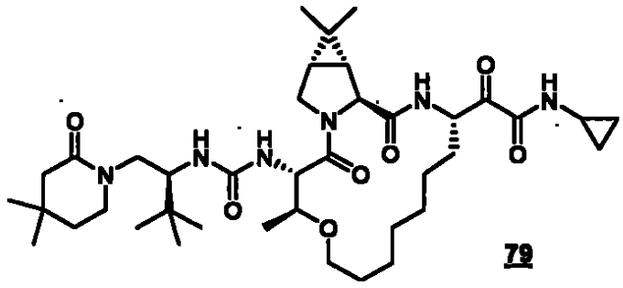


La N-Boc amina **65n** (60 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregaron 20 gotas de solución del bicarbonato de sodio acuoso saturado seguido de una solución del isoclanato **59a** en tolueno (1,2 eq, 0,6 ml de una solución 0,2M en tolueno) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se diluyó con diclorometano (60 ml) y se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/(hexanos-diclorometano 1:1), 1:9 a 1:1) para dar el

601

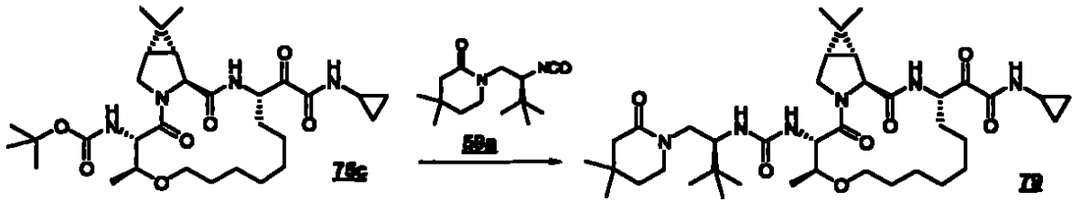
producto **78** (51 mg, 67%) como un sólido blanco. ^{1}H RMN ($CDCl_3$, 500 MHz) δ 8,17 (br s, 1H), 6,42-6,79 (br s, 1H), 5,90 (ddt, 1H, *J* = 5,6, 10,7, 17,0 Hz), 5,73 (br s, 1H), 5,57 (br s, 1H), 5,27 (d, 1H, *J* = 17,0 Hz), 5,22 (d, 1H, *J* = 10,0 Hz), 4,62 (dd, 1H, *J* = 9,1, 9,7 Hz), 4,52 (br s, 1H), 4,29 (m, 2H), 3,86-4,11 (m, 4H), 3,64 (m, 3H), 3,17 (m, 2H), 2,74 (d, 1H, *J* = 11,9 Hz), 2,24 (d, 1H, *J* = 17,3 Hz), 2,10 (d, 1H, *J* = 17,0 Hz), 1,95 (m, 4H), 1,24-1,68 (m, 11H), 1,16 (d, 3H, *J* = 5,9 Hz), 1,11 (m, 1H), 1,02 (s, 3H), 1,01 (s, 6H), 0,95 (s, 9H), 0,87 (s, 3H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 196,8, 172,9, 171,6, 170,7, 159,4, 158,2, 133,6, 117,5, 75,7, 68,2, 60,8, 56,0, 55,3, 48,5, 46,8, 46,2, 44,9, 42,3, 35,7, 34,8, 32,3, 31,6, 30,2, 28,6, 28,4, 27,8, 27,7, 27,1, 27,0, 26,8, 24,8, 24,5, 19,3, 16,5, 13,6 ppm. HRMS calculado para $C_{39}H_{65}N_6O_7$ $[M+1]^+$: 729,4915, experimental 729,4917.

Ejemplo Preparativo 79



79

Paso A



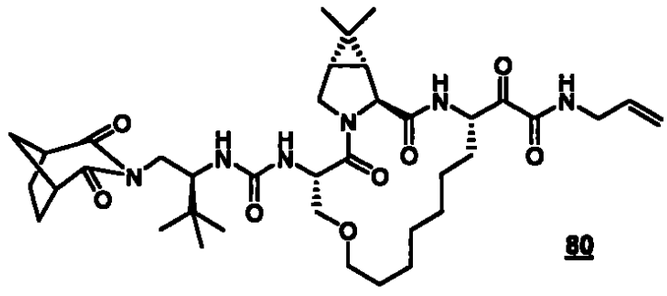
75c **59a** **79**

La N-Boc amina **75c** (60 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregaron 20 gotas de solución del bicarbonato de sodio acuoso saturado seguido de una solución del isocianato

604
602

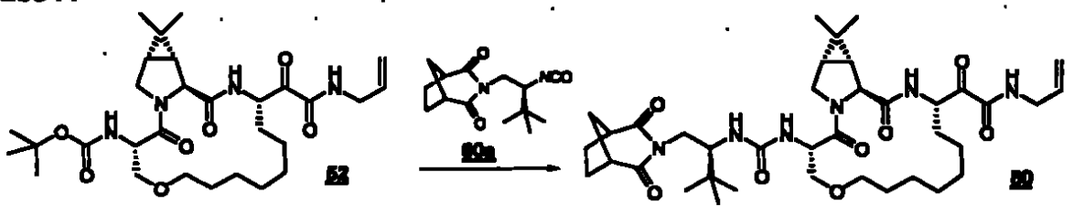
59a en tolueno (1,2 eq, 0,6 ml de una solución 0,2M en tolueno) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se diluyó con diclorometano (60 ml) y se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/(hexanos-diclorometano 1:1), 1:9 a 1:1) para dar el producto 79 (36 mg, 48%) como un sólido blanco. ^{1}H RMN ($CDCl_3$, 500 MHz) δ 8,19 (br s, 1H), 6,38-6,70 (br s, 1H), 5,73 (br s, 1H), 5,55 (d, 1H, *J* = 7,8 Hz), 4,61 (t, 1H, *J* = 9,7 Hz), 4,51 (br s, 1H), 4,27 (m, 2H), 4,05 (dd, 1H, *J* = 5,0, 10,4 Hz), 3,95 (dd, 1H, *J* = 9,4, 9,7 Hz); 3,62 (m, 3H), 3,18 (m, 2H), 2,90 (ddd, 1H, *J* = 3,7, 7,2, 14,8 Hz), 2,73 (d, 1H, *J* = 12,6 Hz), 2,21 (d, 1H, *J* = 17,0 Hz), 2,09 (d, 1H, *J* = 17,3 Hz), 1,93 (br s, 4H), 1,27-1,68 (m, 11H), 1,15 (d, 3H, *J* = 5,9 Hz), 1,11 (m, 1H), 1,02 (s, 3H), 1,00 (s, 6H), 0,94 (s, 9H), 0,87 (m, 2H), 0,86 (s, 3H), 0,73 (m, 2H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 197,1, 172,9, 171,6, 170,6, 160,9, 158,2, 75,6, 68,3, 60,7, 56,0, 55,3, 48,5, 46,7, 46,3, 44,9, 35,7, 34,8, 32,4, 31,6, 30,2, 29,7, 28,6, 28,5, 27,8, 27,7, 27,0, 26,7, 24,8, 24,7, 23,1, 19,3, 16,5, 13,6, 6,7, 6,6 ppm. HRMS calculado para $C_{39}H_{65}N_6O_7$ $[M+1]^+$: 729,4915, experimental 729,4926.

Ejemplo Preparativo 80



80

Paso A



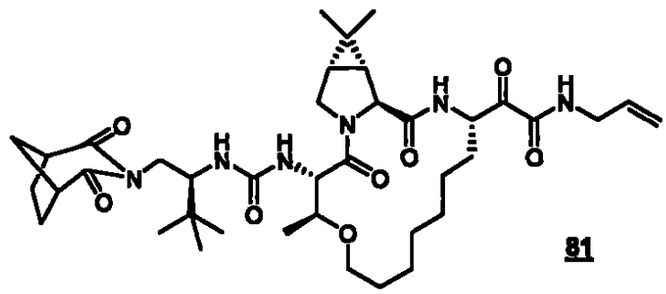
82 59a 80

605

663

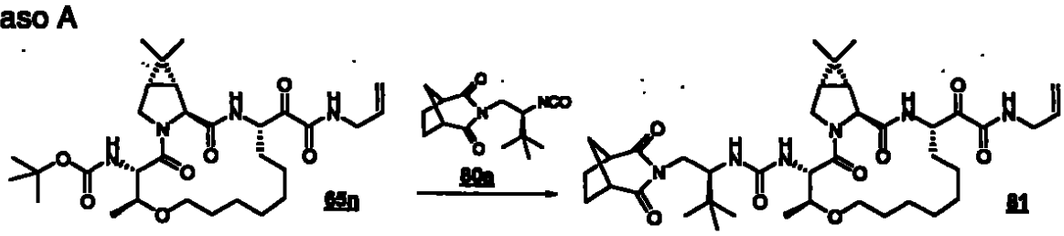
La N-Boc amina **52** (60 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregaron 20 gotas de solución acuosa saturada de bicarbonato de sodio seguido de una solución del isocianato **80a** en tolueno (1,2 eq, 0,8 ml de una solución 0,155M en tolueno) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se diluyó con diclorometano (60 ml) y se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos, 2:8 a 6:4) para dar el producto **80** (41 mg, 61%) como un sólido blanco. ^{1}H RMN ($CDCl_3$, 500 MHz) δ 8,01 (d, 1H, *J* = 8,2 Hz), 7,65 (br s, 1H), 6,01 (br s, 1H), 5,91 (ddt, 1H, *J* = 5,6, 10,0, 17,0 Hz), 5,68 (dd, 1H, *J* = 9,1, 9,4 Hz), 5,27 (dd, 1H, *J* = 1,2, 17,0 Hz), 5,23 (dd, 1H, *J* = 1,2, 10,0 Hz), 5,20 (m, 1H), 4,98 (br s, 1H); 4,59 (s, 1H), 4,13 (d, 1H, *J* = 10,7 Hz), 4,01 (m, 3H), 3,89 (ddd, 1H, *J* = 2,2, 10,4, 10,7 Hz), 3,79 (dd, 1H, *J* = 3,4, 12,9 Hz), 3,76 (m, 1H), 3,56 (m, 2H), 3,36 (dd, 1H, *J* = 4,1, 7,5 Hz), 3,31 (m, 1H), 3,18 (brs, 1H), 3,14 (br s, 1H), 2,22 (d, 1H, *J* = 10,7 Hz), 2,07 (br s, 2H), 1,73-2,00 (m, 5H), 1,25-1,70 (m, 11H), 1,16 (m, 1H), 1,02 (s, 3H), 0,96 (s, 9H), 0,86 (s, 3H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 198,8, 177,4, 172,1, 171,3, 159,3, 157,9, 133,4, 117,7, 71,4, 70,7, 60,7, 56,7, 53,4, 50,8, 48,6, 45,4, 45,2, 42,2, 39,4, 34,7, 33,1, 32,2, 31,0, 28,7, 27,7, 27,5, 27,3, 26,9, 24,3, 19,3, 13,5 ppm. HRMS calculado para $C_{38}H_{59}N_6O_8$ $[M+1]^+$: 727,4394, experimental 727,4387.

Ejemplo Preparativo 81



81

Paso A

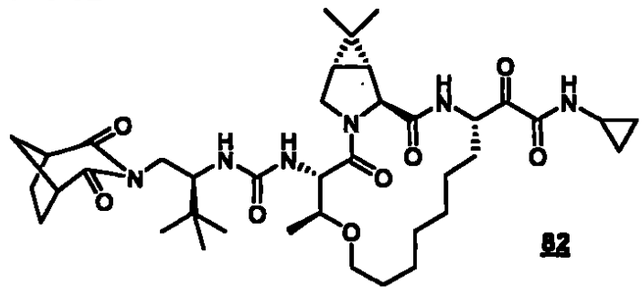


Boc-65n 80a 81

La N-Boc amina **65n** (60 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregaron 20 gotas de solución acuosa saturada de bicarbonato de sodio seguido de una solución del isocianato **80a** en tolueno (1,2 eq, 0,8 ml de una solución 0,155M en tolueno) y la agitación se continuó durante 10 min. El baño de enfriamiento se removió y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se diluyó con diclorometano (60 ml) y se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos; 2:8 a 6:4) para dar el producto **81** (54 mg, 70%) como un sólido blanco. ^{1}H RMN ($CDCl_3$, 500 MHz) δ 8,12 (br s, 1H), 7,39-7,79 (br s, 1H), 6,29 (br s, 1H), 5,91 (ddt, 1H, *J* = 5,9, 10,4, 17,0 Hz), 5,71 (br s, 1H), 5,40 (br s, 1H), 5,27 (dd, 1H, *J* = 1,2, 17,0 Hz), 5,23 (dd, 1H, *J* = 1,2, 10,4 Hz), 4,67 (dd, 1H, *J* = 7,8, 8,1 Hz); 4,50 (br s, 1H), 4,24 (d, 1H, *J* = 10,7 Hz), 4,07 (dd, 1H, *J* = 5,3, 10,4 Hz), 4,03 (m, 1H), 3,97 (ddd, 1H, *J* = 5,6, 5,9, 15,7 Hz), 3,81 (m, 2H), 3,73 (m, 1H), 3,67 (d, 1H, *J* = 12,2 Hz), 3,62 (m, 1H), 3,20 (s, 2H), 3,07

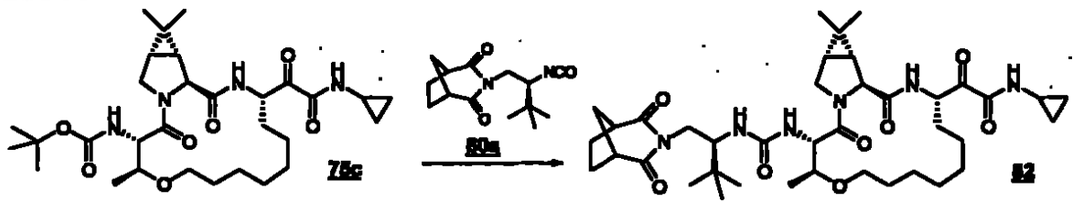
(s, 1H), 2,29 (d, 1H, J = 11,0 Hz), 2,07 (br s, 3H), 1,93 (br s, 2H), 1,83 (br s, 3H), 1,28-1,68 (m, 10H), 1,17 (d, 3H, J = 5,9 Hz), 1,11 (m, 1H), 1,01 (s, 3H), 0,99 (s, 9H), 0,83 (s, 3H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 198,5, 177,1, 172,8, 171,5, 159,4, 158,0, 133,4, 117,7, 75,5, 68,1, 60,8, 57,4, 55,9, 48,7, 45,4, 42,3, 40,4, 34,8, 32,8, 31,7, 28,6, 27,8, 27,6, 27,4, 26,9, 26,8, 24,7, 24,4, 19,4, 16,2, 13,5 ppm. HRMS calculado para $C_{39}H_{61}N_6O_8$ $[M+1]^+$: 741,4551, experimental 741,4543.

Ejemplo Preparativo 82



82

Paso A

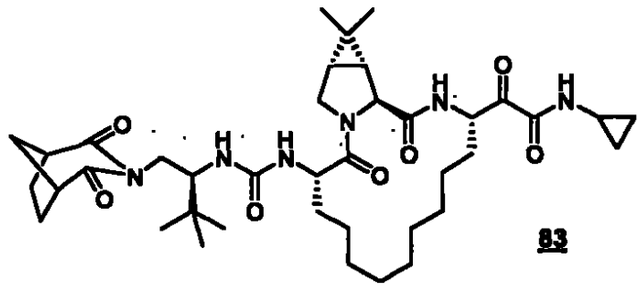


La N-Boc amina **75c** (60 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano seco y se enfrió a 0°C. Luego, se agregaron 20 gotas de solución acuosa saturada de bicarbonato de sodio seguido de una solución del isocianato **80a** en tolueno (1,2 eq, 0,8 ml de una solución 0,155 en tolueno) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se diluyó con diclorometano (60 ml) y se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de

606

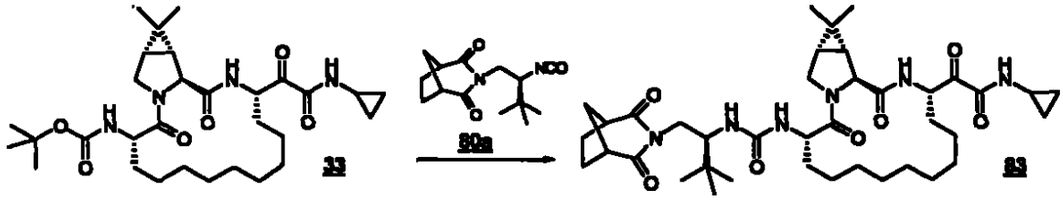
sílice (gradiente: acetona/hexanos; 2:8 a 6:4) para dar el producto **82** (50 mg, 65%) como un sólido blanco. ^{1}H RMN ($CDCl_3$, 500 MHz) δ 8,12 (br s, 1H), 7,38-7,68 (br s, 1H), 6,28 (br s, 1H), 5,68 (br s, 1H), 5,39 (br s, 1H), 4,66 (dd, 1H, *J* = 7,5, 7,5 Hz), 4,49 (br s, 1H), 4,23 (d, 1H, *J* = 10,4 Hz), 4,06 (dd, 1H, *J* = 5,0, 10,4 Hz); 3,81 (m, 2H), 3,71 (m, 1H), 3,67 (d, 1H, *J* = 12,2 Hz), 3,61 (m, 1H), 3,19 (br s, 2H), 3,07 (s, 1H), 2,89 (ddd, 1H, *J* = 3,7, 7,5, 14,8 Hz), 2,29 (d, 1H, *J* = 11,0 Hz), 1,98-2,13 (m, 3H), 1,75-1,96 (m, 6H), 1,26-1,67 (m, 9H), 1,17 (d, 3H, *J* = 5,9 Hz), 1,10 (m, 1H), 1,00 (s, 3H), 0,98 (s, 9H), 0,90 (m, 2H), 0,83 (s, 3H), 0,72 (m, 2H); ^{13}C RMN ($CDCl_3$, 125 MHz) δ 198,9, 178,8, 172,8, 171,5, 160,9, 158,0, 75,5, 68,1, 60,8, 57,4, 55,9, 48,7, 45,4, 40,2, 34,8, 32,8, 31,7, 28,6, 27,8, 27,7, 27,4, 26,9, 26,8, 24,8, 24,4, 23,1, 19,3, 16,2, 13,5, 6,9, 6,8 ppm.

Ejemplo Preparativo 83



83

Paso A



33 **80a** **83**

La N-Boc amina **33** (60 mg) se disolvió en 10 ml de solución de HCl 4M en dioxanos. La solución resultante se agitó a temperatura ambiente durante 30 min. Se eliminaron todos los volátiles a presión reducida y el residuo se colocó en alto vacío durante 3 h. La sal de amina resultante se disolvió en 5 ml de diclorometano

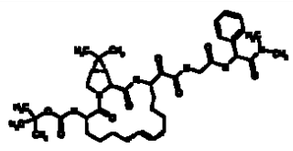
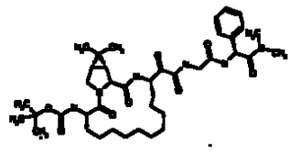
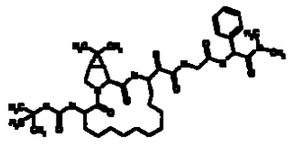
1609
609

seco y se enfrió a 0°C. Luego, se agregaron 20 gotas de solución acuosa saturada de bicarbonato de sodio seguido de una solución del isocianato **80a** en tolueno (1,2 eq, 0,8 ml de una solución 0,155 en tolueno) y la agitación se continuó durante 10 min. El baño de enfriamiento se retiró y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se diluyó con diclorometano (60 ml) y se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se sometió a cromatografía sobre gel de sílice (gradiente: acetona/hexanos, 1:9 a 1:1) para dar el producto **83** (63 mg, 81%) como un sólido blanco.

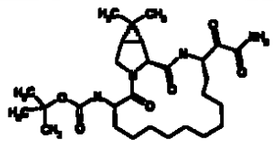
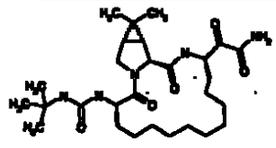
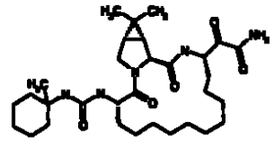
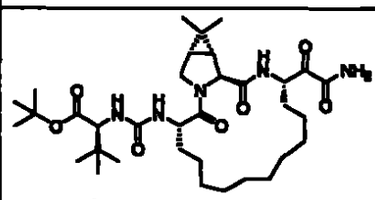
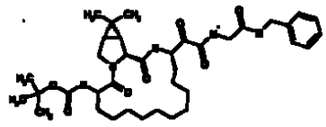
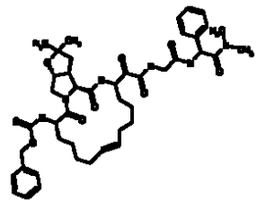
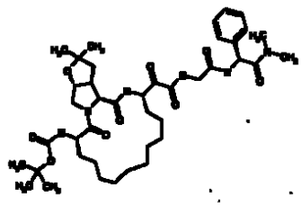
En las siguientes **Tablas 1** y **2** se muestran compuestos que sirven de ejemplo. Los valores de Ki para los compuestos se clasifican de la siguiente manera:

"A" para valores de KI menores que 100 nM, "B" para valores de Ki mayores o iguales que 100 nM pero menores que 1μM y "C" para valores de KI mayores o iguales que 1μM.

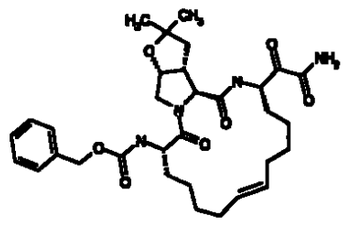
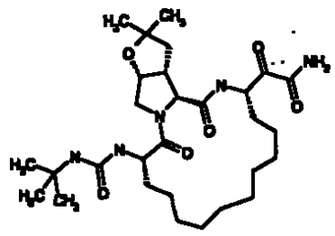
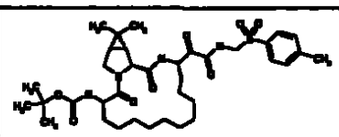
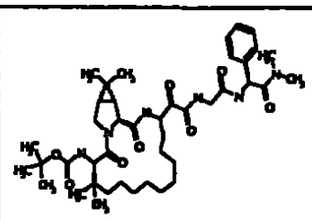
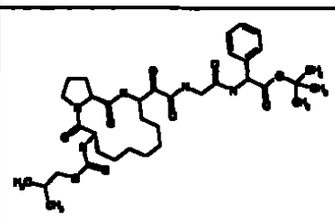
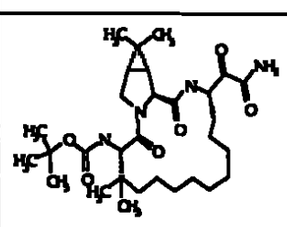
Tabla 1

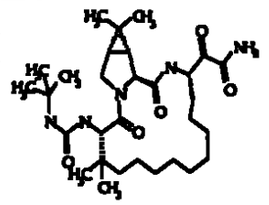
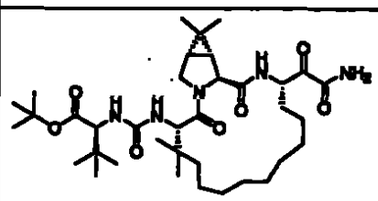
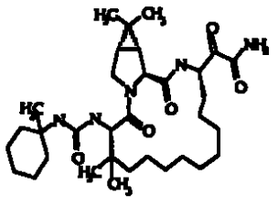
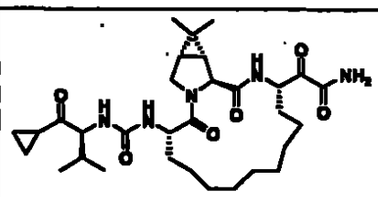
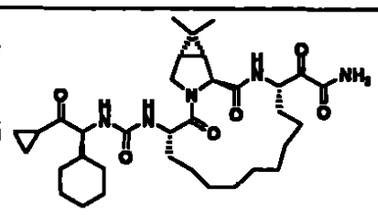
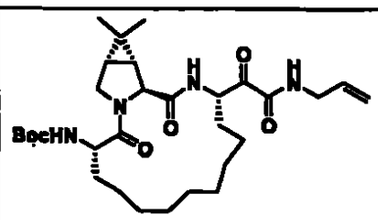
Ejemplo	Estructura	*Actividad de unión*
1		*A*
2		*A*
3		*A*

608

Ejemplo	Estructura	*Actividad de unión*
4		*A*
5		*A*
6		*A*
7		*A*
8		*A*
9		*A*
10		*A*

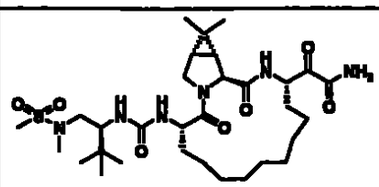
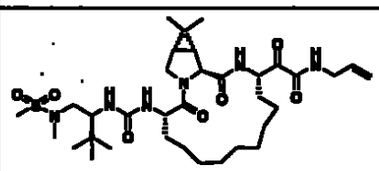
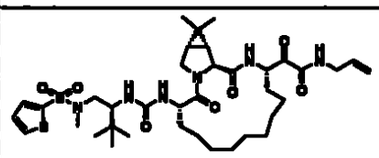
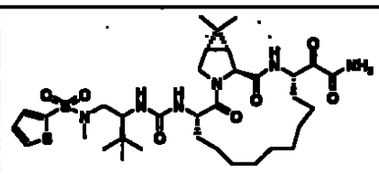
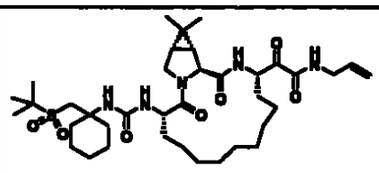
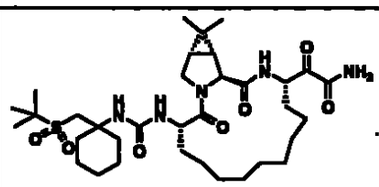
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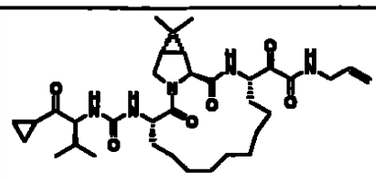
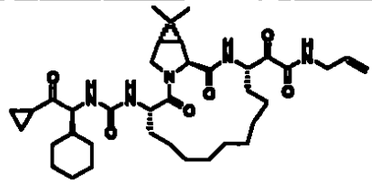
Ejemplo	Estructura	*Actividad de unión*
11		*C*
12		*B*
13		*A*
14		*A*
15		*C*
16		*C*

Ejemplo	Estructura	*Actividad de unión*
17		*A*
18		*A*
19		*A*
20		A
21		A
22		A

613

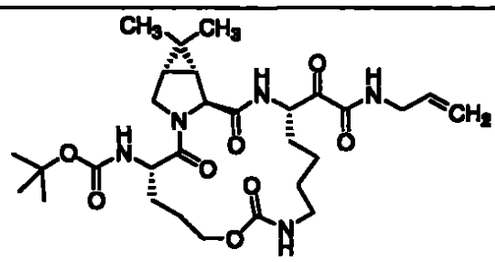
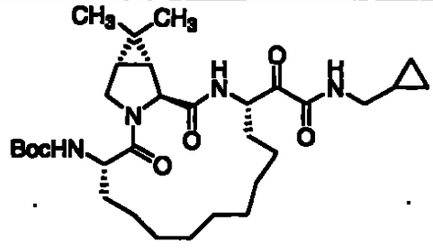
611

Ejemplo	Estructura	*Actividad de unión*
23		A
24		A
25		A
26		A
27		A
28		A

Ejemplo	Estructura	*Actividad de unión*
29		A
30		A

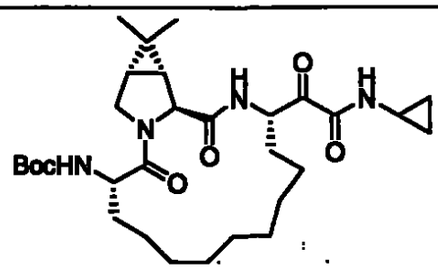
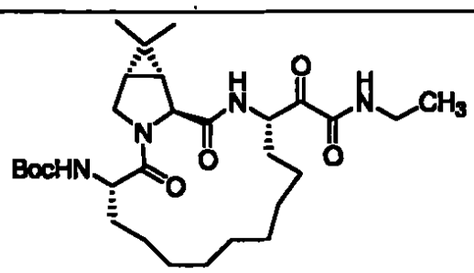
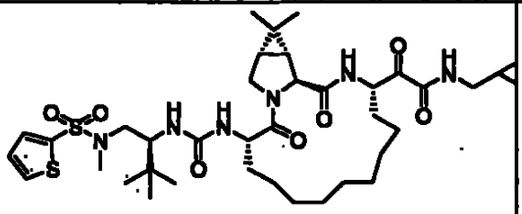
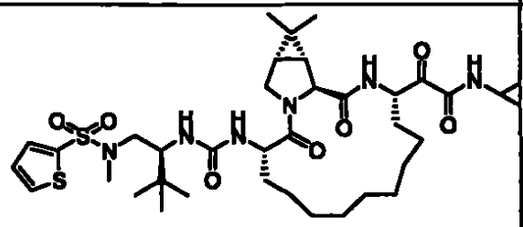
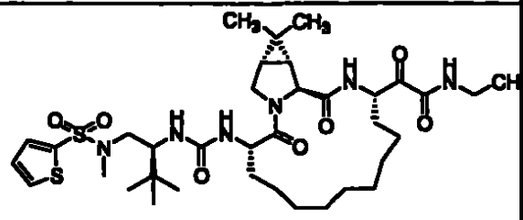
A continuación se enumeran compuestos representativos adicionales de la invención que muestran excelente actividad inhibidora de la proteasa del VHC en la Tabla 2.

Tabla 2

Entrada	Estructura	Actividad K_i* (nM)
31		--
32		B

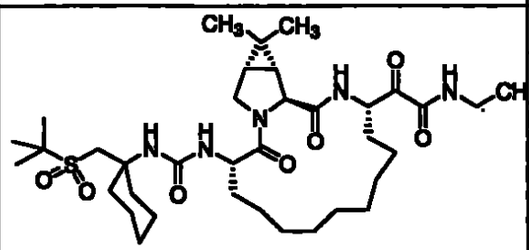
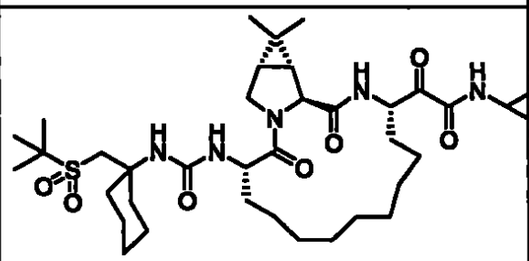
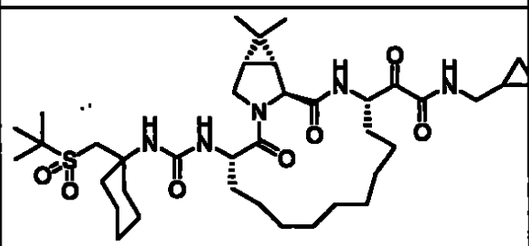
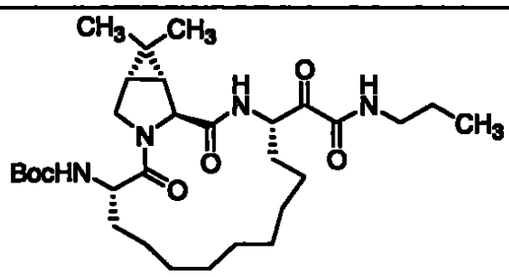
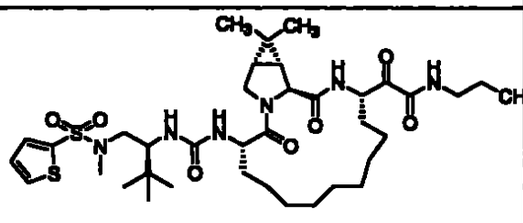
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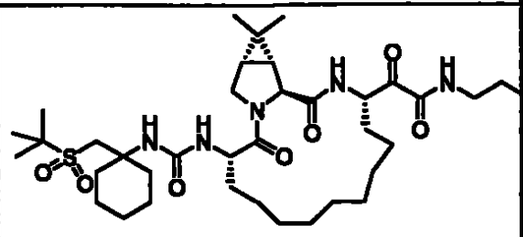
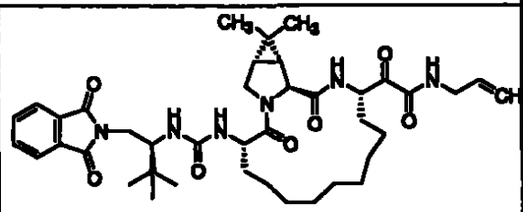
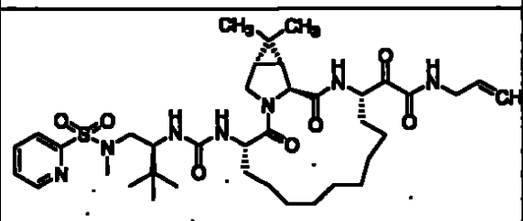
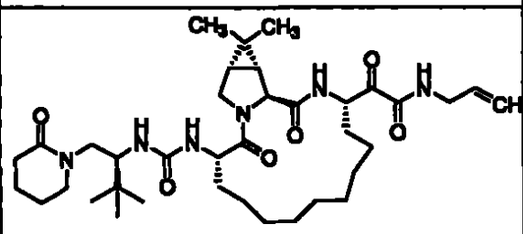
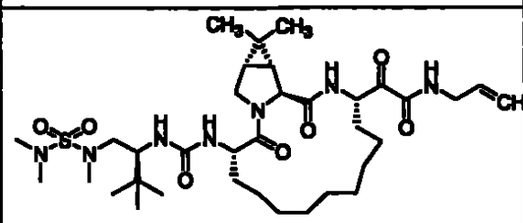
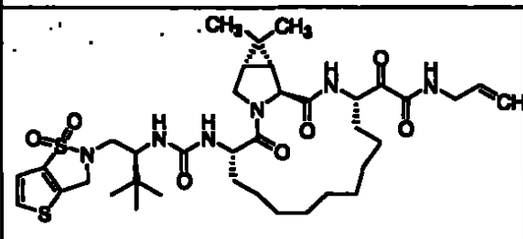
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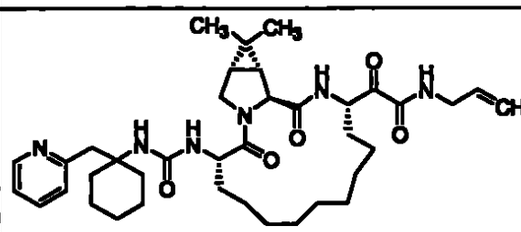
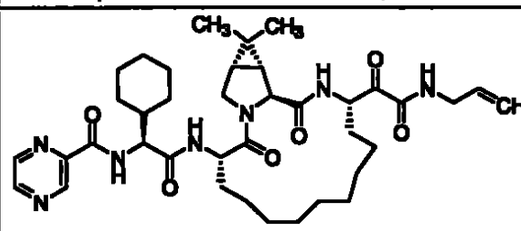
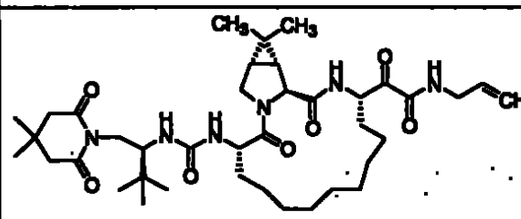
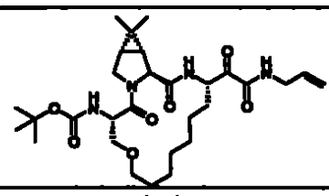
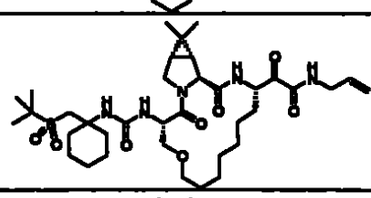
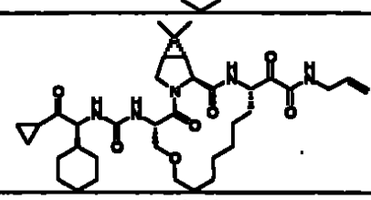
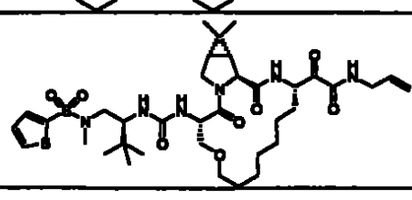
Entrada	Estructura	Actividad K_i^* (nM)
33		A
34		A
35		A
36		A
37		A

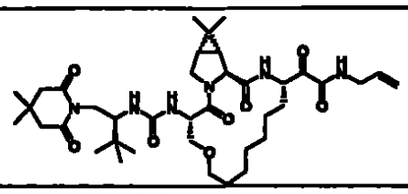
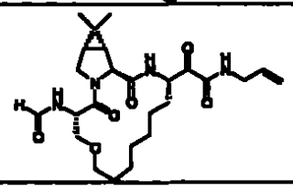
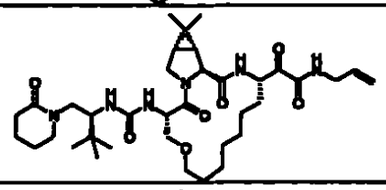
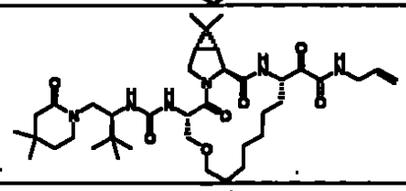
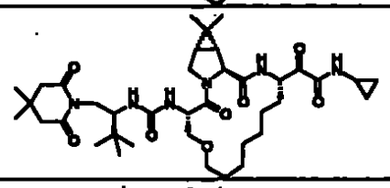
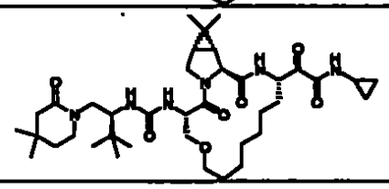
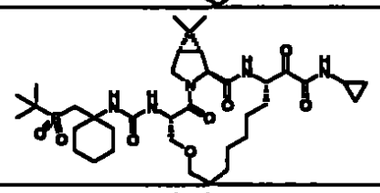
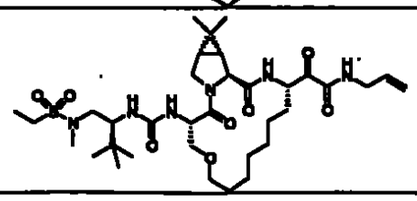
616

614

Entrada	Estructura	Actividad K_i* (nM)
38		A
39		A
40		A
41		NA
42		A

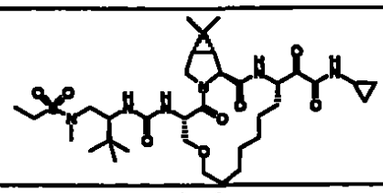
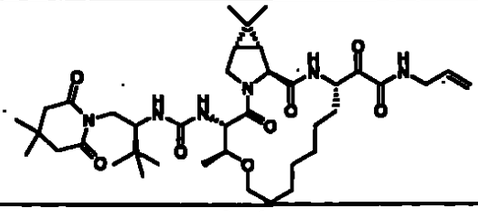
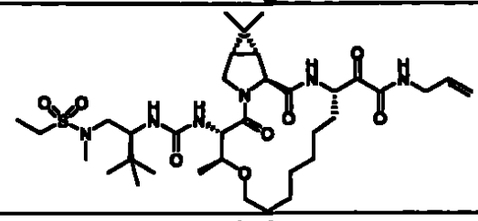
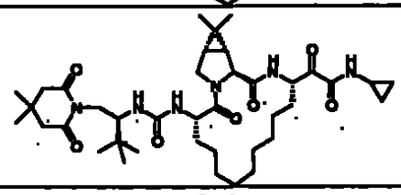
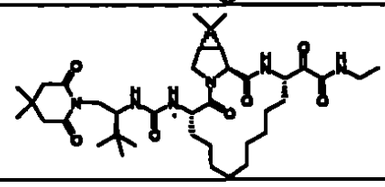
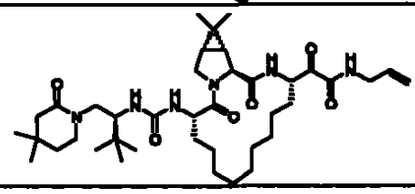
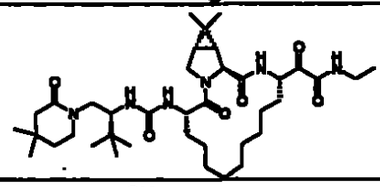
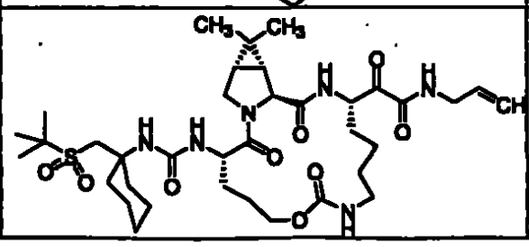
Entrada	Estructura	Actividad K_i* (nM)
43		A
44		A
45		A
46		A
47		A
48		A

Entrada	Estructura	Actividad K_i* (nM)
49		A
50		A
51		A
52		B
53		A
54		B
55		A

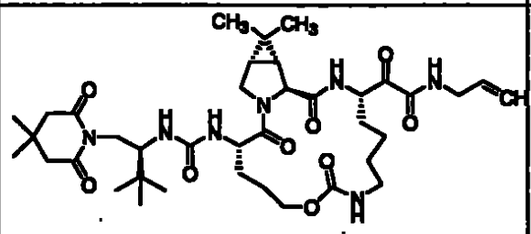
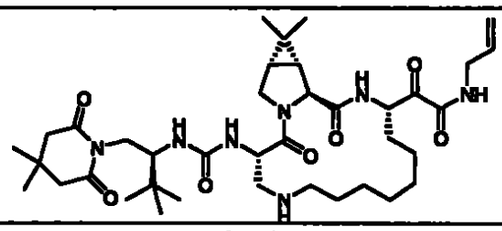
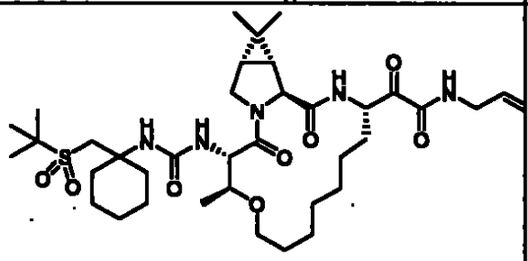
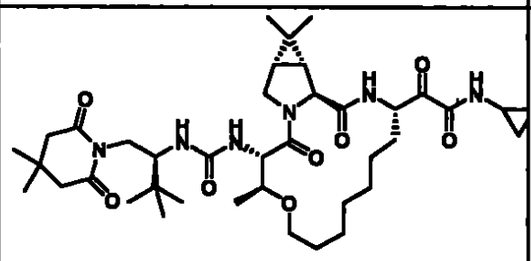
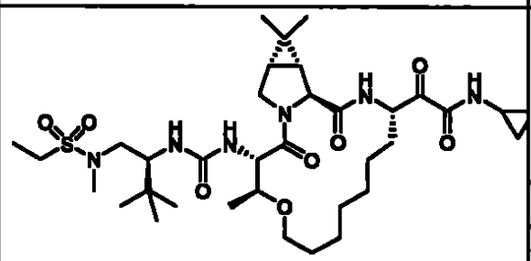
Entrada	Estructura	Actividad K_i* (nM)
56		A
57		C
58		A
59		A
60		A
61		A
62		A
63		A

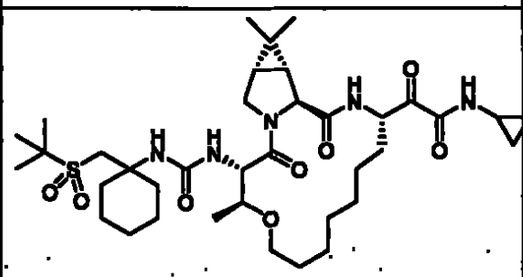
620

618

Entrada	Estructura	Actividad K_i^* (nM)
64		A
65		A
66		A
67		A
68		A
69		A
70		A
71		A

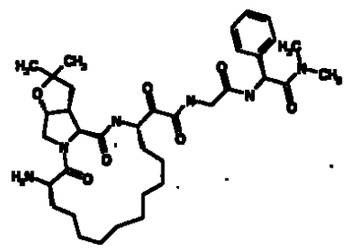
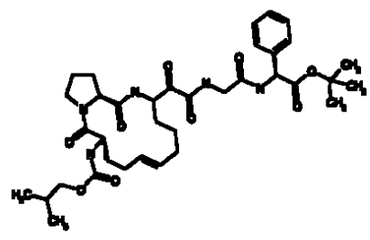
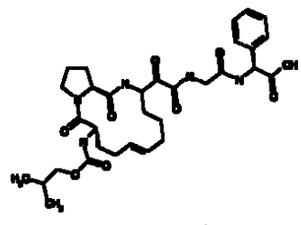
619

Entrada	Estructura	Actividad K_i* (nM)
72		A
73		NA
74		A
75		A
76		A

Entrada	Estructura	Actividad K_i* (nM)
77		A

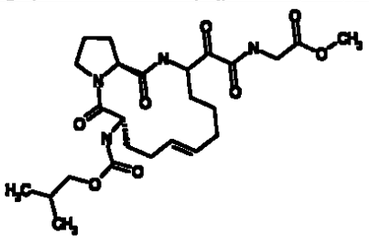
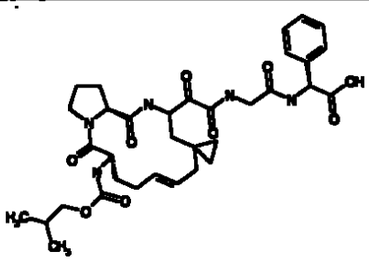
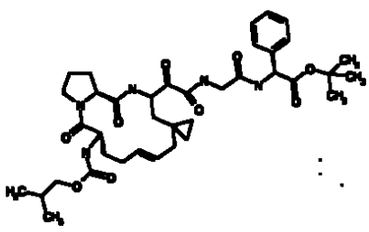
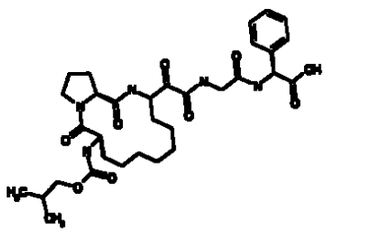
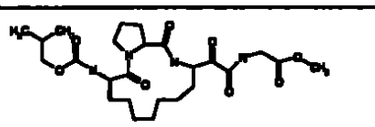
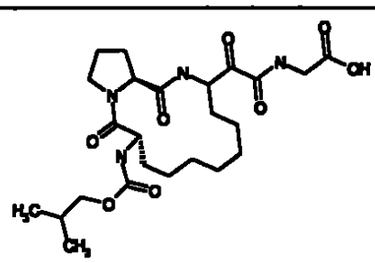
También se muestran compuestos adicionales en la Tabla 2A:

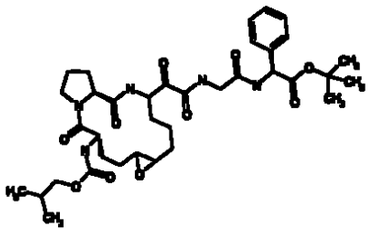
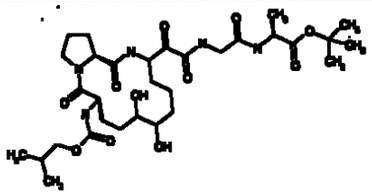
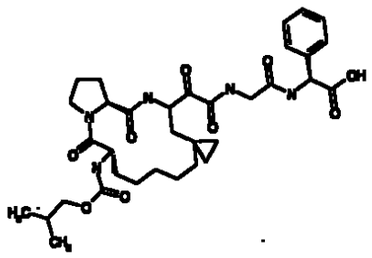
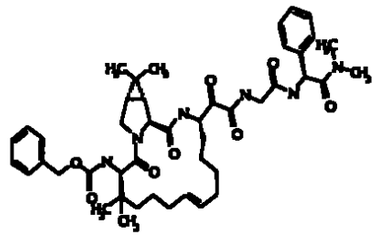
Tabla 2A

Ejemplo	Estructura	Actividad de unión
78		C
79		C
80		C

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Ejemplo	Estructura	Actividad de unión
81		C
82		C
83		C
84		B
85		C
86		C

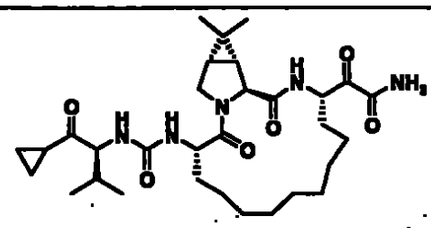
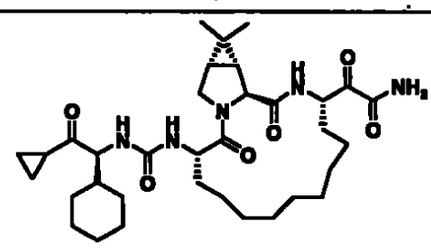
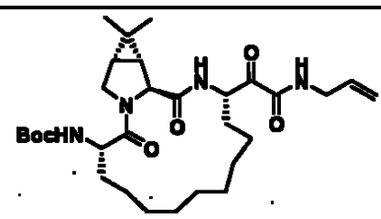
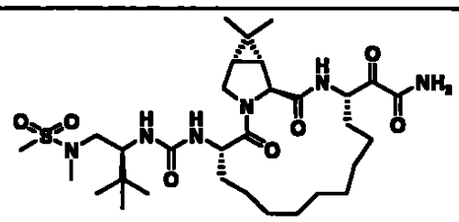
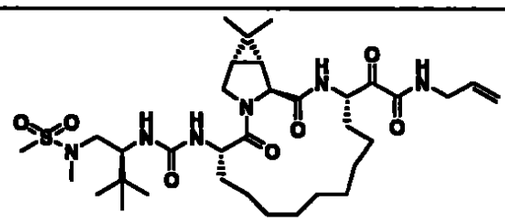
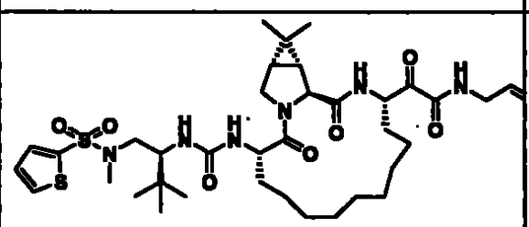
Ejemplo	Estructura	Actividad de unión
87		*C*
88		*C*
89		*C*
90		*B*

La **Tabla 3** muestra las actividades (KI*) de ciertos compuestos representativos de la invención:

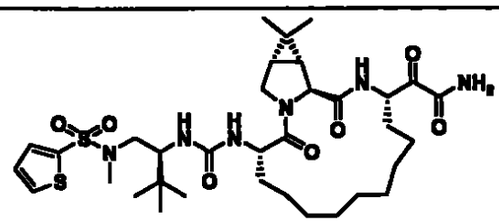
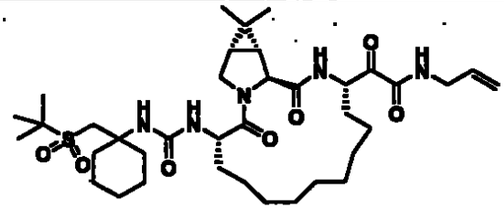
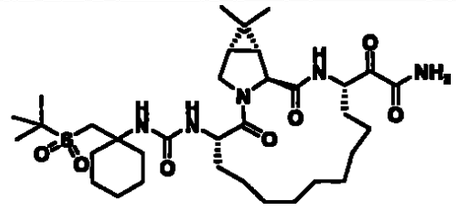
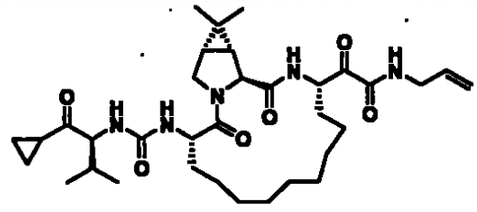
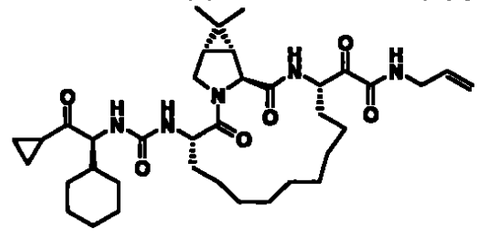
625

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Tabla 3. Compuestos Representativos con actividad inhibidora

Entrada	Número de compuesto	Estructura	Actividad K_i* (nM)
1	20		11
2	21		11
3	22		36
4	23		3
5	24		3
6	25		3

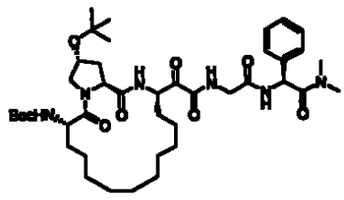
626
624

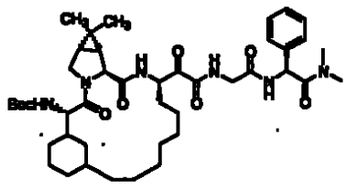
Entrada	Número de compuesto	Estructura	Actividad K_i* (nM)
7	26		2
8	27		5
9	28		5
10	29		20
11	30		5

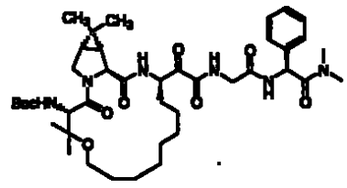
En general, siguiendo los procedimientos descriptos anteriormente, también se pueden preparar los siguientes compuestos y usarse como inhibidores de proteasa del VHC:

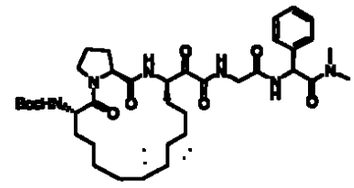
627

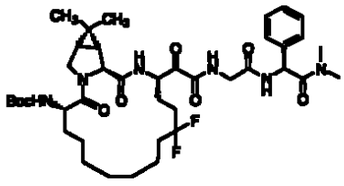
625

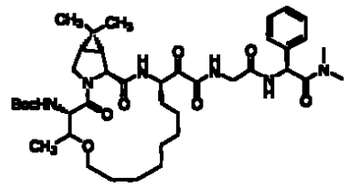


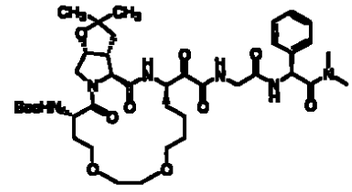


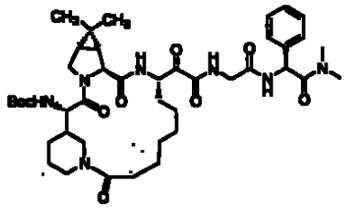


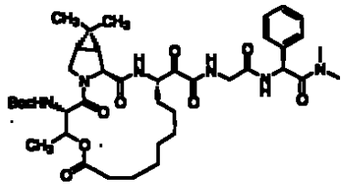


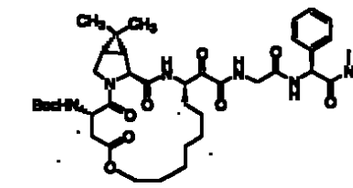




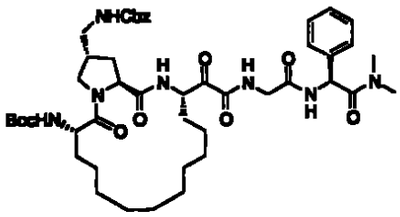
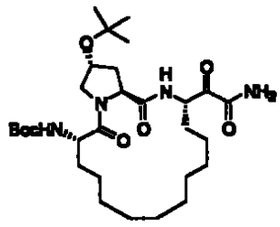
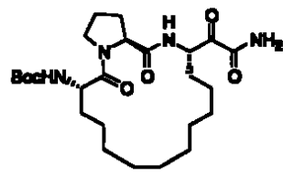
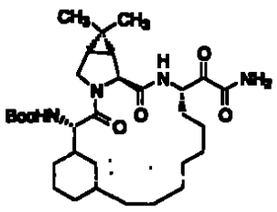
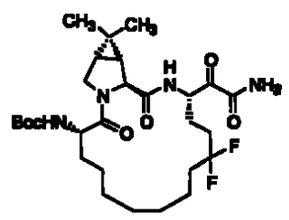
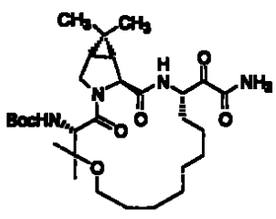
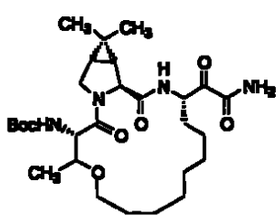
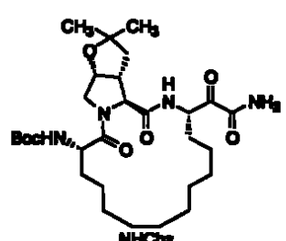
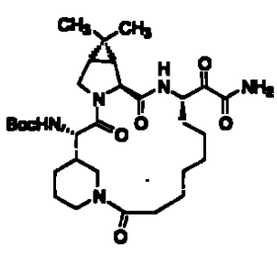
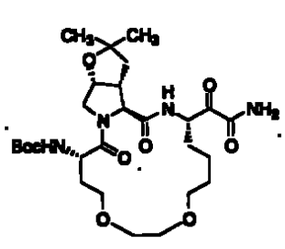
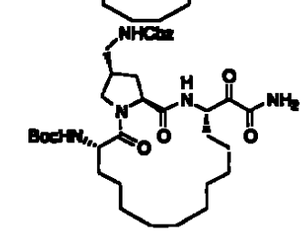


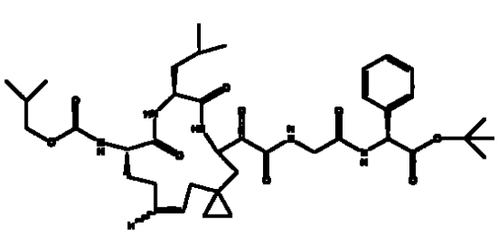
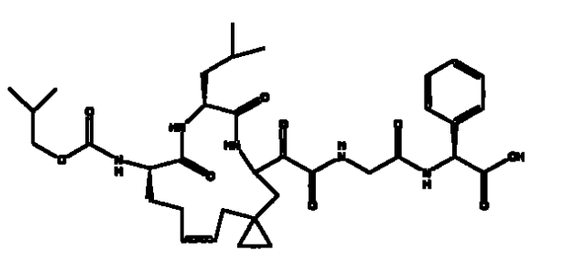






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La presente invención se refiere a inhibidores novedosos de proteasas del VHC. Esta utilidad se manifiesta en su capacidad para inhibir la serina proteasa NS2/NS4a del VHC según se demuestra en los siguientes ensayos *in vitro*.

Ensayo para determinar la Actividad Inhibidora de la proteasa del VHC

Ensayo Espectrofotométrico: Se realizaron ensayos epectrofotométricos para la serina proteasa del VHC sobre los compuestos de la invención siguiendo el procedimiento descripto por *R. Zhang et al., Analytical Biochemistry*, 270 (1999) 268-275, cuya revelación se incorpora a la presente a modo de referencia. El ensayo basado en la proteólisis de los sustratos con grupos éster cromogénicos es adecuado para el monitoreo continuo de la actividad de proteasa NS3 del VHC. Los sustratos derivaron del lado P de la secuencia de unión NS5A-NS5B (Ac-DTEDVVX(Nva), en la cual X = A o P) cuyos grupos carboxilo C-terminales se esterificaron con uno de cuatro alcoholes cromótoros diferentes (3 o 4-nitrofenol, 7-hidroxi-4-metil-cumarina o 4-fenilazofenol). A continuación se presenta la síntesis, caracterización y aplicación de estos ésteres sustratos espectrofotométricos a la exploración de alta definición y la evaluación cinética detallada de los inhibidores de la proteasa NS3 del VHC.

Materiales y Métodos:

Materiales: Se obtuvieron reactivos químicos para los buffers relacionados con los ensayos de Sigma Chemical Company (St. Louis, Missouri). Los reactivos para la síntesis de péptidos fueron de Aldrich Chemicals, Novabiochem (San Diego, California), Applied Biosystems (Foster City, California) y Perseptive Biosystems (Framingham, Massachusetts). Los péptidos se sintetizaron manualmente o en un sintetizador modelo 431A automatizado ABI (de Applied Biosystems). El espectrómetro UV/VIS Spectrometer modelo LAMBDA 12 fue de Perkin Elmer (Norwalk, Connecticut) y se obtuvieron placas UV de 96 pocillos de Corning (Corning, New York). El bloque de pre-calentamiento fue de

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USA Scientific (Ocala, Florida) y el agitador de placas de 96 pocillos fue de Labline Instruments (Melrose Park, Illinois). Se obtuvo un lector de placas de microtitulación Spectramax Plus con monocromador de Molecular Devices (Sunnyvale, California).

Preparación de la enzima: la proteasa heterodimérica recombinante NS3/NS4A del VHC (hebra 1a) se preparó utilizando los procedimientos publicados previamente (D. L. Sali *et al*, *Biochemistry*, 37 (1998) 3392-3401). Las concentraciones de proteína se determinaron por el método del colorante Biorad empleando patrones de proteasa de VHC recombinante cuantificados previamente por análisis de aminoácidos. Antes de comenzar el ensayo, el buffer de conservación de enzima (fosfato de sodio 50 mM, pH 8,0, NaCl 300 mM, 10% de glicerol, 0,05% de lauril maltósido y DTT 10 mM) se intercambió por el buffer de ensayo (MOPS 25 mM, pH 6,5, NaCl 300 mM, 10% de glicerol, 0,05% de lauril maltósido, EDTA 5 μM y DTT5 μM), empleando una columna pre-empacada Biorad Bio-Spin P-6.

Síntesis y Purificación del Sustrato: La síntesis de los sustratos se realizó según lo informado por *R. Zhang et al.*, (*ibid.*) y se inició mediante anclaje de Fmoc-Nva-OH a una resina de cloruro de 2-clorotritilo usando un protocolo estándar (K. Barlos *et al.*, *Int. J. Pept. Protein Res.*, 37 (1991), 513-520). Posteriormente los péptidos se ensamblaron, empleando química de Fmoc, ya sea manualmente o en un sintetizador automático de péptidos ABI modelo 431. Los fragmentos de péptido N-acetilados y totalmente protegidos se escindieron de la resina ya sea con ácido acético 10% (HOAc) y trifluoroetanol 10% (TFE) en diclorometano (DCM) durante 30 min, o mediante ácido trifluoroacético (TFA) 2% en DCM durante 10 min. El filtrado combinado y el lavado de DCM se evaporaron azeotrópicamente (o se extrajo repetidamente mediante solución acuosa de

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Na_2CO_3) para eliminar el ácido empleado en la ruptura. La fase de DCM se secó sobre Na_2SO_4 y se evaporó.

Los sustratos con grupo éster se ensamblaron usando procedimientos de acoplamiento ácido-alcohol estándar (*K. Holmber et al., Acta Chem. Scand.*, B33 (1979) 410-412). Los fragmentos de péptido se disolvieron en piridina anhidra (30-60 mg/ml) a lo cual se agregó 10 equivalentes molares de cromóforo y una cantidad catalítica (0,1 eq.) de ácido para-toluensulfónico (pTSA). Se agregó diciclohexilcarbodiimida (DCC, 3 eq.) para iniciar las reacciones de acoplamiento. La formación de producto se monitoreó mediante HPLC y se descubrió que se completaba después de 12-72 horas de reacción a temperatura ambiente. La piridina usada como solvente se evaporó al vacío y además se eliminó mediante evaporación azeotrópica con tolueno. El péptido éster se desprotegió con TFA 95% en DCM durante dos horas y se extrajo tres veces con etil éter anhidro para eliminar el exceso de cromóforo. El sustrato desprotegido se purificó mediante HPLC de fase reversa sobre una columna C3 o C8 con un gradiente de acetonitrilo de 30% a 60% (usando seis volúmenes de columna). El rendimiento global a continuación de la purificación con HPLC fue de aproximadamente el 20-30%. La masa molecular se confirmó mediante espectroscopía de masa de ionización por electroaspersión. Los sustratos se conservaron en forma de polvo seco bajo desecación.

Espectros de Sustratos y Productos: Los espectros de los sustratos y los correspondientes productos cromóforos se obtuvieron en el buffer de ensayo de pH 6,5. Los coeficientes de extinción se determinaron a la longitud de onda de los picos óptimos en cubetas de 1 cm (340 nm para 3-Np y HMC, 370 nm para PAP y 400 nm para 4-Np) usando múltiples diluciones. La longitud de onda de pico óptimo se definió como aquella longitud de onda que produce la máxima

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diferencia de fraccionamiento en absorbancia entre sustrato y producto (DO del producto – DO del sustrato)/DO del sustrato).

Ensayo de Proteasa: se realizaron ensayos de proteasa de VHC a 30°C usando 200 µl de mezcla de reacción en una placa de microtitulación de 96 pocillos. Se optimizaron las condiciones del buffer de ensayo (MOPS 25 mM, pH 6,5, NaCl 300 mM, glicerol 10%, lauril maltósido 0,05%, EDTA 5 µM y DTT 5 µM) para el heterodímero NS3/NS4A (D. L. Sall *et al*, *Ibid.*)). Típicamente, se colocaron en pocillos 150 µl de mezclas de buffer, sustrato e inhibitor (concentración final de DMSO ≤4% v/v) y se dejó preincubar a 30°C durante aproximadamente 3 minutos. Luego se usaron cincuenta µls de proteasa precalentada (12 nM, 30°C) en buffer de ensayo para iniciar la reacción (200 µl de volumen final). Se monitorearon las placas durante la extensión del ensayo (60 minutos) para detectar el cambio de absorbancia a la longitud de onda adecuada (340 nm para 3-Np y HMC, 370 nm para PAP y 400 nm para 4-Np) usando un lector de placas de microtitulación Spectromax Plus equipado con un monocromador (se pueden obtener resultados aceptables con lectores que utilizan filtros de corte). La ruptura proteolítica de la unión éster entre el Nva y el cromóforo se monitoreó a la longitud de onda adecuada contra un blanco sin enzima como control de hidrólisis no enzimática. La evaluación de los parámetros cinéticos del sustrato se realizó en un rango de concentración de sustrato de 30 veces (~6-200 µm). Las velocidades iniciales se determinaron usando una regresión lineal y se obtuvieron las constantes cinéticas ajustando los datos a la ecuación de Michaelis-Menten usando un análisis de regresión no lineal (Mac Curve Fit 1.1, K. Raner). Las cantidades de producción (k_{cat}) se calcularon suponiendo que le enzima se encontraba totalmente activa.

Evaluación de Inhibidores e Inactivadores: Se determinaron experimentalmente las constantes de inhibición (K_i^*) para los inhibidores competitivos Ac-D-(D-Gla)-L-

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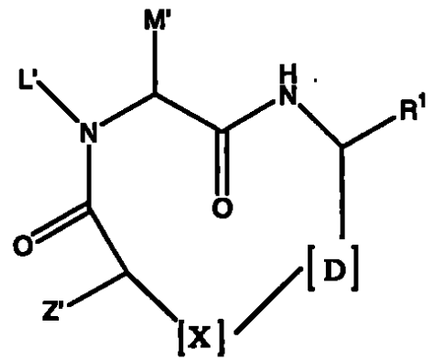
I-(Cha)-C-OH (27), Ac-DTEDVVA(Nva)-OH y Ac-DTEDVVP(Nva)-OH a concentraciones fijas de enzima y sustrato graficando v_o/v_i vs. concentración del inhibidor ($[I]_o$) de acuerdo con la ecuación reordenada de Michaelis-Menten para la cinética de inhibición competitiva: $v_o/v_i = 1 + [I]_o/(K_i (1 + [S]_o/K_m))$, donde v_o es la velocidad inicial no inhibida, v_i es la velocidad inicial en presencia de un inhibidor a cualquier concentración dada del inhibidor ($[I]_o$), y $[S]_o$ es la concentración del sustrato usada. Los datos resultantes se ajustaron usando regresión lineal y la pendiente resultante, $1/(K_i(1+[S]_o/K_m)$, se empleó para calcular el valor de K_i^*.

Los valores obtenidos de K_i para los diversos macrocicios de la presente invención se dan en las **Tablas 1, 2 y 2A**, en las cuales los compuestos se han organizado en el orden de rangos de valores de K_i^*, al igual que en la **Tabla 3**. A partir de estos resultados de ensayos, sería evidente para un experto en la técnica que los compuestos de la invención poseen una utilidad excelente como inhibidores de la serina proteasa NS3.

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REIVINDICACIONES

1. Un compuesto que posee la estructura general que se muestra en la Fórmula 1:



Fórmula 1

o sales, solvatos o ésteres aceptables para uso farmacéutico de dicho compuesto en el cual:

(1) R^1 es $-C(O)R^5$ o $-B(OR)_2$;

(2) R^5 es H, -OH, $-OR^8$, $-NR^9R^{10}$, $-C(O)OR^8$, $-C(O)NR^9R^{10}$, $-CF_3$, $-C_2F_5$, $-C_3F_7$, $-CF_2R^6$, $-R^6$, $-C(O)R^7$ o $NR^7SO_2R^8$;

(3) R^7 es H, -OH, $-OR^8$ o $-CHR^9R^{10}$;

(4) R^6, R^8, R^9 y R^{10} pueden ser iguales o diferentes, seleccionándose cada uno independientemente del grupo que consiste en H, alquilo, alquenilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, arilalquilo, heteroarilalquilo, R^{14},

$-CH(R^{1'})CH(R^{1'})C(O)OR^{11}$,

$-[CH(R^{1'})]_pC(O)OR^{11}$,

$-[CH(R^{1'})]_pC(O)NR^{12}R^{13}$,

$-[CH(R^{1'})]_pS(O_2)R^{11}$,

$-[CH(R^{1'})]_pC(O)R^{11}$,

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-$[CH(R^{1'})]_pS(O_2)NR^{12}R^{13}$,

-$CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$,

-$CH(R^{1'})CH(R^{1'})C(O)NR^{12}R^{13}$,

-$CH(R^{1'})CH(R^{1'})S(O_2)R^{11}$,

-$CH(R^{1'})CH(R^{1'})S(O_2)NR^{12}R^{13}$,

-$CH(R^{1'})CH(R^{1'})C(O)R^{11}$,

-$[CH(R^{1'})]_pCH(OH)R^{11}$,

-$CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$,

-$C(O)N(H)CH(R^{2'})C(O)OR^{11}$,

-$C(O)N(H)CH(R^{2'})C(O)R^{11}$,

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

-$CH(R^{1'})C(O)N(H)CH(R^{2'})R'$,

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

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

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

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

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

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

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

en los cuales $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, R^{12} y R^{13} pueden ser iguales o diferentes, seleccionándose cada uno independientemente del grupo conformado por: H, halógeno, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, alcoxi, ariloxi, alquenilo, alquinilo, alquil-arilo, alquil-heteroarilo, heterocicloalquilo, aril-alquilo y heteroaralquilo;

o R^{12} y R^{13} se juntan de forma tal que la combinación es cicloalquilo, heterocicloalquilo, arilo o heteroarilo;

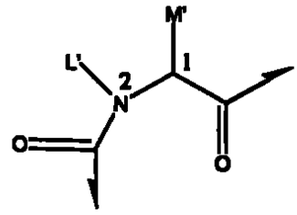
R^{14} se encuentra presente o no y si se encuentra presente se selecciona del grupo conformado por: H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, alquil-arilo, alilo, alquil-heteroarilo, alcoxi, aril-alquilo, alquenilo, alquinilo y heteroaralquilo;

(5) R y R' se encuentran presentes o no y si se encuentran presentes pueden ser iguales o diferentes, seleccionándose cada uno independientemente del grupo conformado por: H, OH, alquilo C_1-C_{10}, alquenilo C_2-C_{10}, cicloalquilo C_3-C_8, heterocicloalquilo C_3-C_8, alcoxi, ariloxi, alquiltio, ariltio, alquilamino, arilamino, amino, amido, ariltioamino, arilcarbonilamino, arilaminocarboxi, alquilaminocarboxi, heteroalquilo, alquenilo, alquinilo, (aril)alquilo, heteroarilalquilo, éster, ácido carboxílico, carbamato, urea, cetona, aldehído, ciano, nitro, halógeno, (cicloalquil)alquilo, arilo, heteroarilo, (alquil)arilo, alquilheteroarilo, alquil-heterociclilo y (heterocicloalquil)alquilo, donde dicho cicloalquilo está compuesto por tres a ocho átomos de carbono, y cero a 6 átomos de oxígeno, nitrógeno, azufre o fósforo y dicho alquilo es de uno a seis átomos de carbono;

(6) L' es H, OH, alquilo, heteroalquilo, arilo, heteroarilo, cicloalquilo o heterociclilo;

(7) M' es H, alquilo, heteroalquilo, arilo, heteroarilo, cicloalquilo, arilalquilo, heterociclilo o una cadena lateral de aminoácido;

o L' y M' se unen para formar una estructura anular tal que la porción de la Fórmula estructural 1 representada por

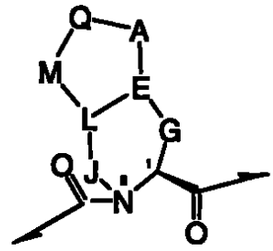


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(habiéndose agregado los números 1 y 2 para mostrar la ubicación de un cierto átomo de carbono y de cierto átomo de nitrógeno, respectivamente)

se representa mediante la Fórmula estructural 2:



Fórmula 2

donde en la Fórmula 2:

E está presente o ausente y si se encuentra presente es C, CH, N o C(R);

J está presente o ausente, y cuando J se encuentra presente, J es $(CH_2)_p$, $(CHR\text{-}CHR')_p$, $(CHR)_p$, $(CRR')_p$, $S(O_2)$, N(H), N(R) u O; cuando J está ausente y G se encuentra presente, L está unido directamente al átomo de nitrógeno marcado como posición 2;

p es un número de 0 a 6;

L está presente o ausente, y cuando L se encuentra presente, L es C(H) o C(R); cuando L está ausente, M está presente o ausente; si M se encuentra presente estando L ausente, entonces M está directa e independientemente unido a E, y J está directa e independientemente unido a E;

G está presente o ausente, y cuando G se encuentra presente, G es $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$ o $(CRR')_p$; cuando G está ausente, J se encuentra presente y E está conectado directamente al átomo de carbono marcado como posición 1;

Q está presente o ausente, y cuando Q se encuentra presente, Q es NR, PR, (CR=CR), $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, $(CHR\text{-}CHR')_p$, O, NR, S, SO, o SO_2; cuando Q se encuentra ausente, M está (i) ya sea directamente unido a A o (ii) a un sustituyente independiente sobre L, seleccionándose dicho sustituyente

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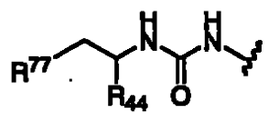
independiente de -OR, -CH(R)(R'), $S(O)_{0-2}R$ o –NRR' o (iii) ausente; cuando ambos Q y M están ausentes, A está ya sea unido directamente a L, o A es un sustituyente independiente sobre E, seleccionándose dicho sustituyente independiente de -OR, -CH(R)(R'), $S(O)_{0-2}R$ o –NRR' o A se encuentra ausente;

A está presente o ausente y si se encuentra presente A es O, O(R), $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, N(R), NRR', S, $S(O_2)$, -OR, CH(R)(R') o NRR'; o A está unido a M para formar un puente cicloalquilo, alifático o heterocíclico;

M está presente o ausente, y cuando M se encuentra presente, M es halógeno, O, OR, N(R), S, $S(O_2)$, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$ o $(CRR')_p$; o M está unido a A para formar un puente cicloalquilo, alifático o heterocicloalquilo;

(8) Z' está representado por cualquiera de (i), (ii), (iii), (iv) o (v) que se muestran a continuación:

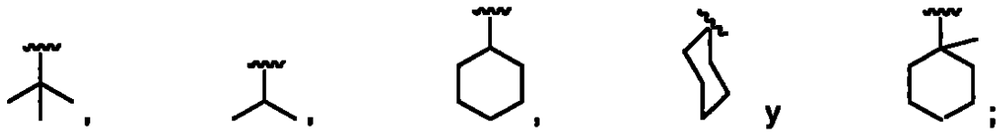
(i)



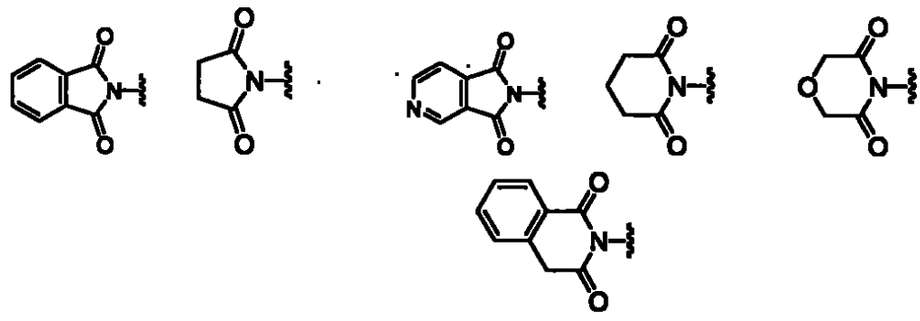
Fórmula A

en la cual:

R^{44} se selecciona del grupo que consiste en:

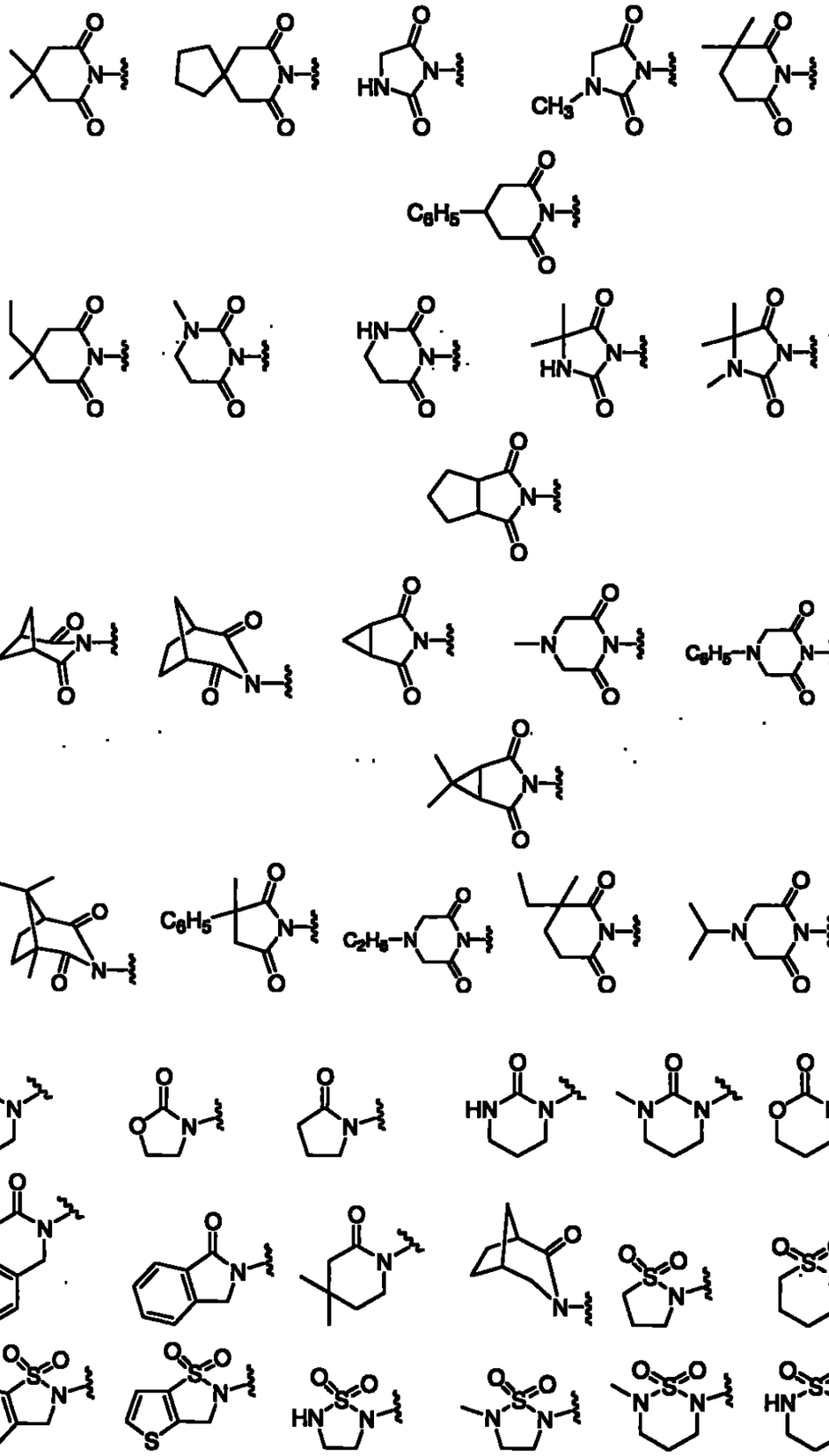


y R^{77} se selecciona del grupo que consiste en:



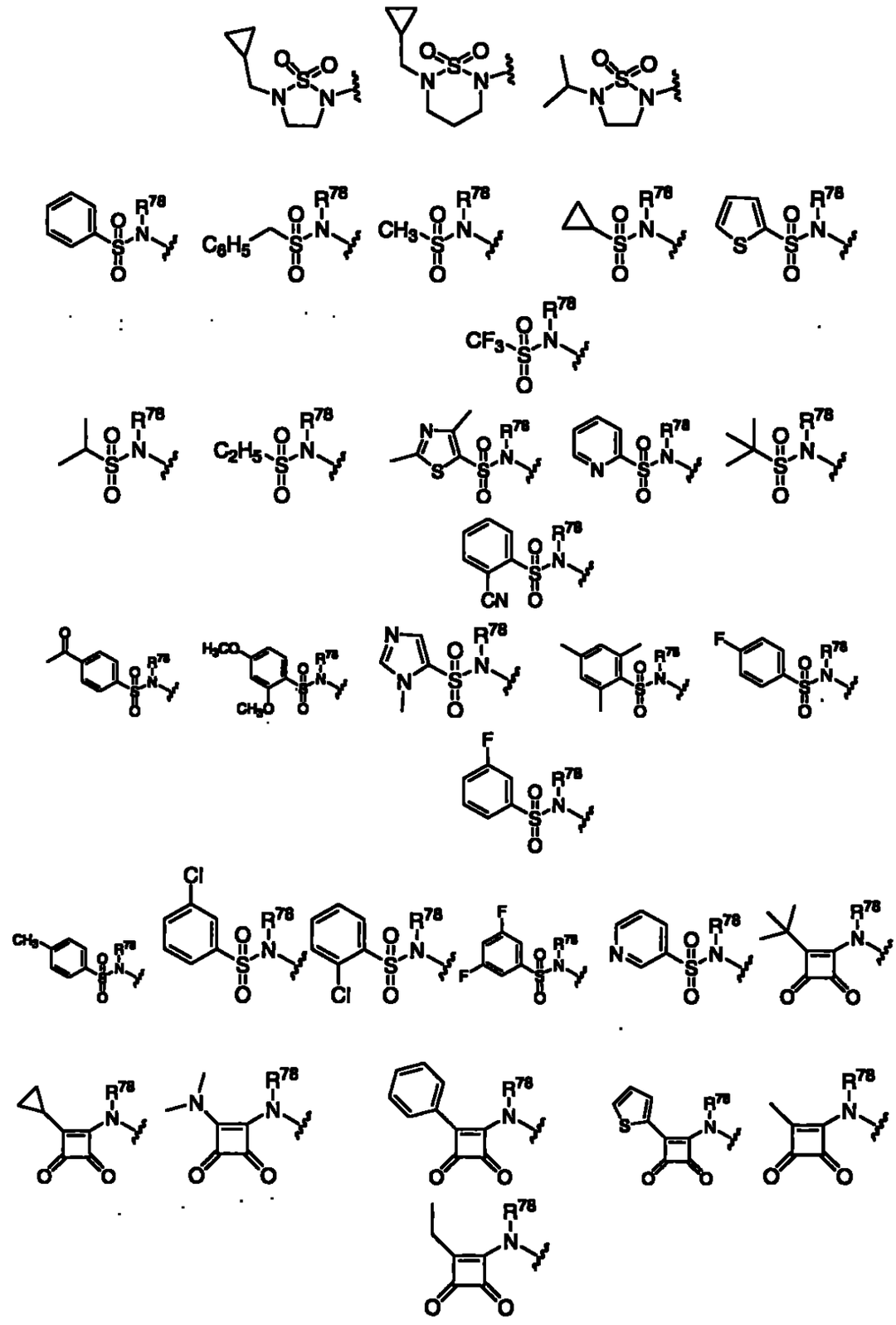
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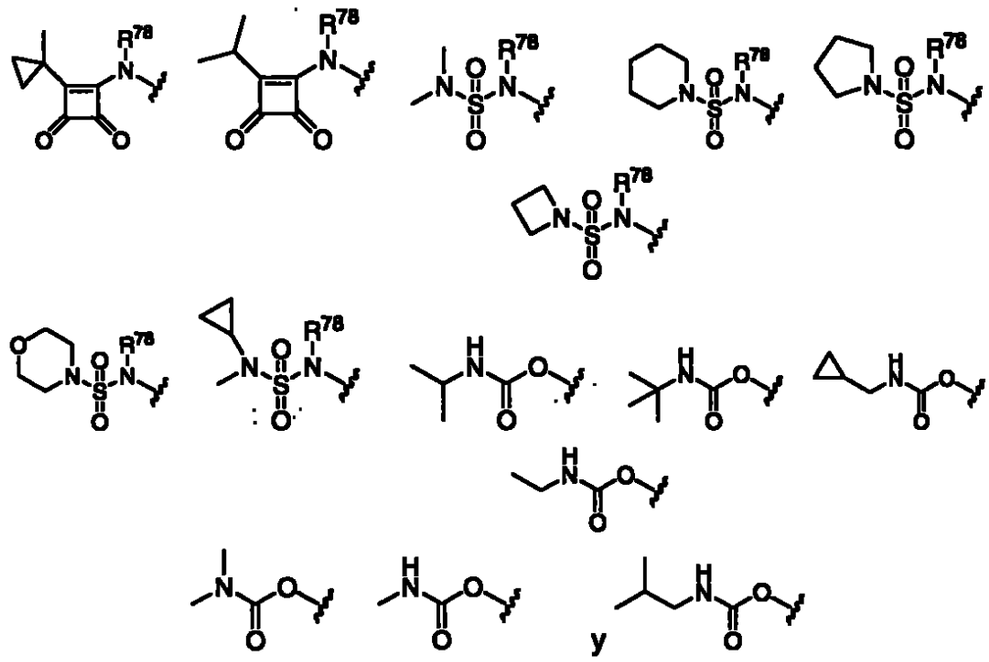
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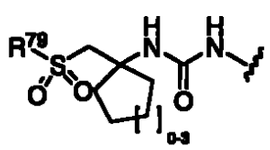
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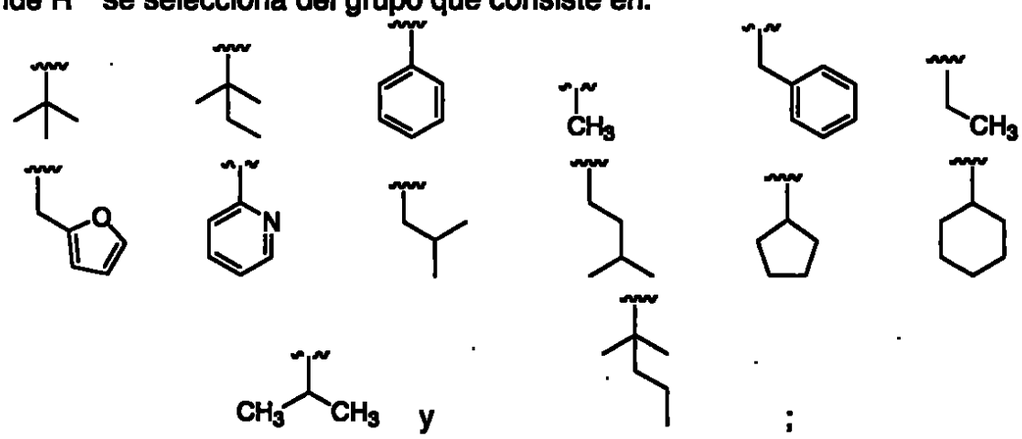
en los cuales R^{78} se selecciona de metilo, etilo, isopropilo, ter-butilo y fenilo;

(ii)



Fórmula B

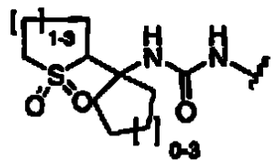
donde R^{79} se selecciona del grupo que consiste en:



(iii)

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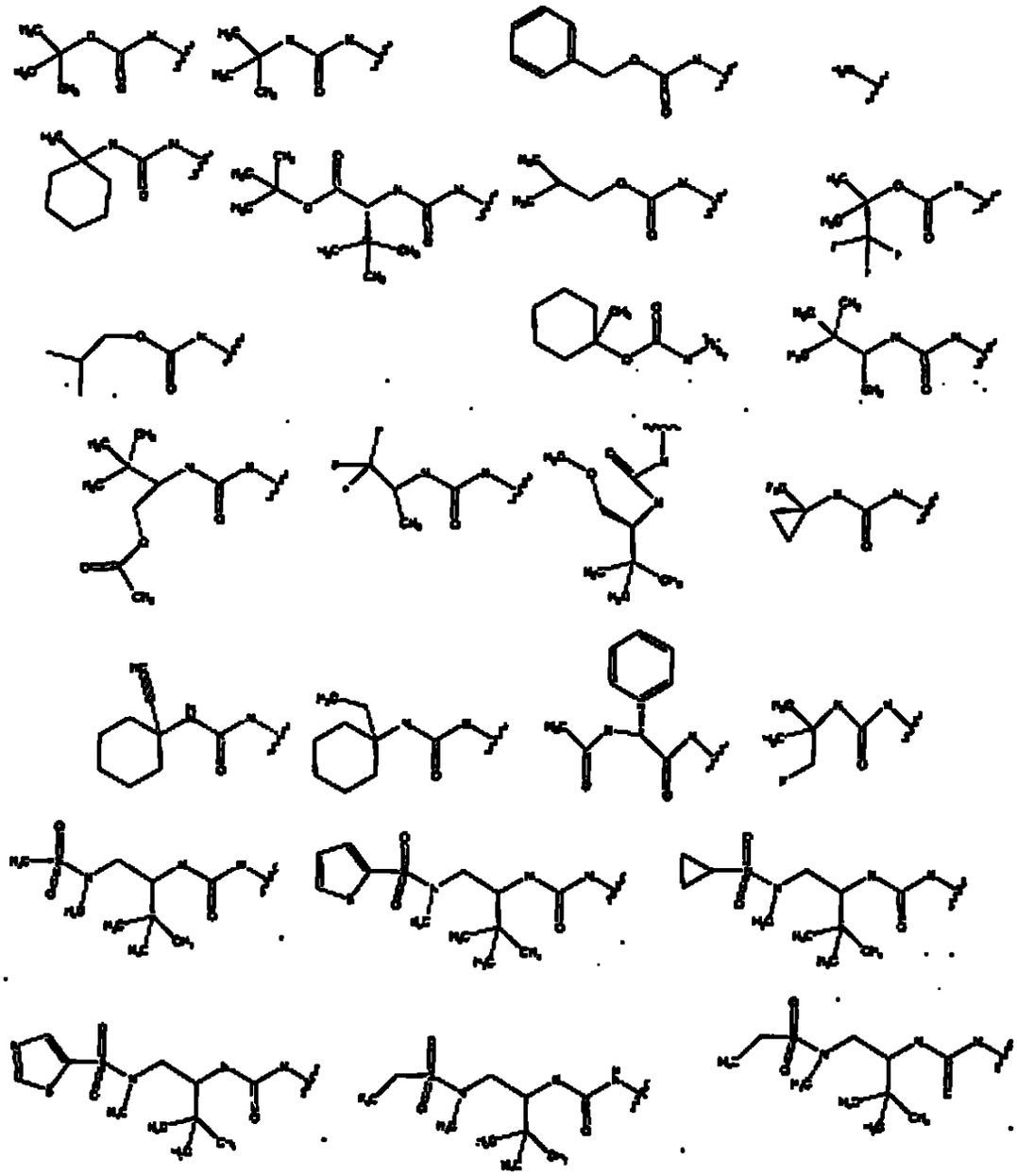
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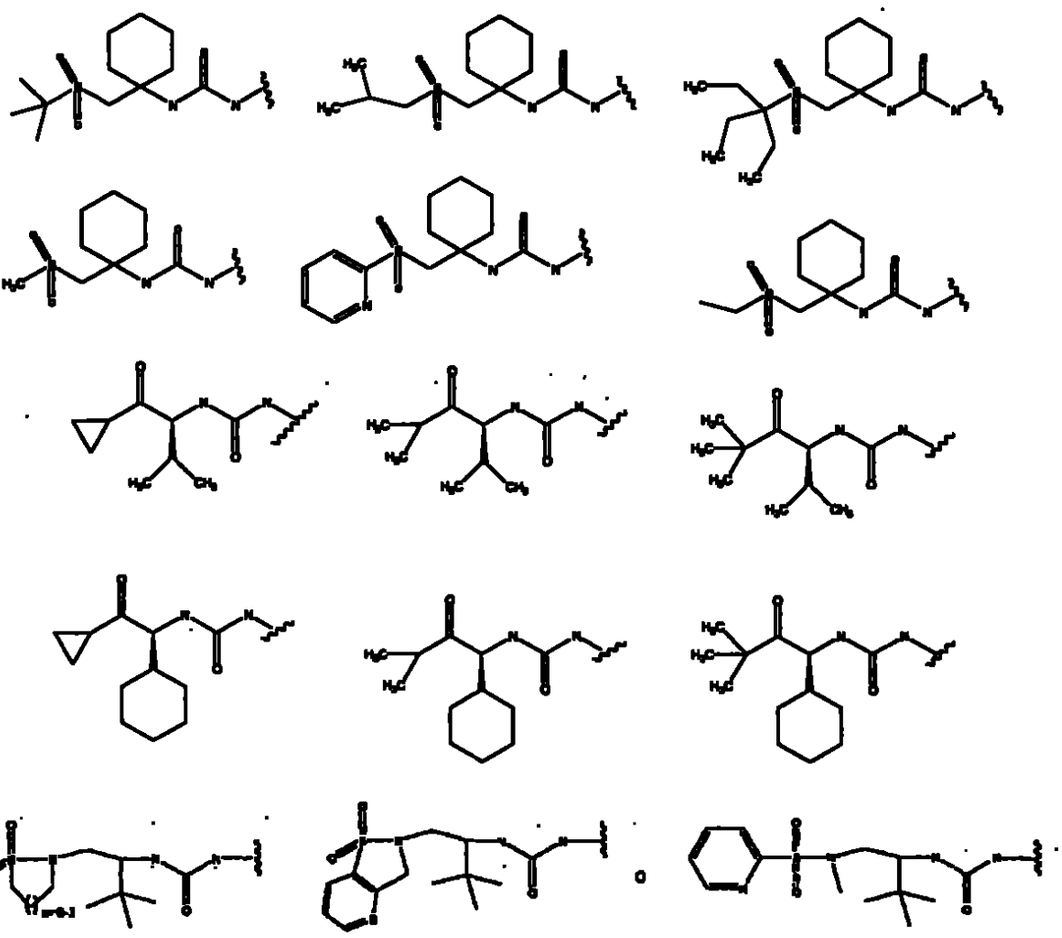


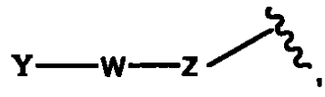
Fórmula C

en la cual el anillo de sulfona está sustituido opcionalmente con alquilo y cicloalquilo;

(iv) el resto:





(v) el resto: 

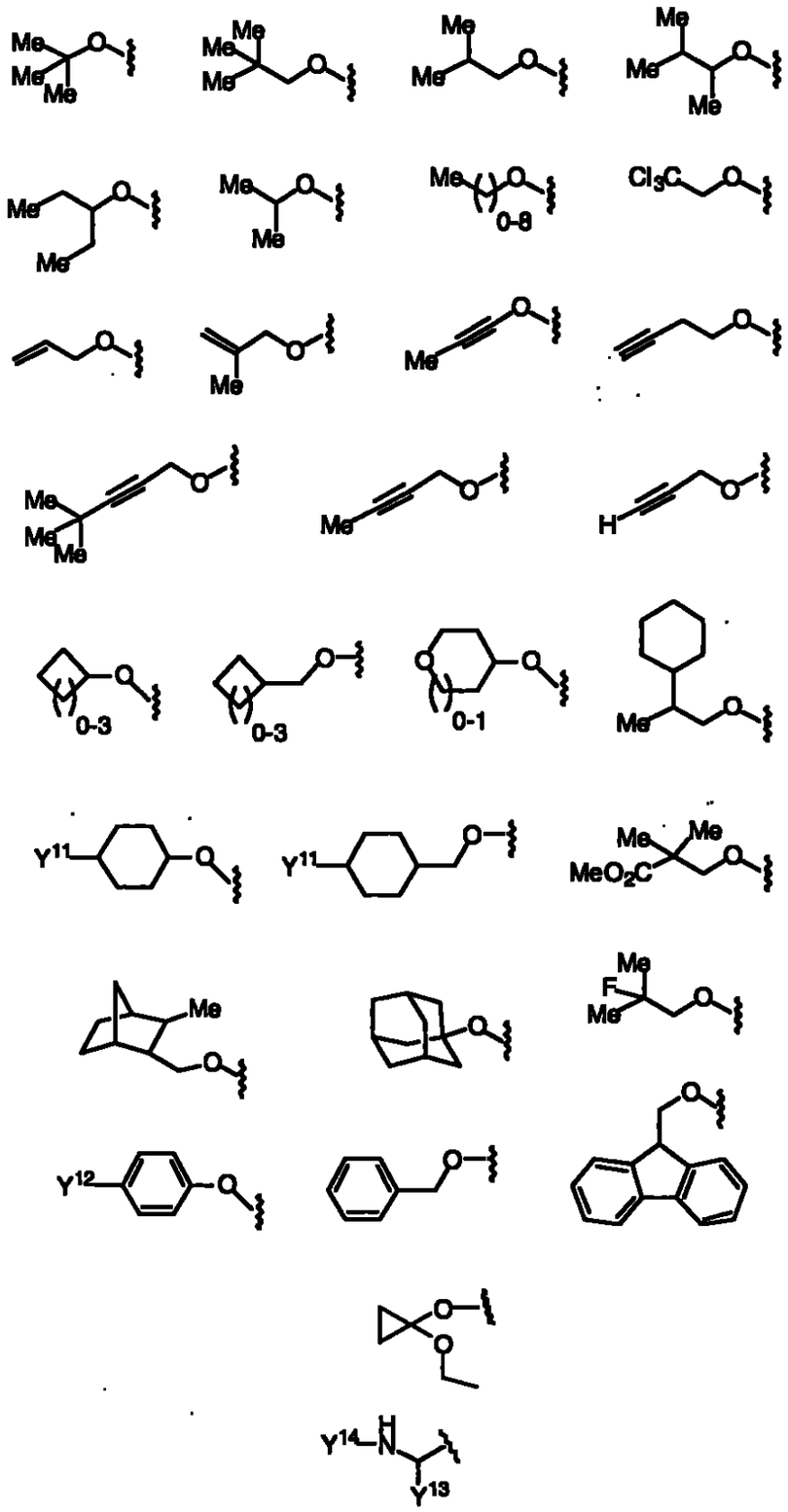
en el cual W es –C(=O)- o -S(O_2)- ;

Z es O o N;

e Y se selecciona del grupo que consiste en:

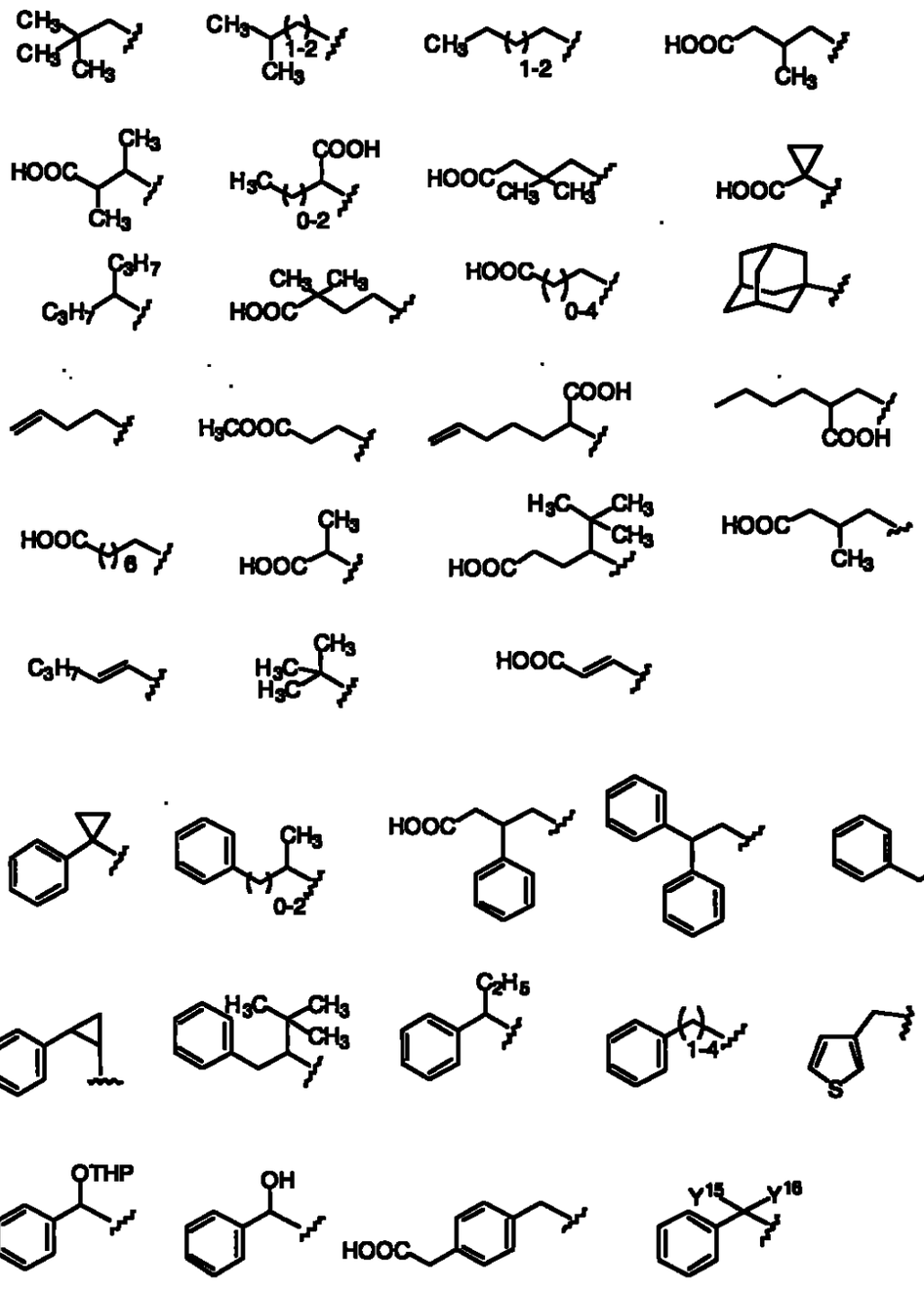
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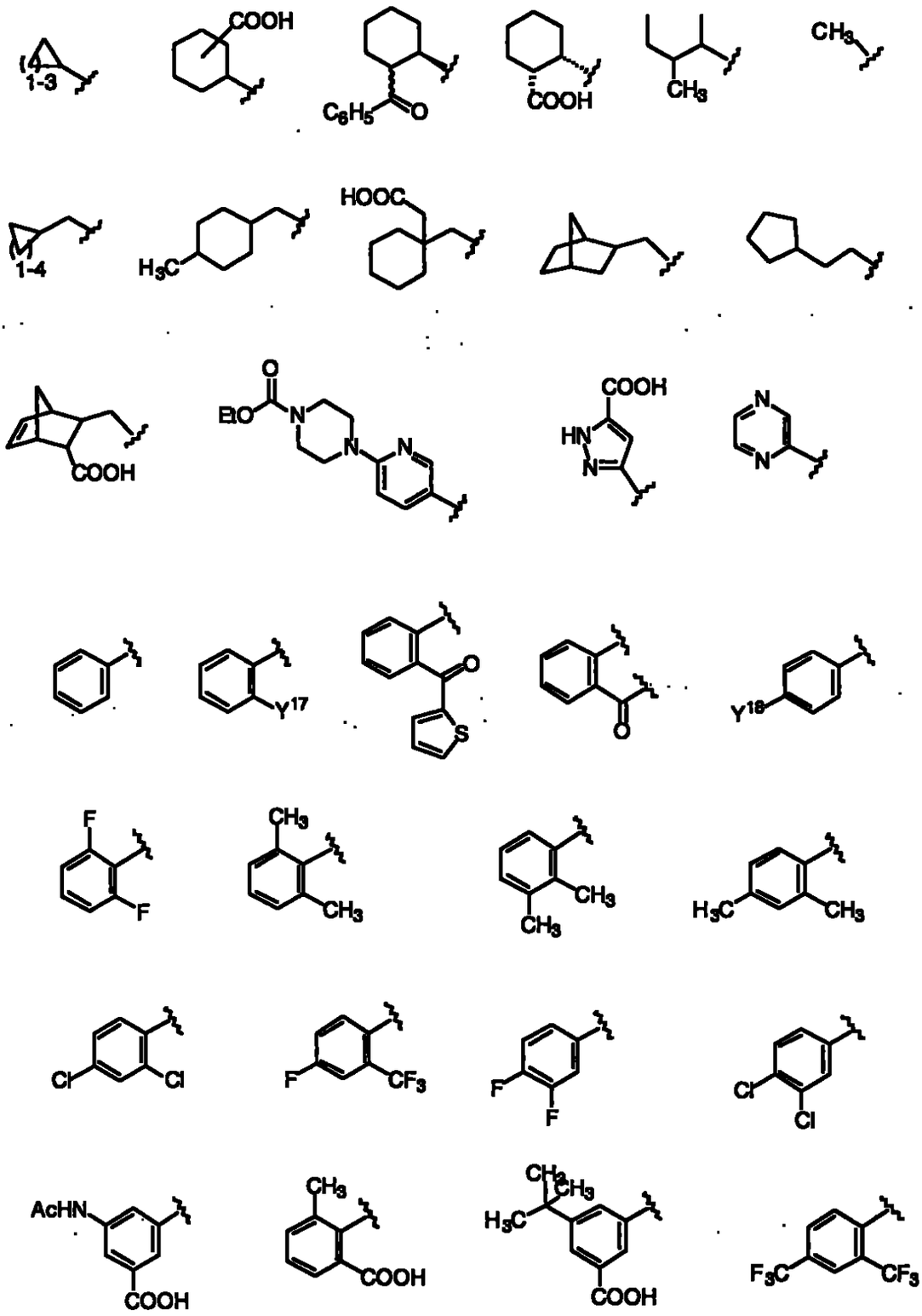
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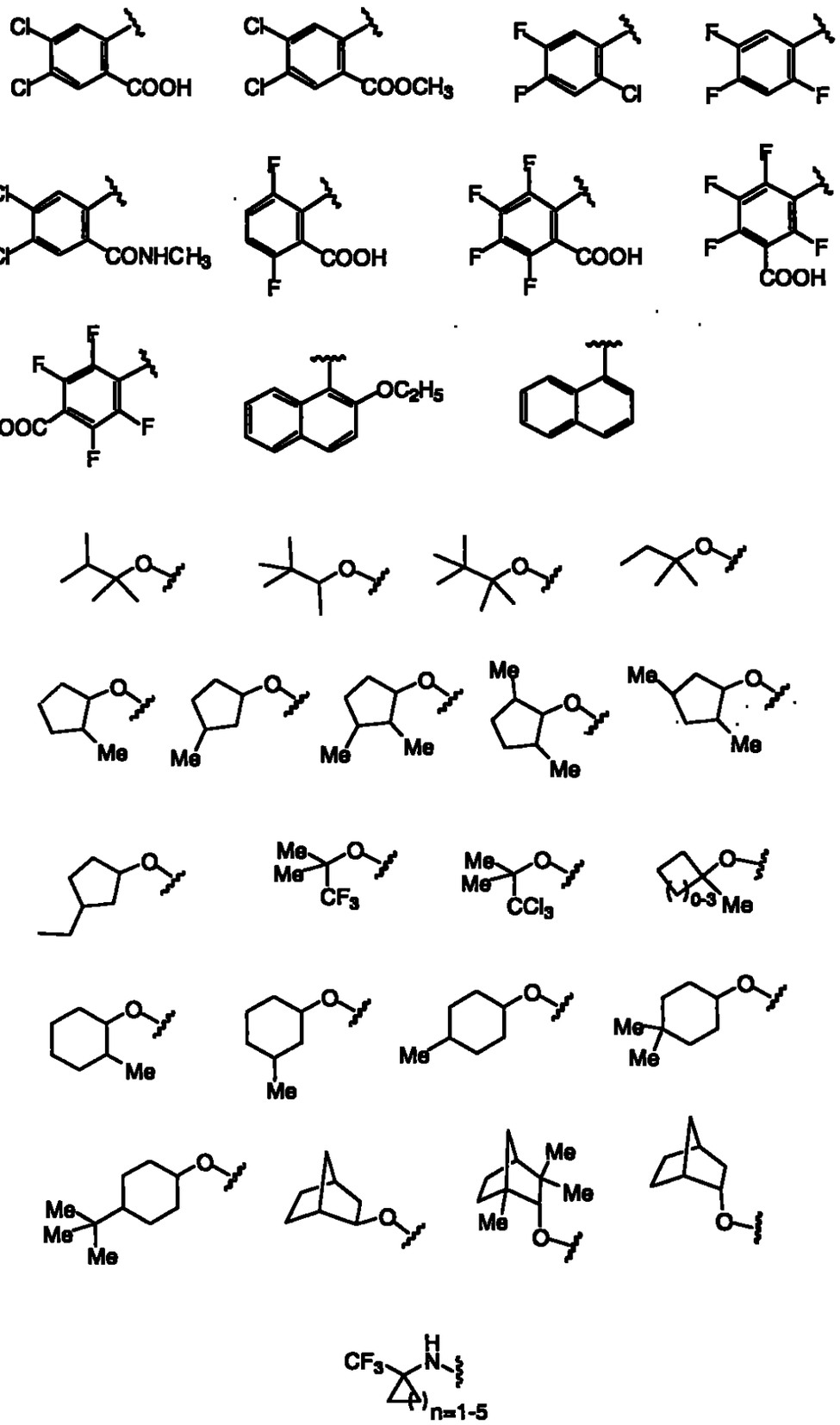

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MeO2C
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Y12

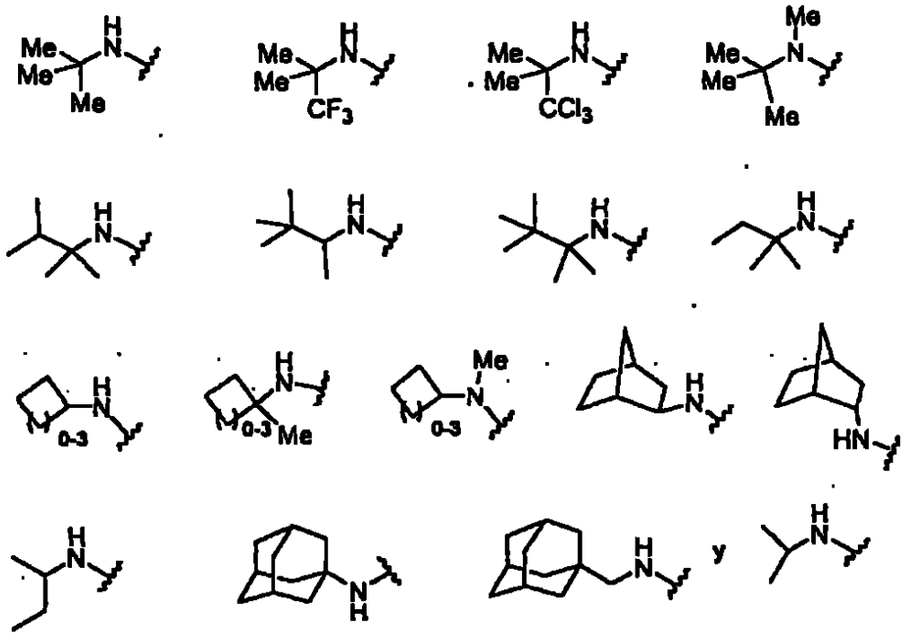
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COOH
CH3
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H3C
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EtO
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COOH
HN
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N
Y17
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Y18
F
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H3C
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Me
CF3
H
N
(CH2)n=1-5

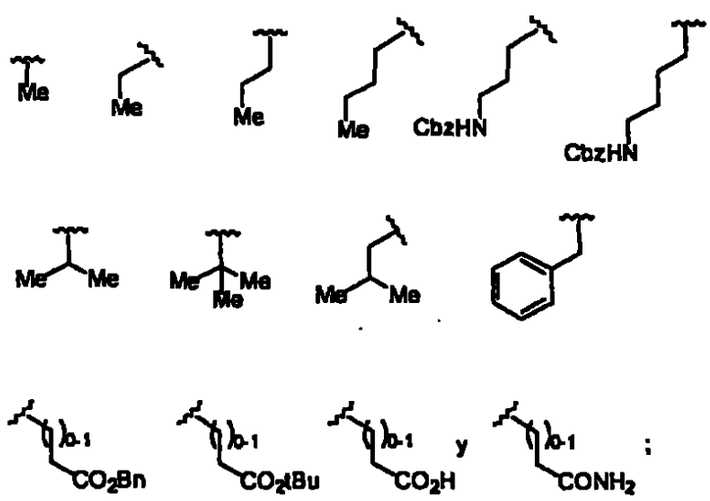


donde:

Y^{11} se selecciona del grupo que consiste en: H, -C(O)OH, -C(O)OEt, -OMe, -Ph, -OPh, -NHMe, -NHAc, -NHPh, $-CH(Me)_2$, 1-triazolilo, 1-imidazolilo y $-NHCH_2COOH$;

Y^{12} se selecciona del grupo que consiste en: H, -C(O)OH, -C(O)OMe, -OMe, F, Cl y Br;

Y^{13} se selecciona del grupo que consiste en los siguientes restos:



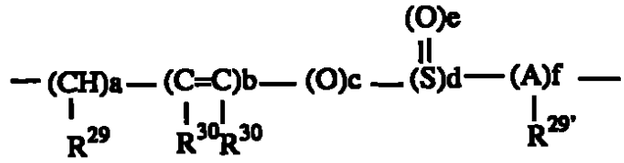
Y^{14} es $MeS(O_2)$-, -Ac, -Boc, -iBoc, -Cbz o -Alloc;

Y^{15} e Y^{16} pueden ser iguales o diferentes y se seleccionan independientemente del grupo que consiste en: alquilo, arilo, heteroalquilo y heteroarilo;

Y^{17} es $-CF_3$, $-NO_2$, $-C(O)NH_2$, -OH, $-C(O)OCH_3$, $-OCH_3$, $-OC_6H_5$, $-C_6H_5$, $-C(O)C_6H_5$, $-NH_2$ o $-C(O)OH$; y

Y^{18} es $-C(O)OCH_3$, $-NO_2$, $-N(CH_3)_2$, F, $-OCH_3$, $-C(H_2)C(O)OH$, -C(O)OH, $-S(O_2)NH_2$, o $-N(H)C(O)CH_3$;

(9) X se representa por la Fórmula estructural 4:



Fórmula 4

donde en la Fórmula 4, a es 2, 3, 4, 5, 6, 7, 8 o 9;

b, c, d, e y f pueden ser iguales o diferentes, siendo cada uno independientemente 0, 1, 2, 3, 4 o 5;

A es C, N, S u O;

R^{29} y $R^{29'}$ se encuentran independientemente presentes o ausentes y si se encuentran presentes pueden ser iguales o diferentes, siendo cada uno independientemente uno o dos sustituyentes seleccionados del grupo conformado por: H, halo, alquilo, arilo, cicloalquilo, cicloalquilamino, cicloalquilaminocarbonilo, ciano, hidroxi, alcoxi, alquiltio, amino, -NH(alquilo), -NH(cicloalquilo), $-N(alquilo)_2$, carboxilo, -C(O)O-alquilo, heteroarilo, aralquilo, alquilarilo, aralquenilo, heteroaralquilo, alquilheteroarilo, heteroaralquenilo, hidroxialquilo, ariloxi, aralcoxi, acilo, aroilo, nitro, ariloxicarbonilo, aralcoxicarbonilo, alquilsulfonilo, arilsulfonilo,

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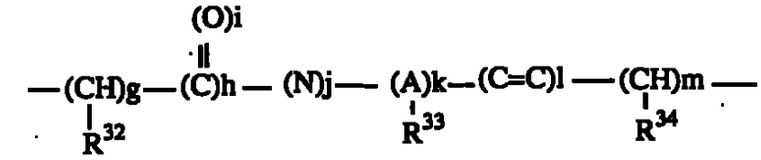
heteroarilsulfonilo, alquilsulfinilo, arilsulfinilo, heteroarilsulfinilo, ariltio, heteroariltio, aralquiltio, heteroaralquiltio, cicloalquenilo, heterociclilo, heterociclenilo, Y_1Y_2N-alquil-, $Y_1Y_2NC(O)$- e $Y_1Y_2NSO_2$-, en los cuales Y_1 e Y_2 pueden ser iguales o diferentes y se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, arilo, y aralquilo;

o

R^{29} y $R^{29'}$ están unidos de manera que la combinación es una cadena alifática o heteroalifática de 0 a 6 carbonos;

R^{30} está presente o ausente y si se encuentra presente es uno o dos sustituyentes seleccionados independientemente del grupo conformado por: H, alquilo, arilo, heteroarilo y cicloalquilo;

(10) D en la Fórmula 1 se representa por la Fórmula estructural 5:



Fórmula 5

donde en la Fórmula 5, R^{32}, R^{33} y R^{34} se encuentran presentes o ausentes y si se encuentran presentes son independientemente uno o dos sustituyentes seleccionados independientemente del grupo que consiste en: H, halo, alquilo, arilo, cicloalquilo, cicloalquilamino, espiroalquilo, cicloalquilaminocarbonilo, ciano, hidroxi, alcoxi, alquiltio, amino, -NH(alquilo), -NH(cicloalquilo), -N(alquilo)$_2$, carboxilo, –C(O)O-alquilo, heteroarilo, aralquilo, alquilarilo, aralquenilo, heteroaralquilo, alquilheteroarilo, heteroaralquenilo, hidroxialquilo, ariloxi, aralcoxi, acilo, aroilo, nitro, ariloxicarbonilo, aralcoxicarbonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquilsulfinilo, arilsulfinilo, heteroarilsulfinilo, ariltio, heteroariltio, aralquiltio, heteroaralquiltio, cicloalquenilo, heterociclilo, heterociclenilo, Y_1Y_2N-alquil-, $Y_1Y_2NC(O)$- e $Y_1Y_2NSO_2$-, en los cuales Y_1 e Y_2 pueden ser iguales o

diferentes y se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, arilo y aralquilo;

o

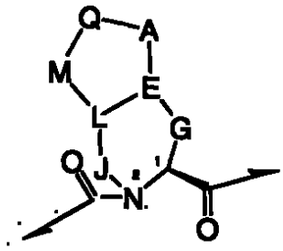
R^{32} y R^{34} están unidos de manera que la combinación forma una porción de un grupo cicloalquilo;

g es 1, 2, 3, 4, 5, 6, 7, 8 o 9;

h, i, j, k, l y m pueden ser iguales o diferentes, siendo cada uno independientemente 0, 1, 2, 3, 4 o 5; y

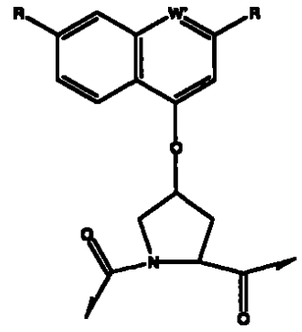
A es C, N, S u O,

(11) siempre que en la Fórmula 1 cuando la Fórmula estructural 2:



Fórmula 2

es



y

W' es CH o N, se aplican ambas exclusiones condicionales (i) y (ii) siguientes:

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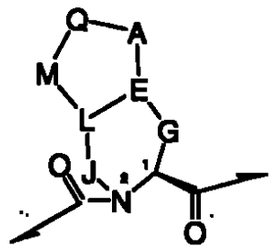
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exclusión condicional (i): Z' no es –NH–R^{36}, en el cual R^{36} es H, arilo C_6, arilo C_{10}, heteroarilo, –C(O)–R^{37}, –C(O)–OR^{37} o –C(O)–NHR^{37}, donde R^{37} es alquilo C_{1-6} o cicloalquilo C_{3-6};

y

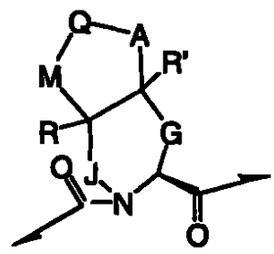
exclusión condicional (ii): R^1 no es–C(O)OH, una sal aceptable para uso farmacéutico de –C(O)OH, un éster de –C(O)OH o –C(O)NHR^{38}, donde R^{38} se selecciona del grupo que consiste en alquilo C_{1-6}, cicloalquilo C_{3-6}, arilo C_6, arilo C_{10} o aralquilo C_{7-16}.

2. El compuesto de acuerdo con la Reivindicación 1, en el cual la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2:



es

Fórmula 2



;

G y J pueden o no encontrarse presentes independientemente y si se encuentran presentes pueden ser iguales o diferentes y se seleccionan independientemente del grupo que consiste en $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$ y $(CRR')_p$;

A y M independientemente pueden o no encontrarse presentes y si se encuentran presentes pueden ser iguales o diferentes y se seleccionan independientemente del grupo que consiste en O, S, $S(O_2)$, N(R), $(CH_2)_p$, $(CHR)_p$,

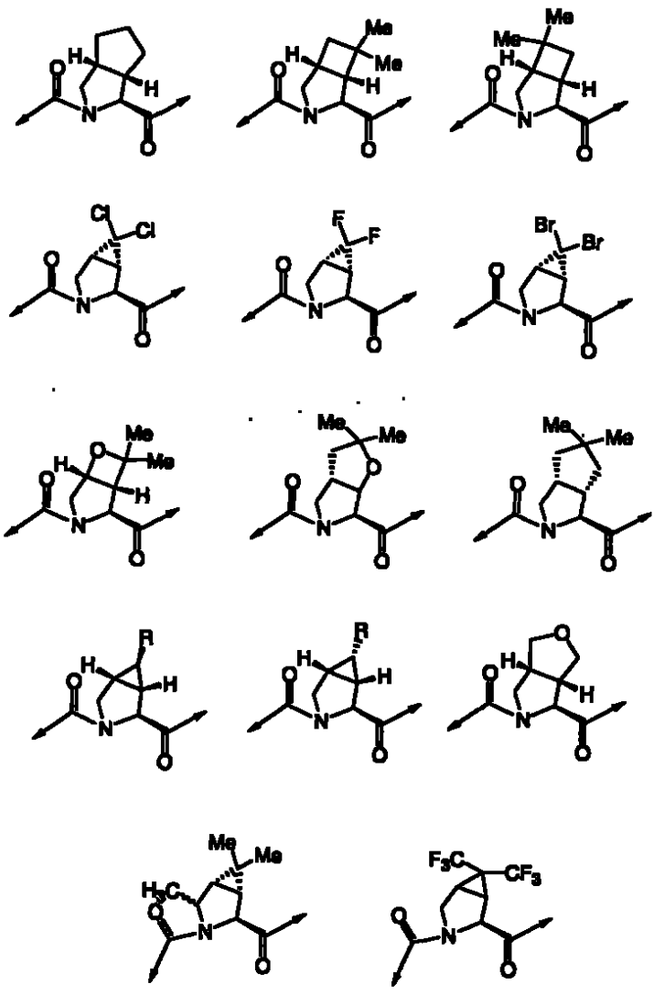
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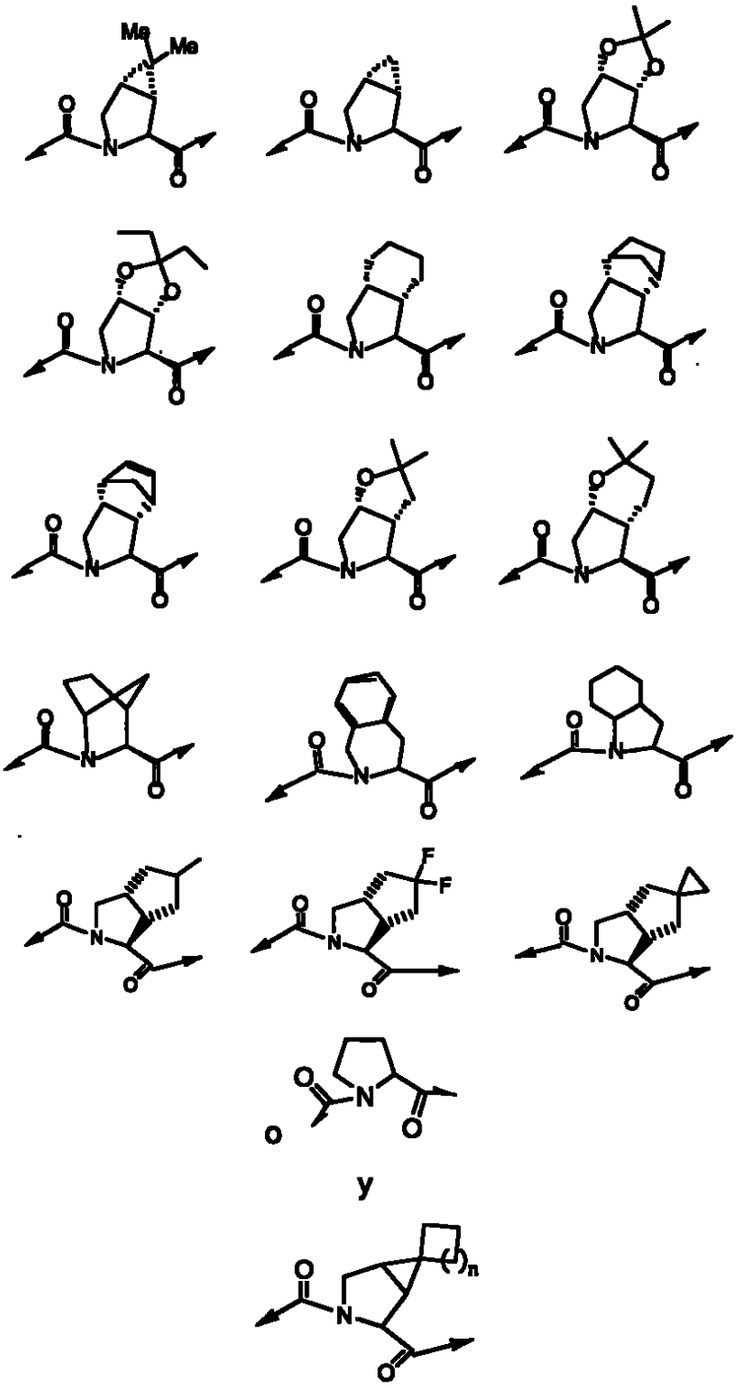
$(CHR\text{-}CHR')_p$ y $(CRR')_p$; o A y M están unidos para formar un puente cicloalquilo o heterocíclico; y

Q puede o no encontrarse presente y si se encuentra presente es $(CH_2)_p$, N(R), O, S, $S(O_2)$, $(CHR)_p$ o $(CRR')_p$.

3. El compuesto de acuerdo con la Reivindicación 2, en el cual la porción representada por la Fórmula etructural 2 se selecciona de las siguientes estructuras:



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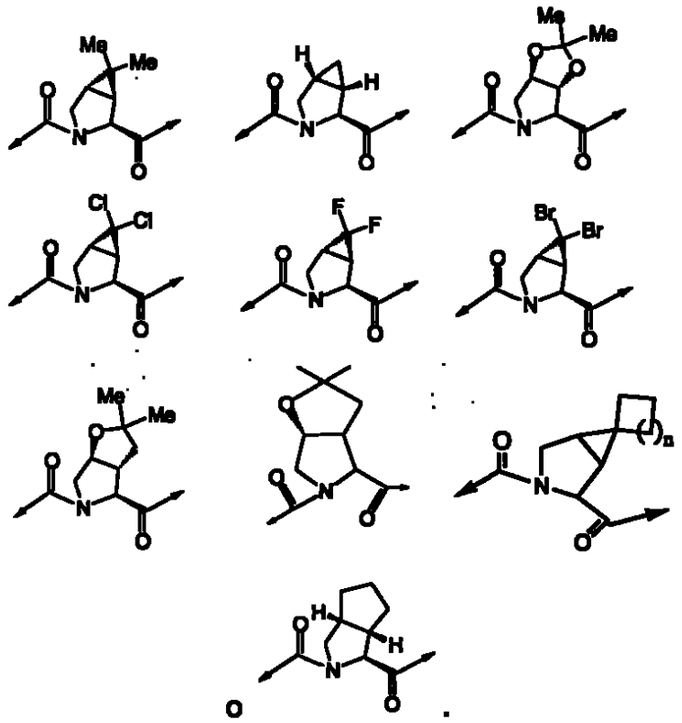
o

y

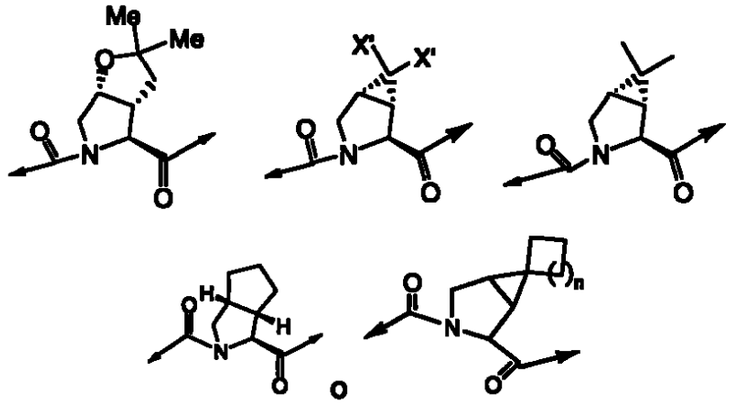
en las cuales n= 0-4.

4. El compuesto de acuerdo con la Reivindicación 3, en el cual la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2 se selecciona de las siguientes estructuras:

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653

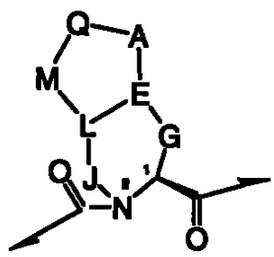


5. El compuesto de acuerdo con la Reivindicación 4, en el cual la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2 se selecciona de las siguientes estructuras:



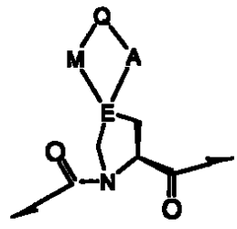
en las cuales X' es H, F, Cl o Br.

6. El compuesto de acuerdo con la Reivindicación 1, en el cual la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2:



es

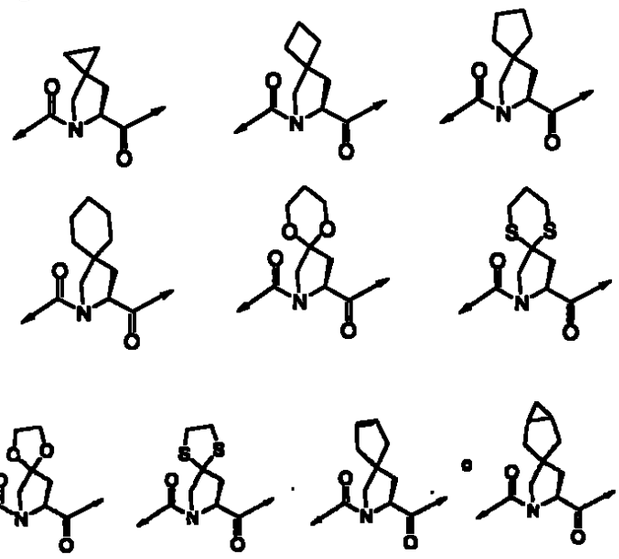
Fórmula 2



; y

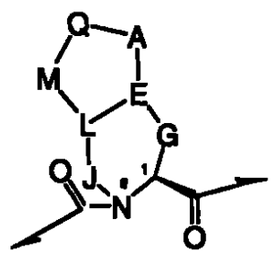
Q puede encontrarse presente o ausente, y si Q se encuentra ausente, M está unido directamente a A.

7. El compuesto de acuerdo con la Reivindicación 6, en el cual la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2 se selecciona de las siguientes estructuras:



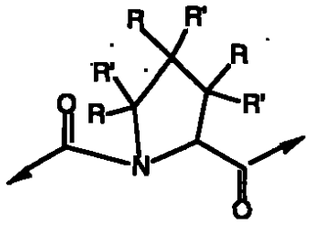
8. El compuesto de acuerdo con la Reivindicación 1, en el cual la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2:

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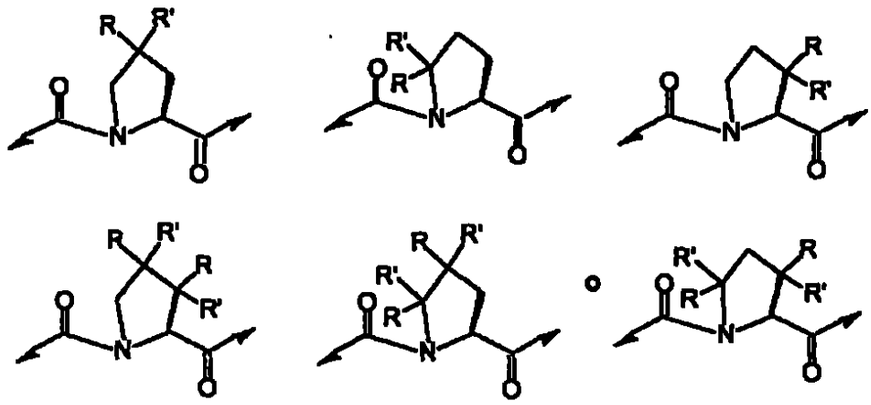


es

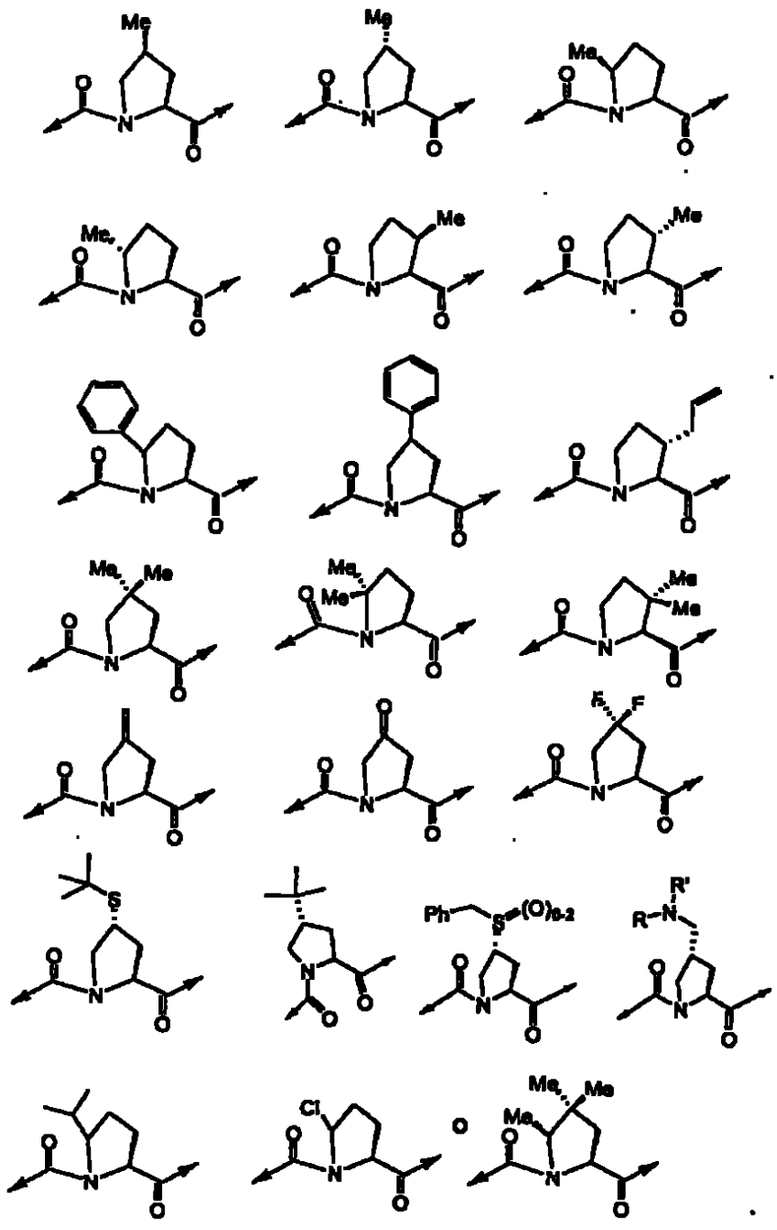
Fórmula 2



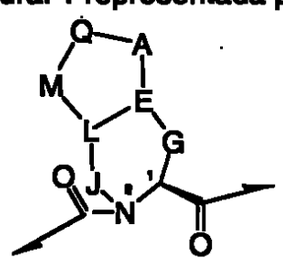
9. El compuesto de acuerdo con la Reivindicación 8, en el cual la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2 se selecciona de las siguientes estructuras:



10. El compuesto de acuerdo con la Reivindicación 9, en el cual la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2 se selecciona de las siguientes estructuras:



11. El compuesto de acuerdo con la Reivindicación 1, en el cual la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2:

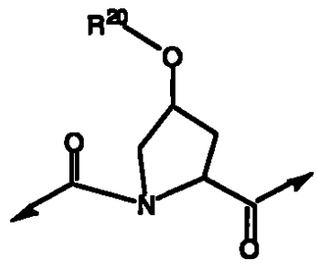


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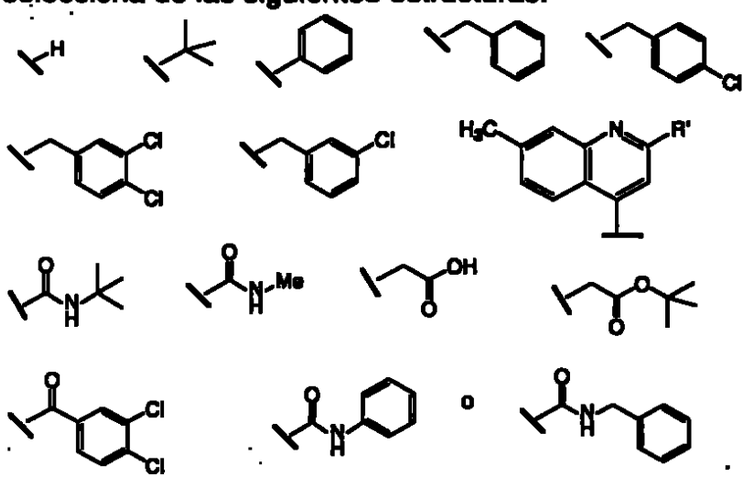
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Fórmula 2

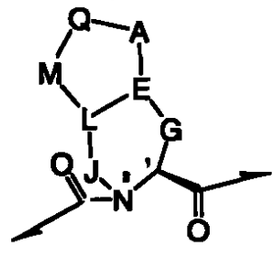


; y

R^{20} se selecciona de las siguientes estructuras:

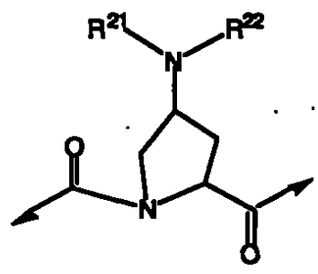


12. El compuesto de acuerdo con la Reivindicación 1, en el cual la porción de la Fórmula estructural 1 representada por la Fórmula estructural 2:



es

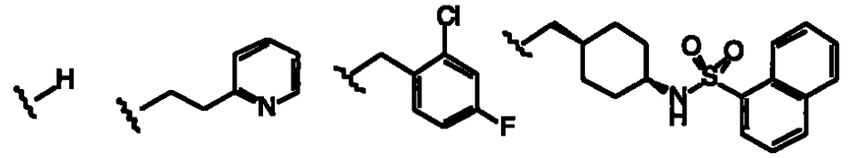
Fórmula 2

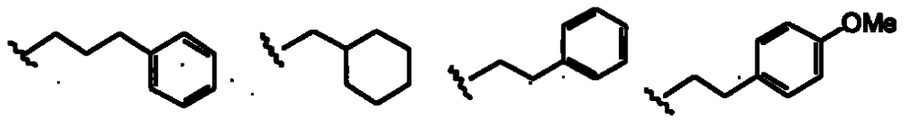


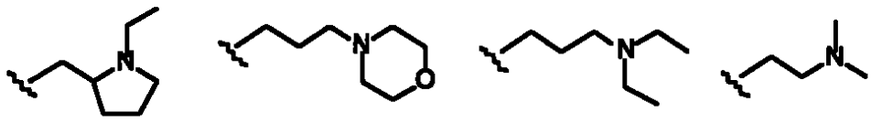
; y

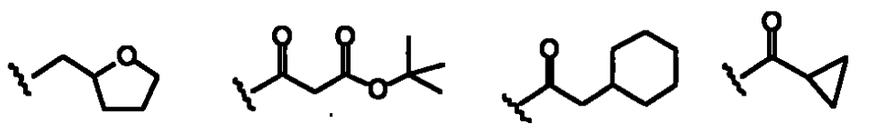
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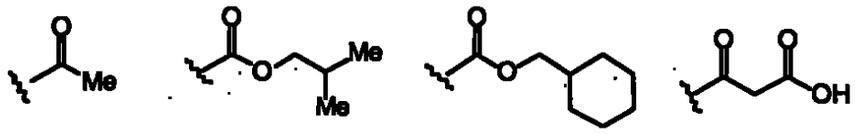
R^{21} y R^{22} pueden ser iguales o diferentes y se seleccionan independientemente del grupo que consiste en las siguientes estructuras:

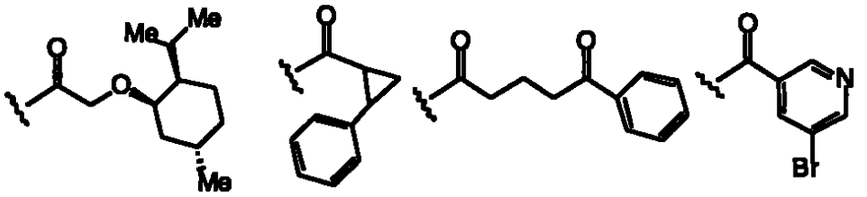


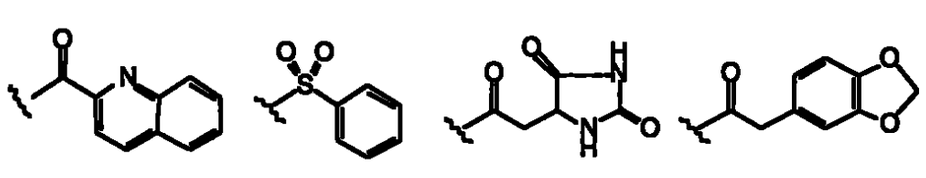


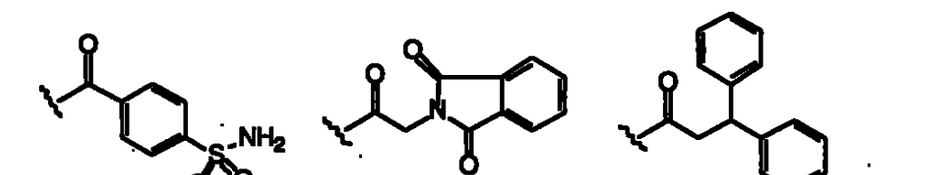




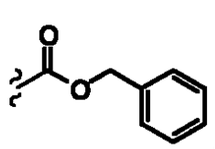








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13. El compuesto de acuerdo con la Reivindicación 1, en el cual L y M se encuentran ausentes y J está unido directamente a E.

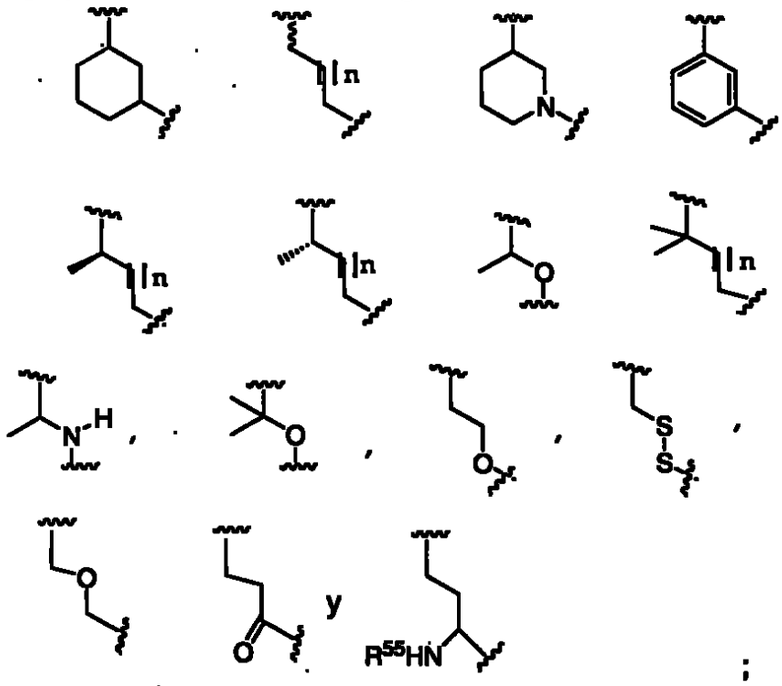
14. El compuesto de acuerdo con la Reivindicación 1, en el cual L, J y M se encuentran ausentes y E está unido directamente a N.

15. El compuesto de acuerdo con la Reivindicación 1, en el cual G y M se encuentran ausentes.

16. El compuesto de acuerdo con la Reivindicación 1, en el cual M' es



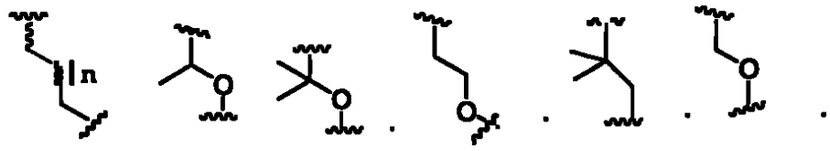
17. El compuesto de acuerdo con la Reivindicación 1, en el cual X se selecciona del grupo que consiste en las siguientes estructuras:



;

y R^{55} es alquilo, cicloalquilo, carbamato o urea; y n= 0-5.

18. El compuesto de acuerdo con la Reivindicación 17, en el cual X se selecciona del grupo que consiste en las siguientes estructuras:



19. El compuesto de acuerdo con la Reivindicación 1, en el cual R^1 es una cetoamida, cetoaldehído, dicetona, cetoácido o cetoéster.

20. El compuesto de acuerdo con la Reivindicación 19, en el cual R^1 es $-C(O)C(O)NR^9R^{10}$;

R^9 es H; y

R^{10} es H, $-R^{14}$, $-[CH(R^{1'})]_pC(O)OR^{11}$,

$-[CH(R^{1'})]_pC(O)NR^{12}R^{13}$,

$-[CH(R^{1'})]_pS(O_2)R^{11}$,

$-[CH(R^{1'})]_pS(O_2)NR^{12}R^{13}$,

$-[CH(R^{1'})]_pC(O)R^{11}$,

$-CH(R^{1'})C(O)N(H)C(H)(R^{2'})C(O)OR^{11}$,

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

$-CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$.

21. El compuesto de acuerdo con la Reivindicación 20, en el cual:

R^{10} es H, $-R^{14}$, $-CH(R^{1'})C(O)OR^{11}$,

$-CH(R^{1'})CH(R^{1'})C(O)OR^{11}$,

$-CH(R^{1'})C(O)NR^{12}R^{13}$,

$-CH(R^{1'})CH(R^{1'})C(O)NR^{12}R^{13}$,

$-CH(R^{1'})CH(R^{1'})S(O_2)R^{11}$,

$-CH(R^{1'})CH(R^{1'})S(O_2)NR^{12}R^{13}$,

$-CH(R^{1'})CH(R^{1'})C(O)R^{11}$,

$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$,

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

$-CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$;

$R^{1'}$ es H o alquilo; y

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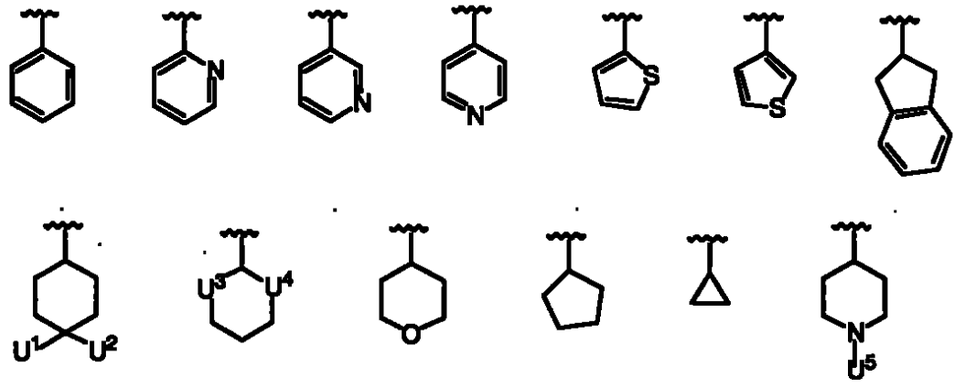
$R^{2'}$ es fenilo, fenilo sustituido, fenilo sustituido con heteroátomo, cicloalquilo, heterocicloalquilo, piperidilo o piriridilo.

22. El compuesto de acuerdo con la Reivindicación 21, en el cual $R^{1'}$ es H.

23. El compuesto de acuerdo con la Reivindicación 20, en el cual R^{11} es H, metilo, etilo, alilo, *ter*-butilo, bencilo, α-metilbencilo, α,α-dimetilbencilo, 1-metilciclopropilo o 1-metilciclopentilo;

$R^{'}$ es hidroximetilo o $-CH_2C(O)NR^{12}R^{13}$;

$R^{2'}$ se selecciona independientemente del grupo que consiste en las siguientes estructuras:

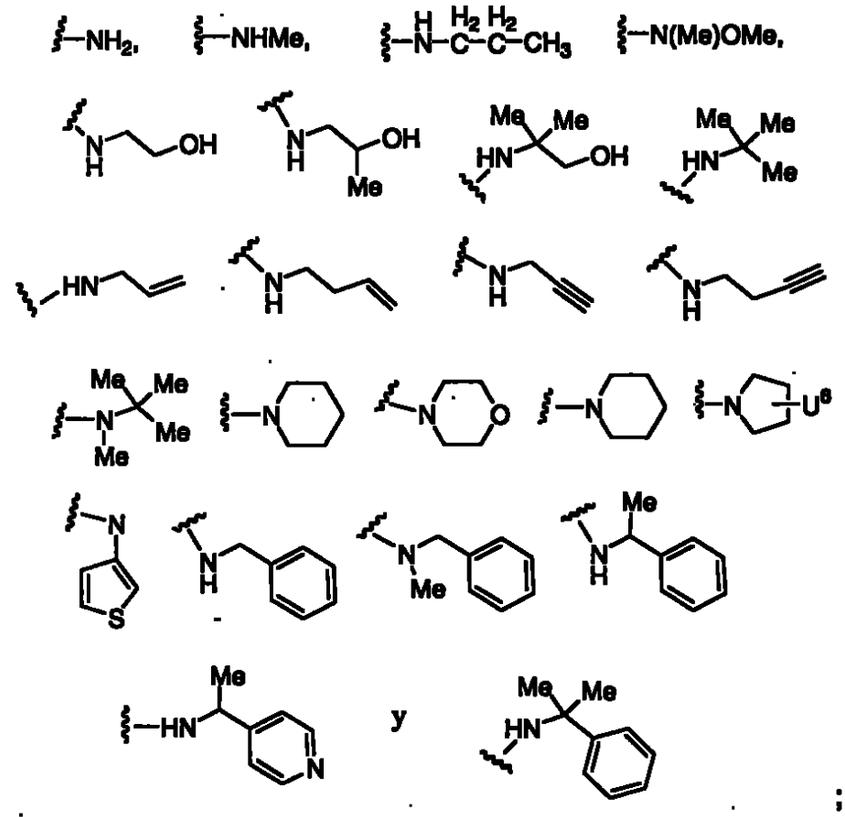


en las cuales U^1 y U^2 pueden ser iguales o diferentes y se seleccionan independientemente del grupo que consiste en: H, F, $-CH_2C(O)OH$, $-CH_2C(O)OMe$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, $-CH_2C(O)NMe_2$, azido, amino, hidroxilo, amino sustituido e hidroxilo sustituido;

U^3 y U^4 son iguales o diferentes y son independientemente O o S;

U^5 es alquilsulfonilo, arilsulfonilo, heteroalquilsulfonilo, heteroarilsulfonilo, alquilcarbonilo, arilcarbonilo, heteroalquilcarbonilo, heteroarilcarbonilo, alcoxicarbonilo, ariloxicarbonilo, heteroariloxicarbonilo, alquilaminocarbonilo, arilaminocarbonilo, o heteroarilaminocarbonilo o una combinación de los mismos;

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



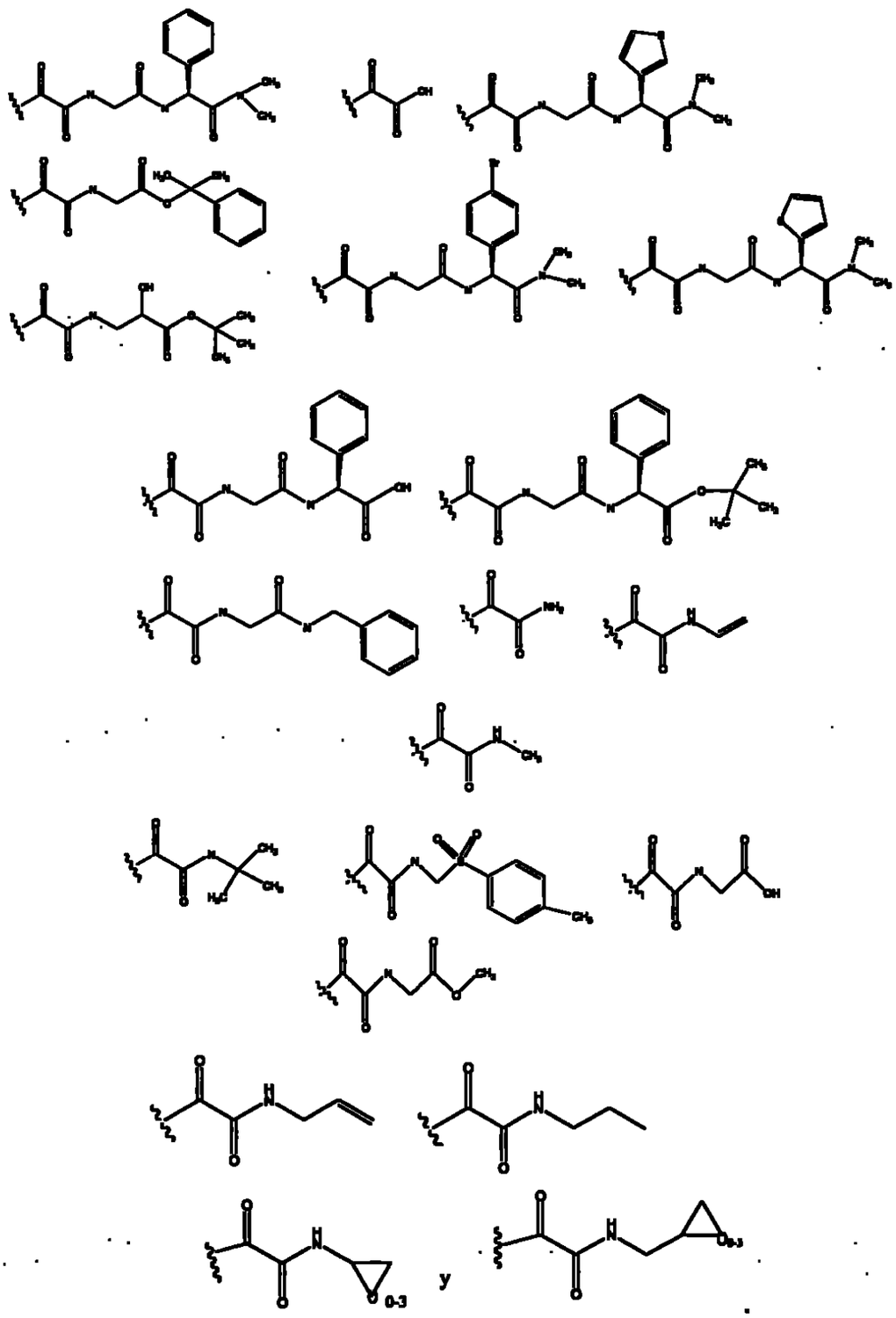
U^6 es H, OH, o CH_2OH, y

R^{14} se selecciona del grupo que consiste en: H, $-CH_3$, Et, *n*-propilo, metoxi, ciclopropilo, *n*-butilo, 1-but-3-inilo, bencilo, α-metilbencilo, fenetilo, alilo, 1-but-3-enilo, $-OCH_3$ y ciclopropilmetilo.

24. El compuesto de acuerdo con la Reivindicación 1, en el cual R^1 se selecciona de las siguientes estructuras:

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25. El compuesto de acuerdo con la Reivindicación 1, en el cual D y X tomados juntos forman una cadena conectora no ramificada parafínica divalente de C7-C12 que forma una porción de un macrociclo de 14-19 miembros.

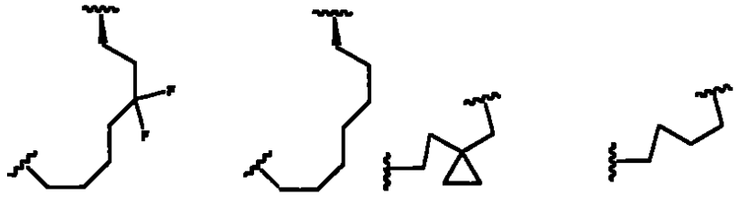
26. El compuesto de acuerdo con la Reivindicación 25, en el cual D y X tomados juntos forman una una cadena conectora no ramificada parafínica de C8 o C9 que forma una porción de un heterociclo de 15 o 16 miembros.

27. El compuesto de acuerdo con la Reivindicación 1, en el cual D y X tomados juntos forman una cadena conectora no ramificada oleffnica divalente de C7-C12 que forma una porción de un macrociclo de 14-19 miembros que posee un grado simple de insaturación.

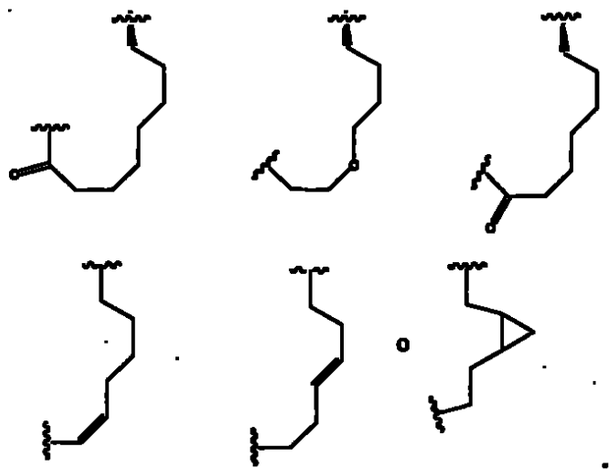
28. El compuesto de acuerdo con la Reivindicación 27, en el cual D y X tomados juntos forman una cadena conectora no ramificada oleffnica de C8 o C9 que forma una poción de un heterociclo de 15 o 16 miembros que posee un grado simple de insaturación.

29. El compuesto de acuerdo con la Reivindicación 1, en el cual D y X tomados juntos forman una cadena alifática no ramificada divalente de C2–C12 que forma una porción de un heterociclo de 9-19 miembros.

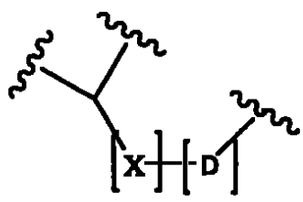
30. El compuesto de acuerdo con la Reivindicación 1, en el cual D se selecciona de las siguientes estructuras:



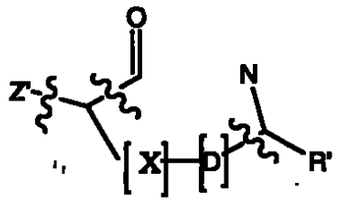
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31. El compuesto de acuerdo con la Reivindicación 1, en el cual la porción representada por la parte

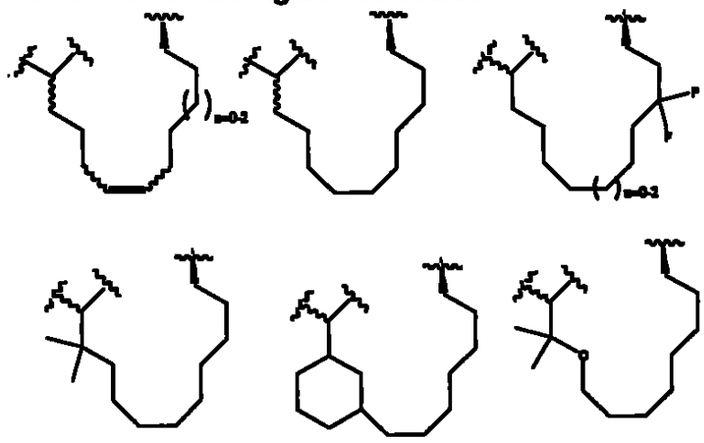


del resto

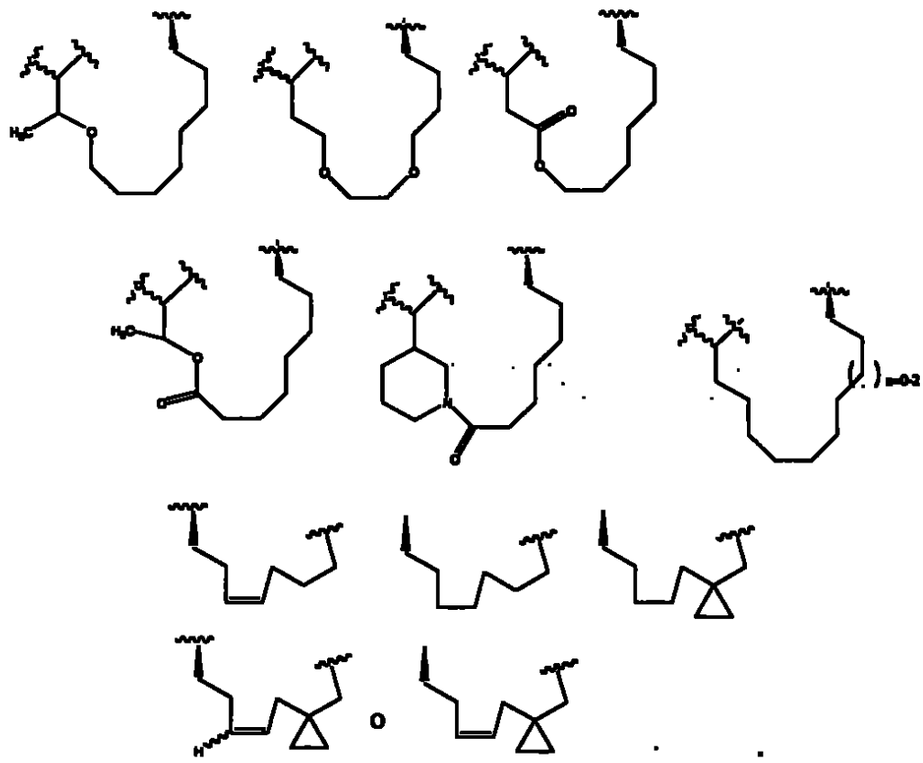


de la Fórmula I

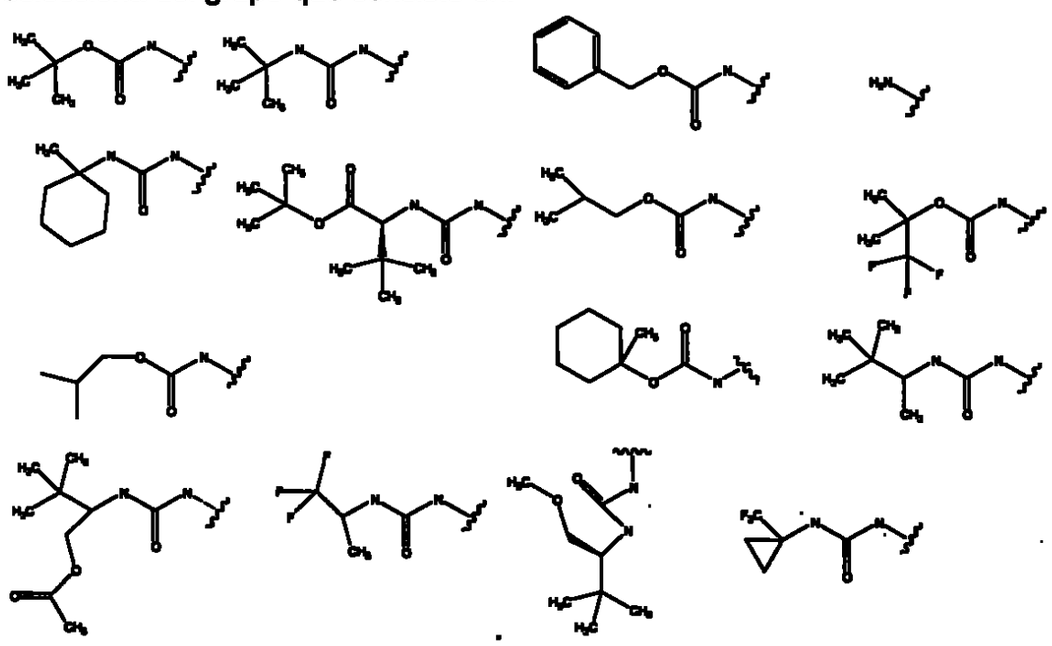
se selecciona de las siguientes estructuras:



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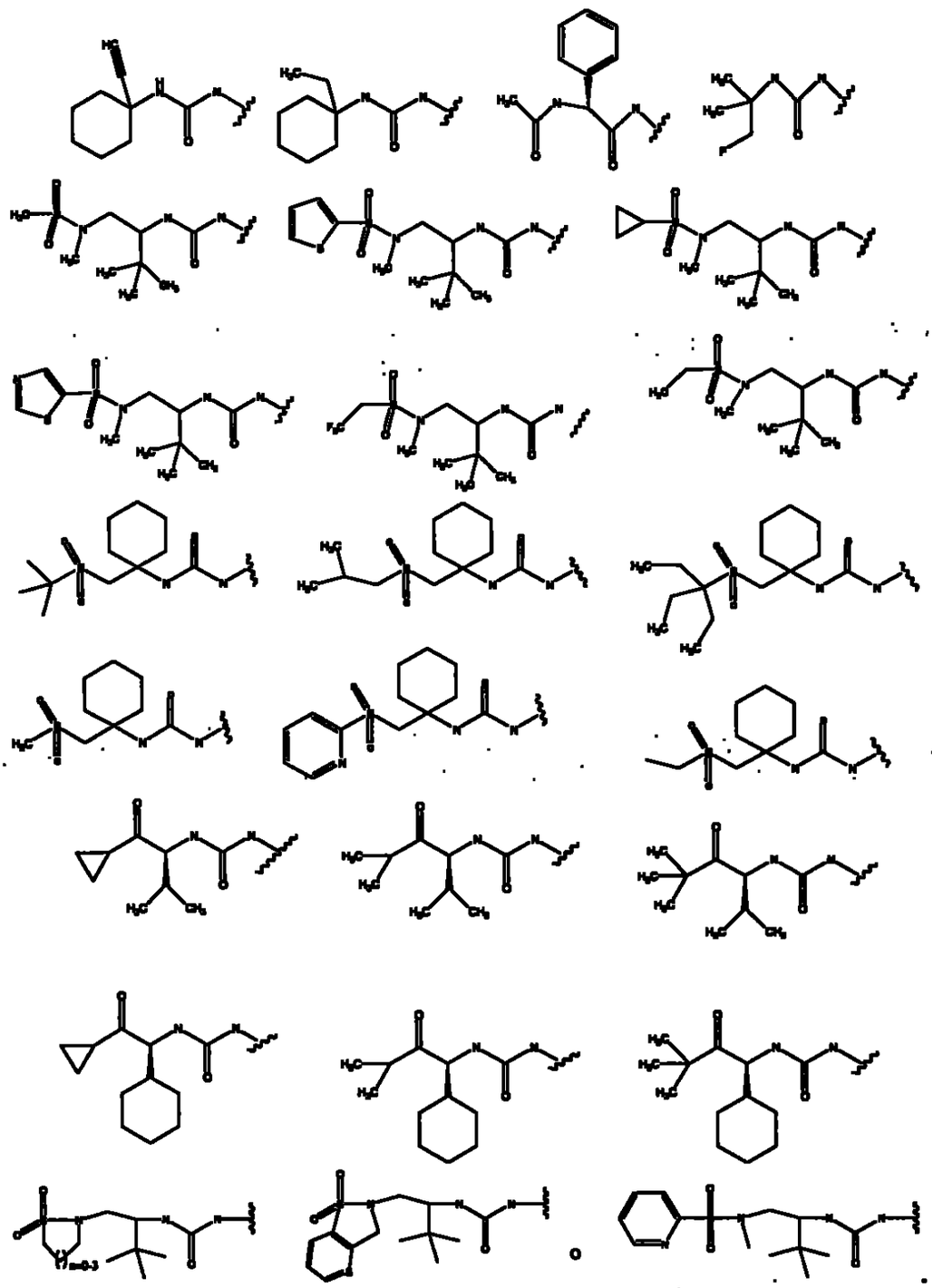


32. El compuesto de acuerdo con la Reivindicación 1, en el cual Z' se selecciona del grupo que consiste en:



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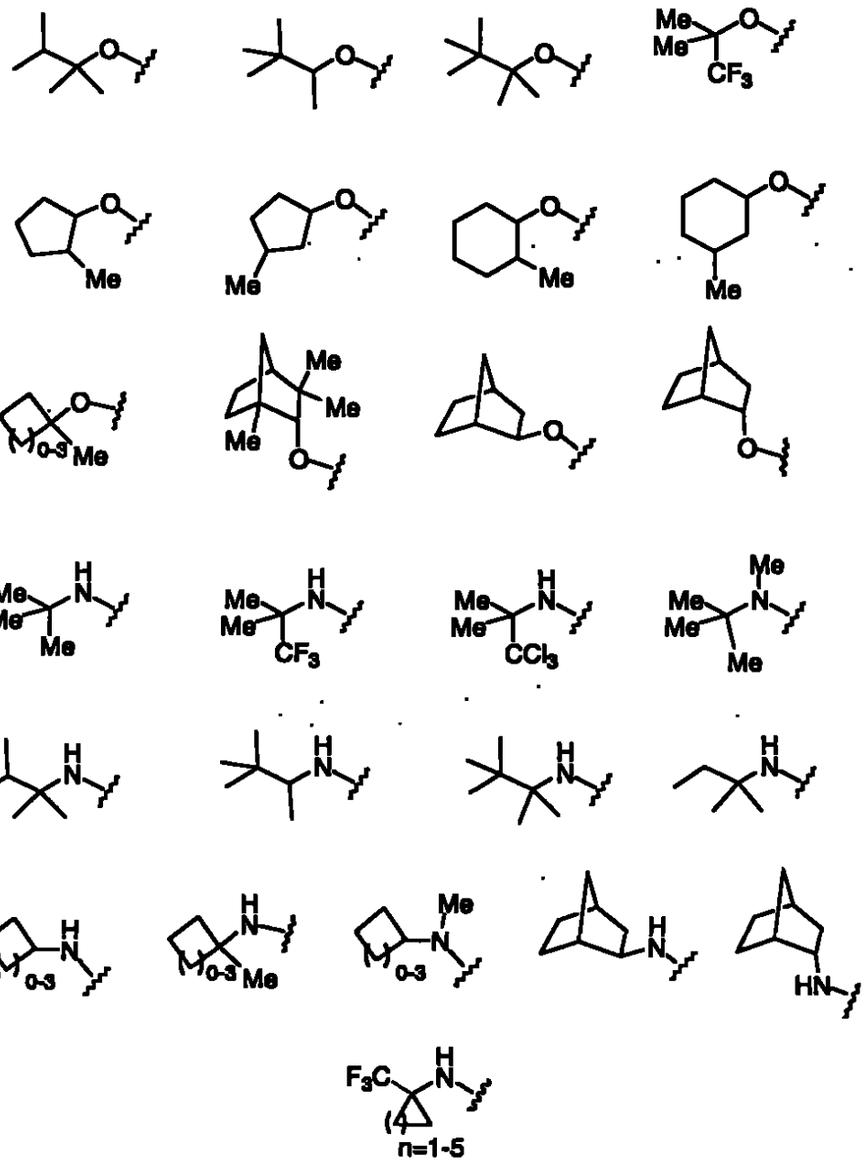


33. El compuesto de acuerdo con la Reivindicación 1, en el cual W es C=O.

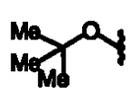
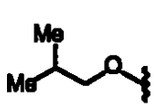
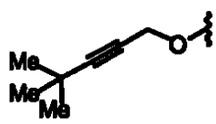
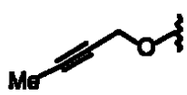
34. El compuesto de acuerdo con la Reivindicación 1, en el cual Z es N.

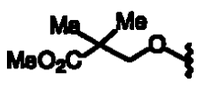
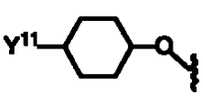
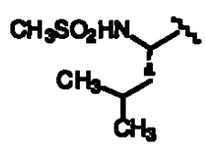
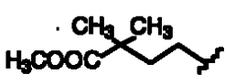
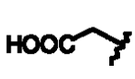
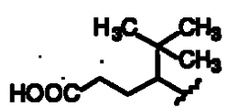
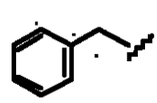
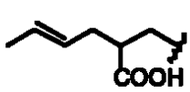
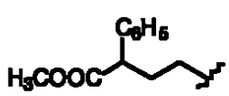
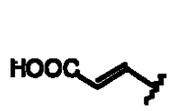
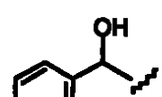
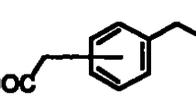
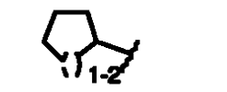
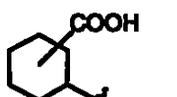
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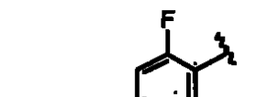
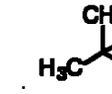
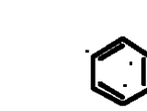
35. El compuesto de acuerdo con la Reivindicación 1, en el cual Y se selecciona del grupo que consiste en las siguientes estructuras:

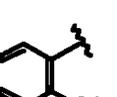
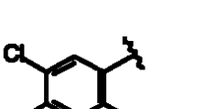
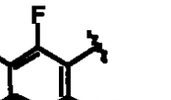
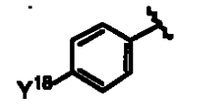
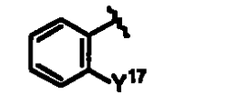


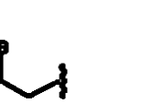
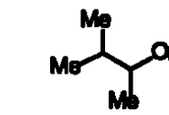
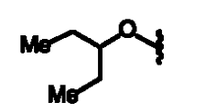
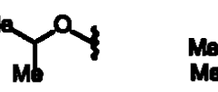
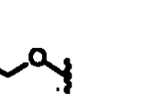
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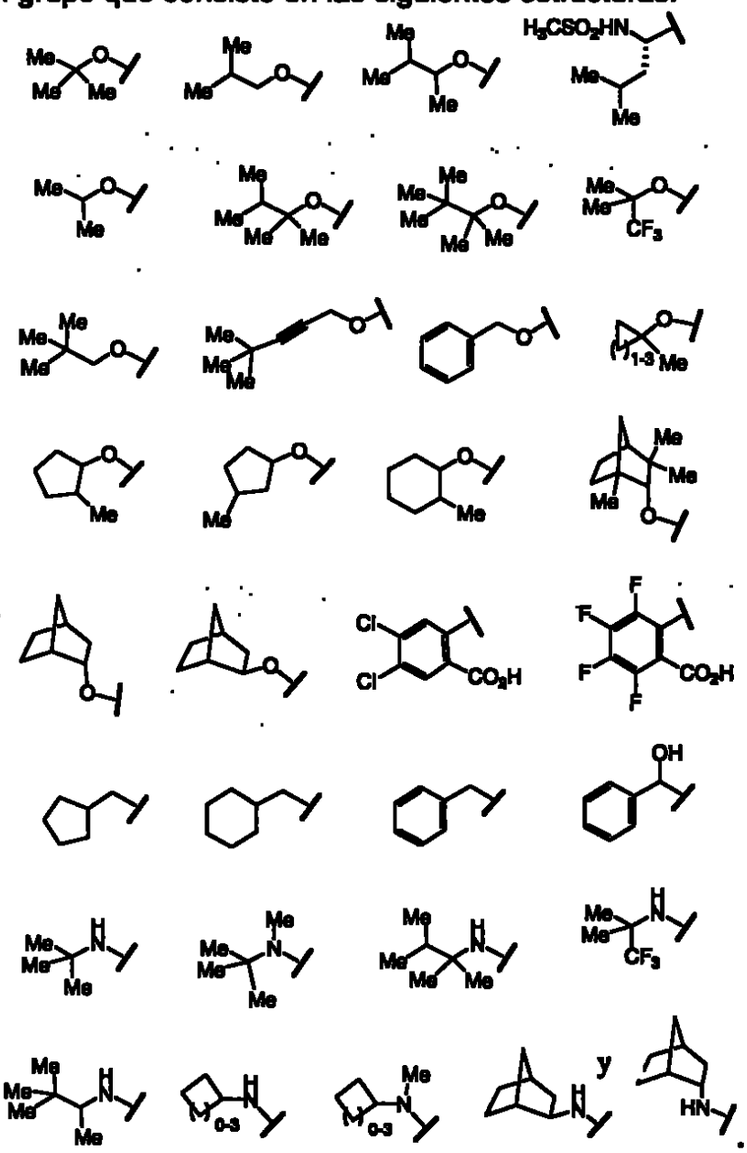
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en las cuales Y^{17} es CF_3, NO_2, $C(O)NH_2$, OH, NH_2 o C(O)OH; e

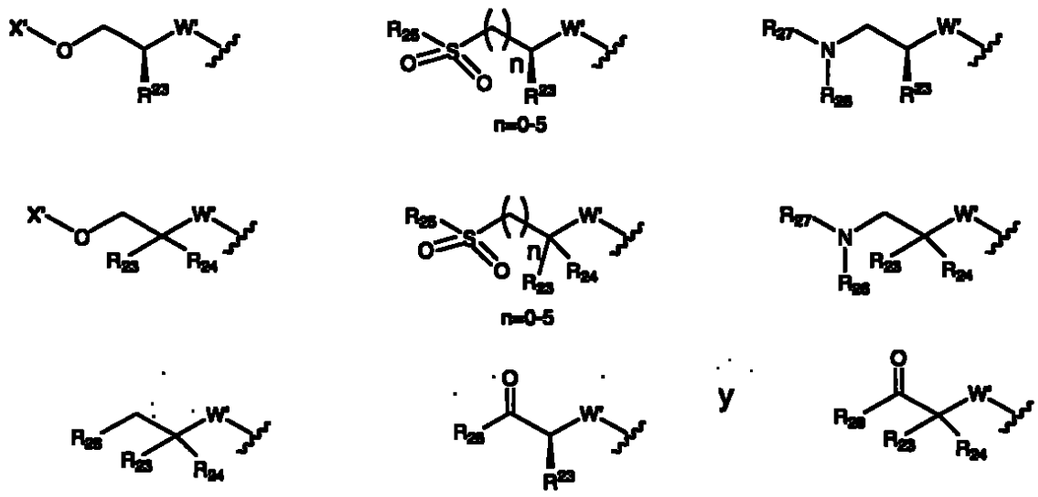
Y^{18} es F o C(O)OH.

36. El compuesto de acuerdo con la Reivindicación 37, en el cual Y se selecciona del grupo que consiste en las siguientes estructuras:



37. El compuesto de acuerdo con la Reivindicación 1, en el cual Y se selecciona del grupo que consiste en las siguientes estructuras:

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W' es N o O;

R^{23} es H, alquilo, arilo, heteroarilo, cicloalquilo o heterocicloalquilo, donde cada uno de dichos arilo, heteroarilo, cicloalquilo, heterocicloalquilo puede estar sustituido con un resto alquilo;

R^{24} es H, alquilo, arilo, heteroarilo, cicloalquilo o heterocicloalquilo, donde cada uno de dichos arilo, heteroarilo, cicloalquilo, heterocicloalquilo puede estar sustituido con un resto alquilo;

o R^{23} y R^{24} tomados juntos forman un anillo cíclico que contiene un carbociclo o heterociclo;

R^{25} es H, alquilo, heteroalquilo, arilo, heteroarilo, alquilamino, arilamino, heteroalquilamino o cicloalquilo,

R^{26} se selecciona del grupo que consiste en: H, carbamato, sulfonamidas, alquilcarbonilo, alquilsulfonilo, arilsulfonilo, heteroarilo, sulfonilo, heteroalquilsulfonilo, ariloxicarbonilo, heteroalcoxicarbonilo, heteroariloxicarbonilo, alquilaminoarbonilo, arilaminocarbonilo y urea;

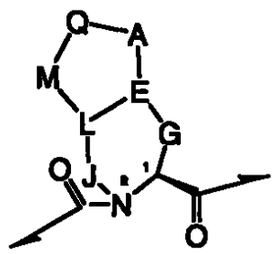
R^{27} es H, alquilo, cicloalquilo, arilo o heteroarilo;

R^{28} es H, alquilo, heteroalquilo, arilo o heteroarilo; y

X'-O- es un éter, éster o carbamato.

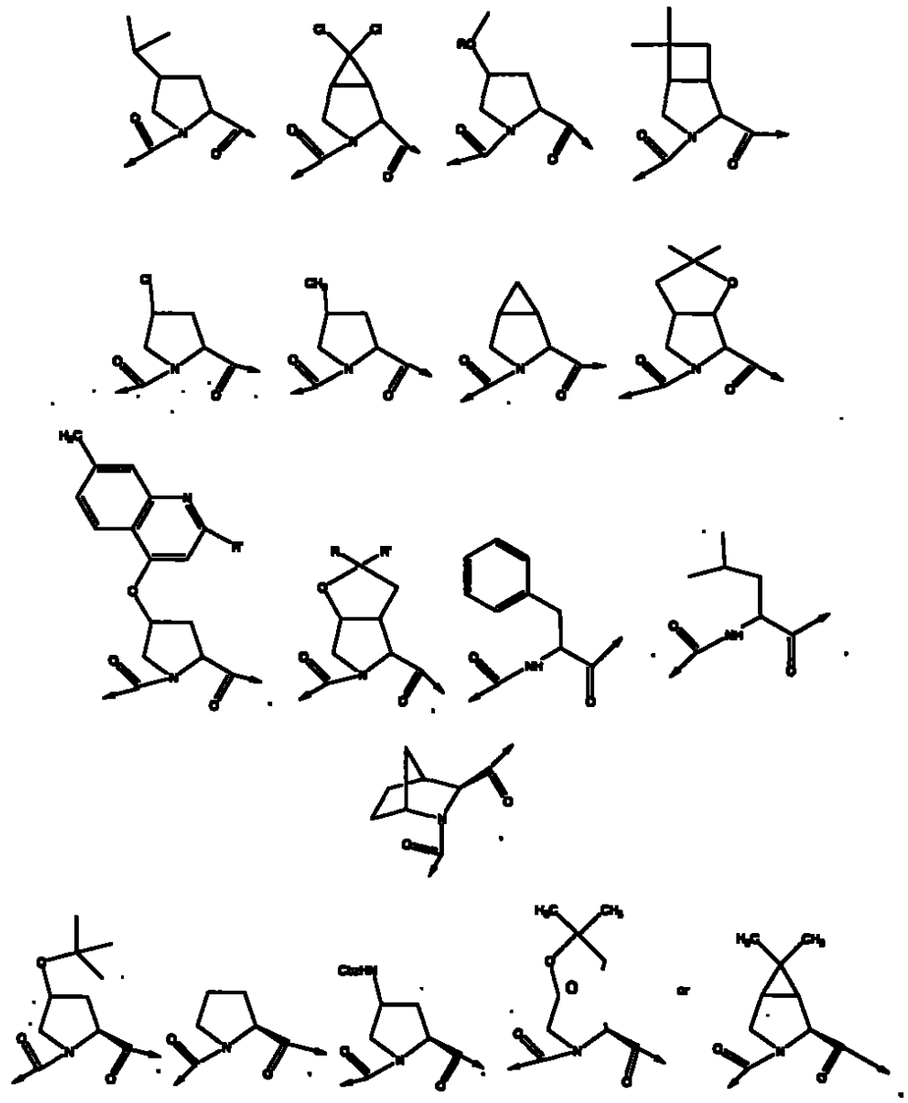
38. El compuesto de acuerdo con la Reivindicación 1, en el cual:

(a) el resto:



Fórmula 2

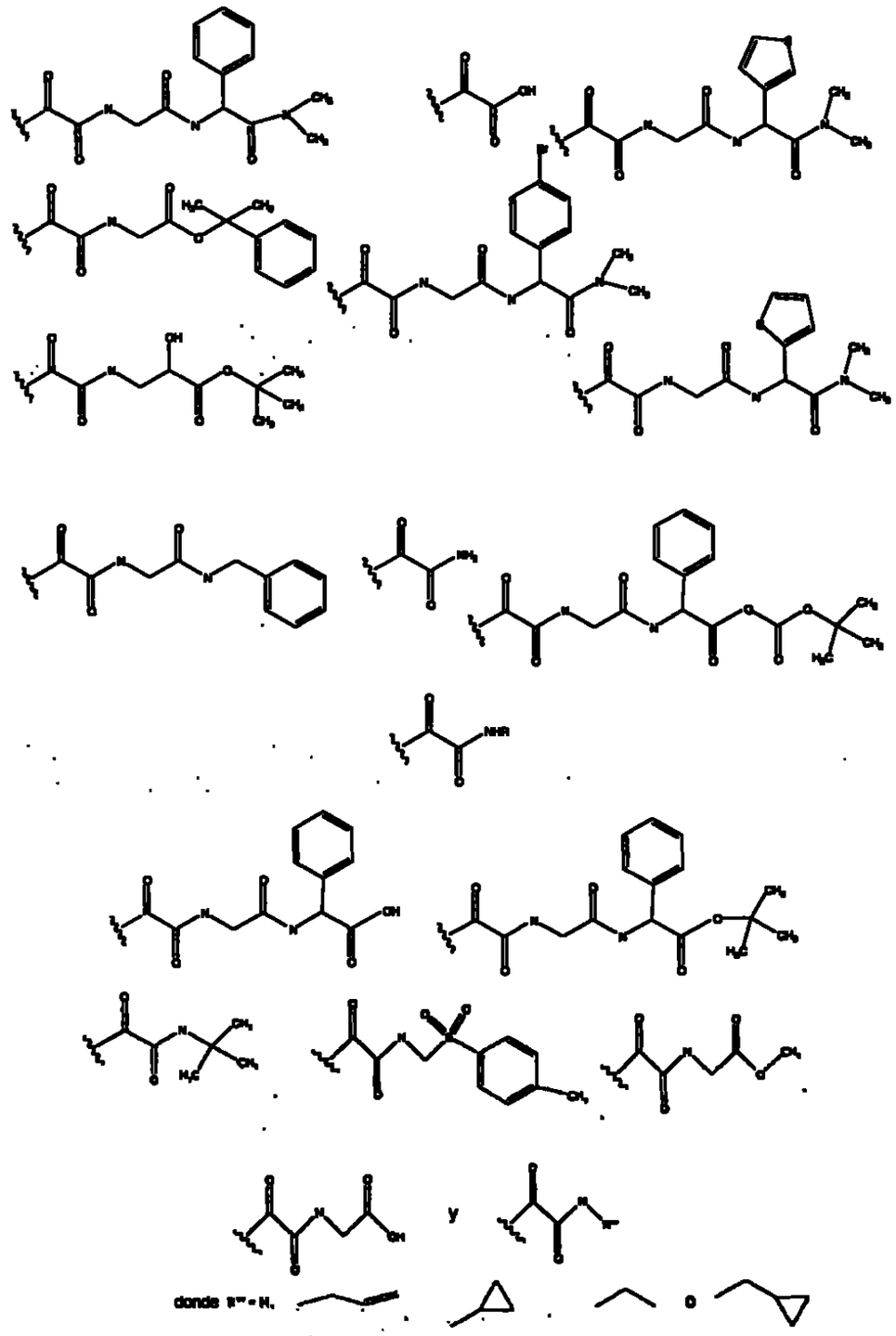
es



(b) R^1 se selecciona de las siguientes estructuras:

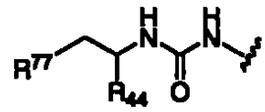
675

673



(c) Z' se representa por cualquiera de (i), (ii) o (iii) que se muestran a continuación:

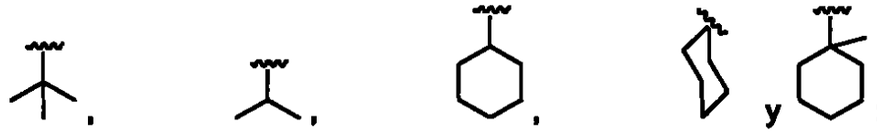
(i)



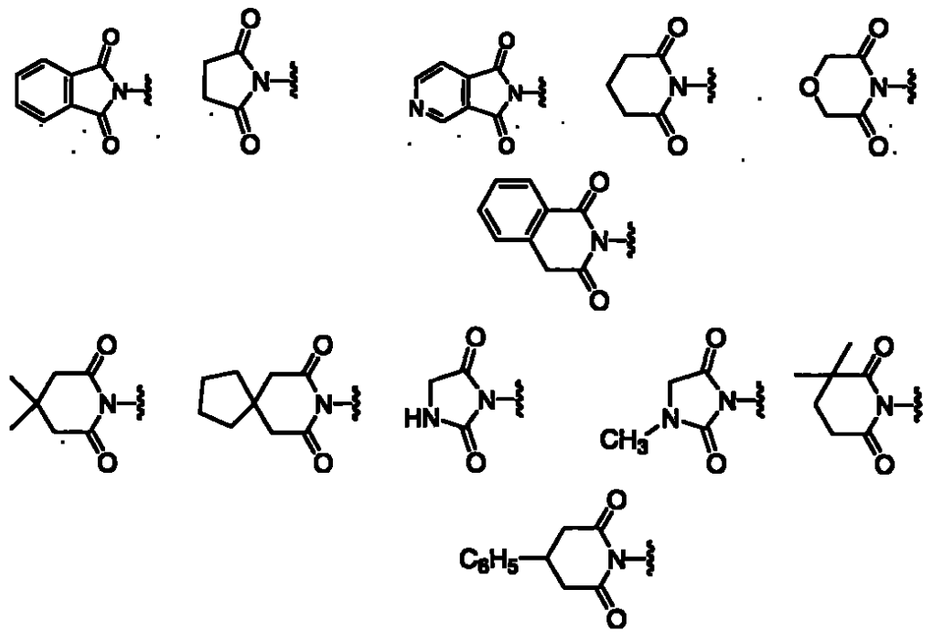
Fórmula A

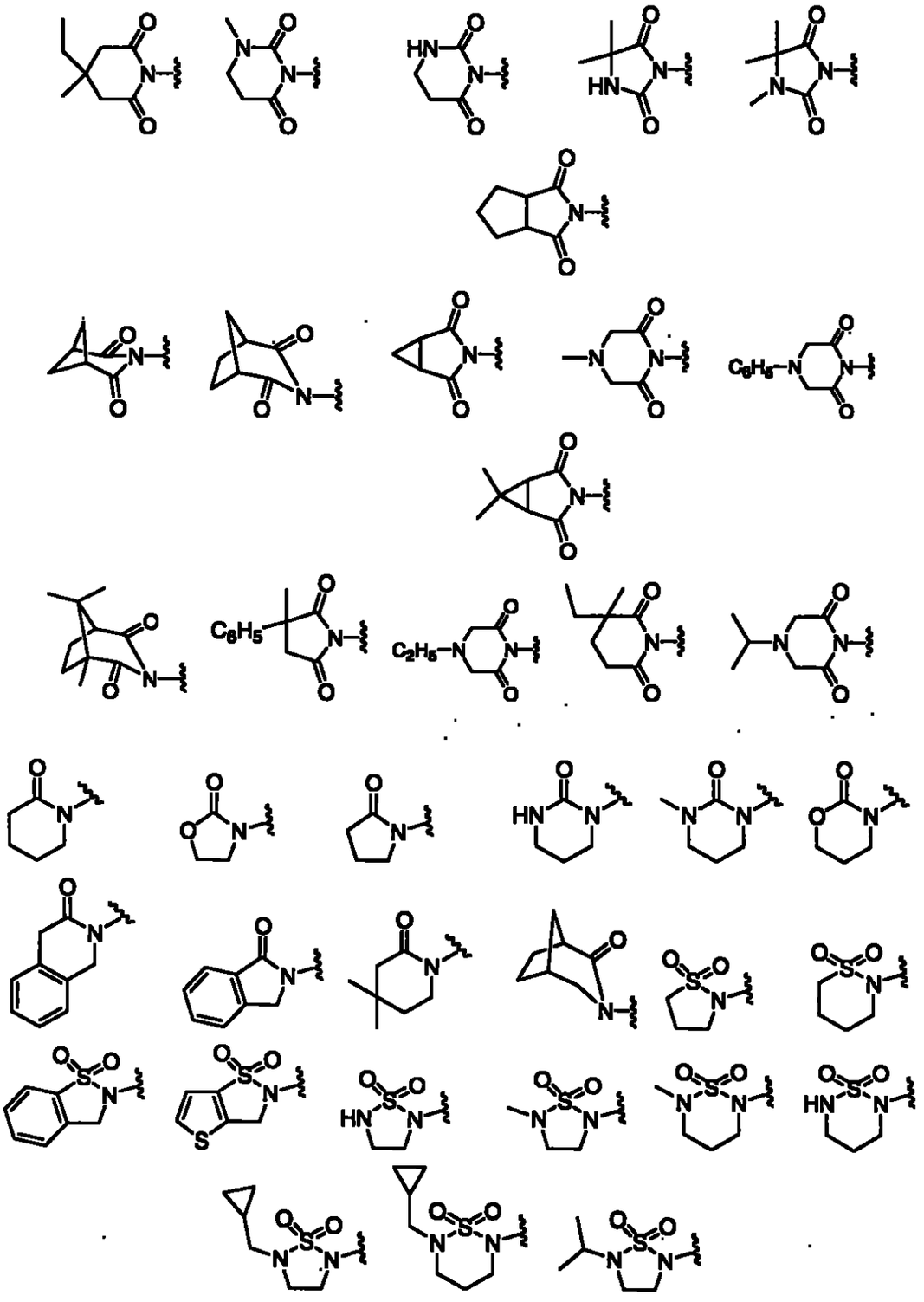
en la cual:

R^{44} se selecciona del grupo que consiste en:

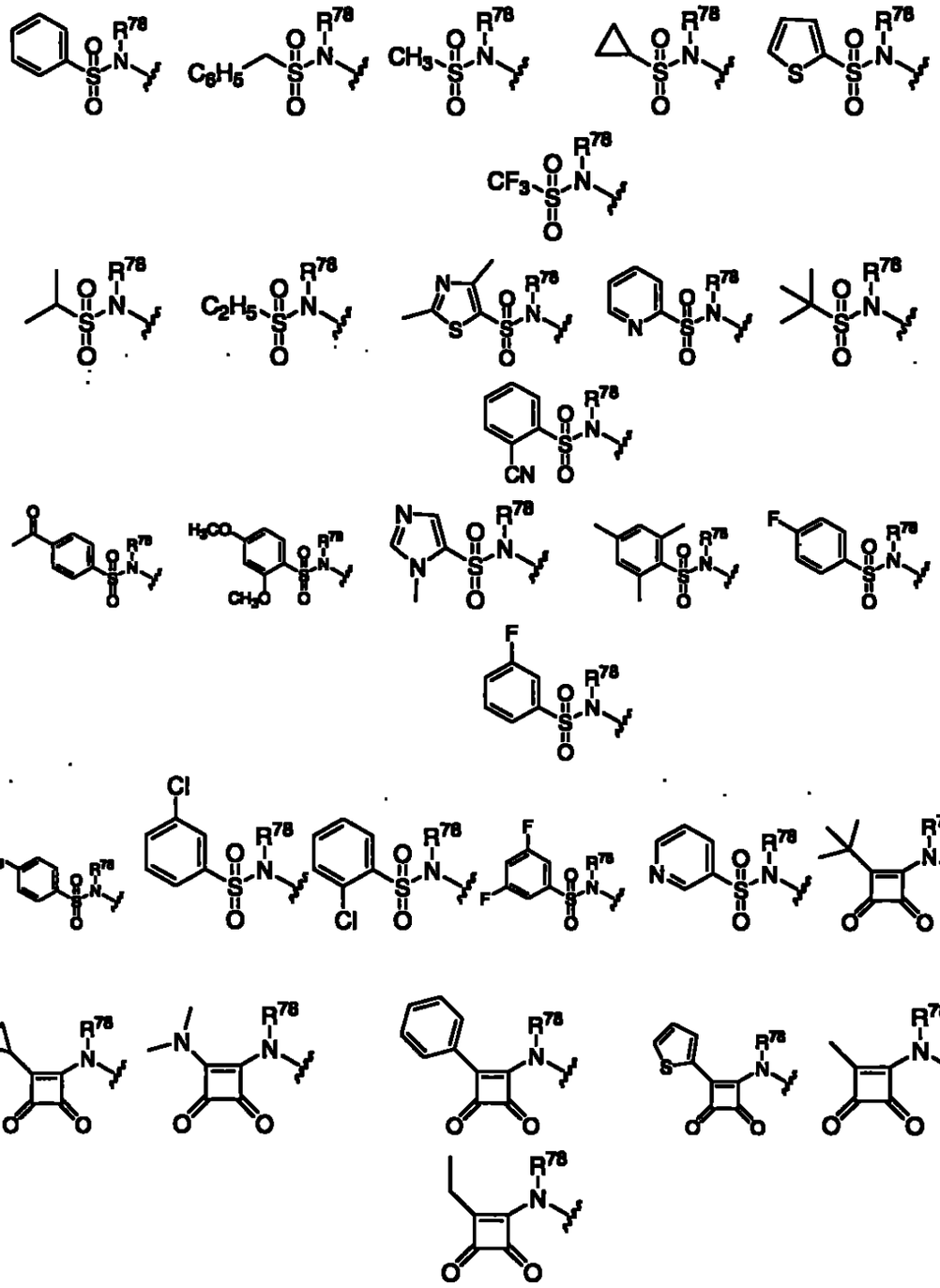


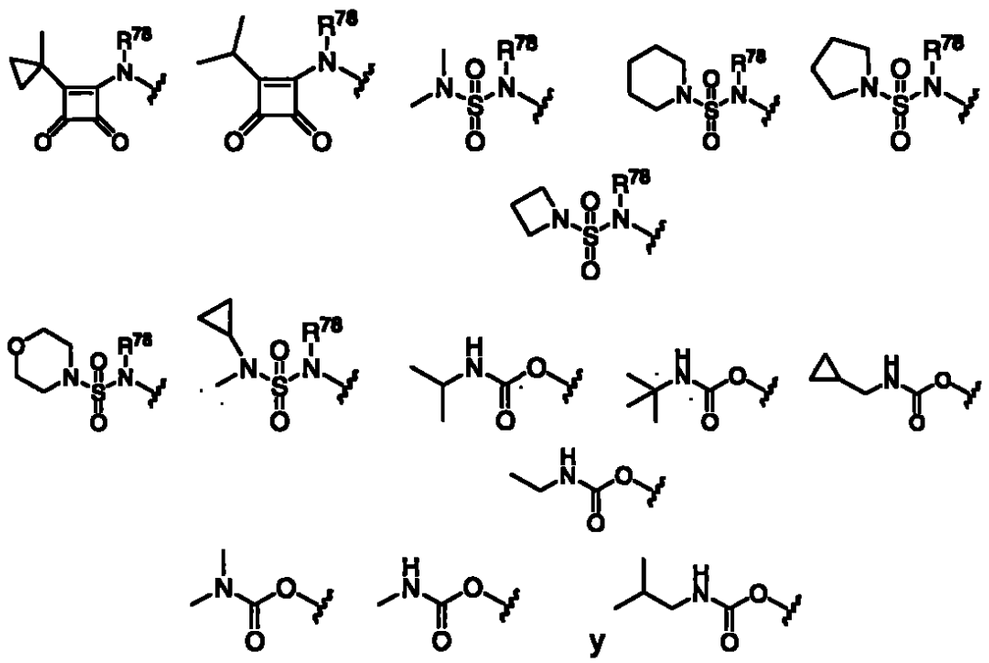
y R^{77} se selecciona del grupo que consiste en:





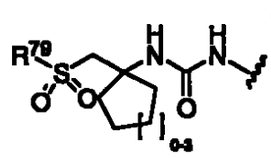
676





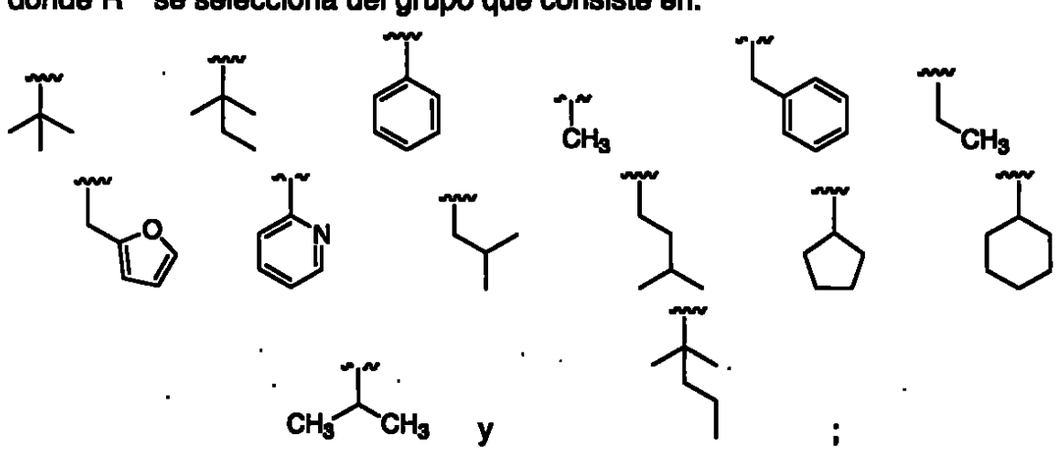
donde R^{78} se selecciona de metilo, etilo, isopropilo, ter-butilo y fenilo;

(ii)

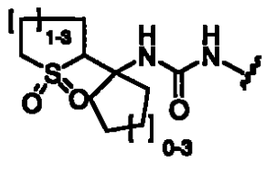


Fórmula B

donde R^{79} se selecciona del grupo que consiste en:



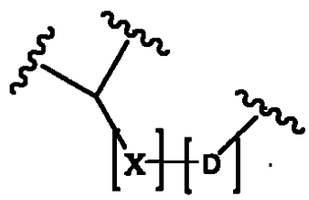
(iii)



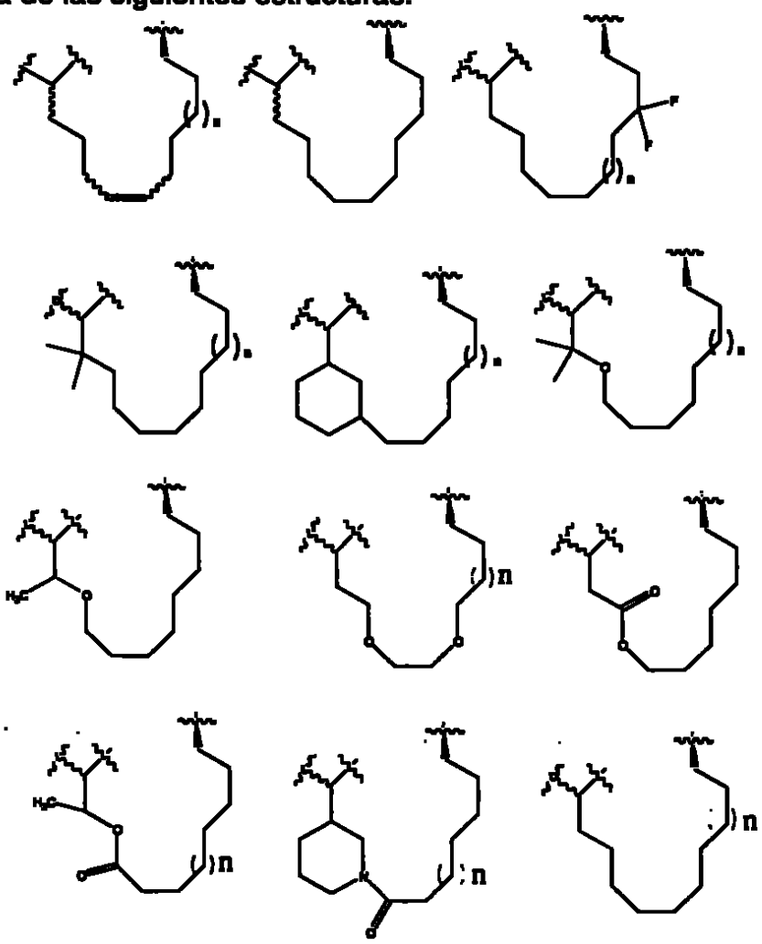
Fórmula C

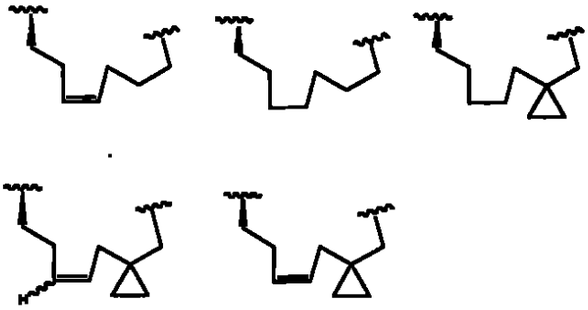
en la cual el anillo sulfona está sustituido opcionalmente con alquilo y cicloalquilo; y

(d) la porción de la Fórmula 1 representada por



se selecciona de las siguientes estructuras:

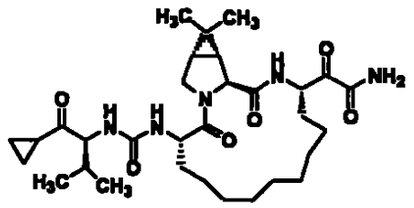


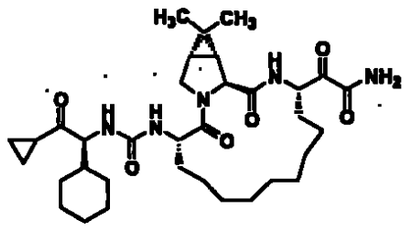


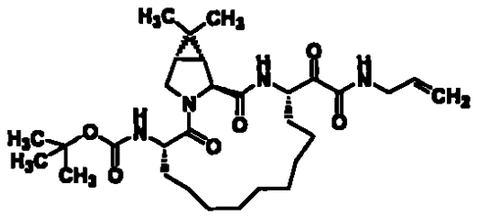
; y

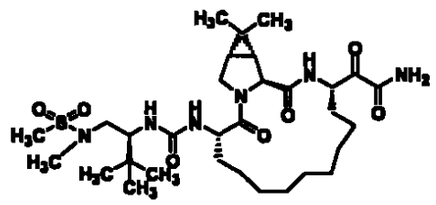
n= 0 a 3.

39. El compuesto de acuerdo con la Reivindicación 1, seleccionado del grupo que consiste en:

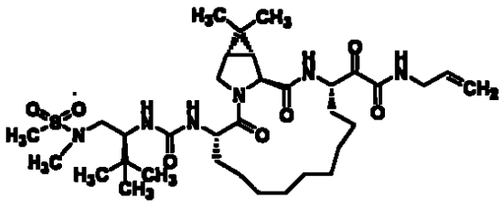


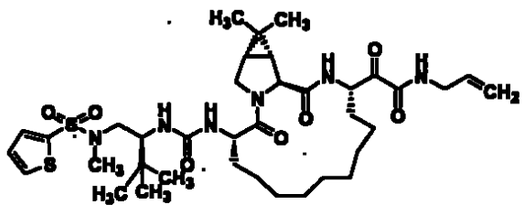


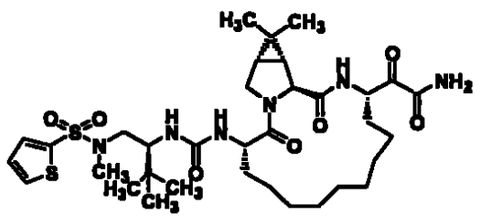


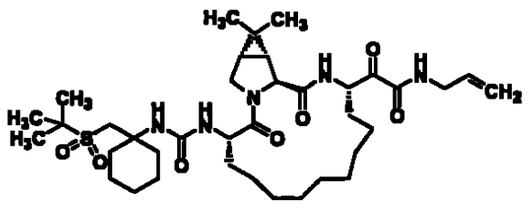


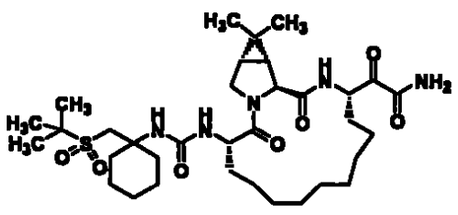
652
680

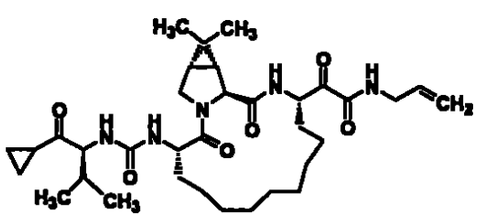


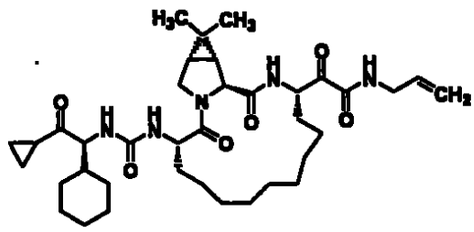


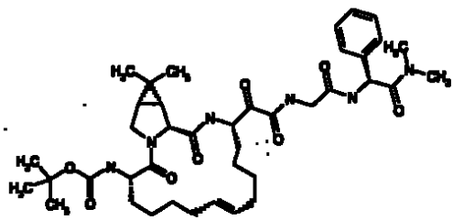


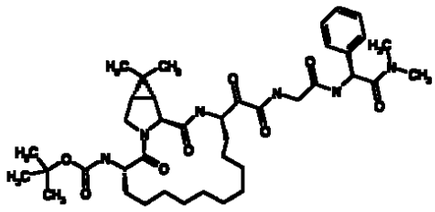


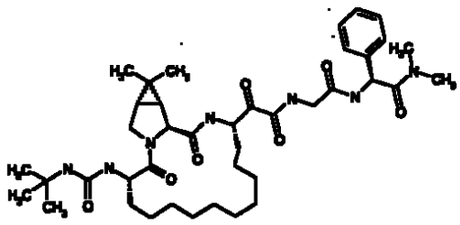


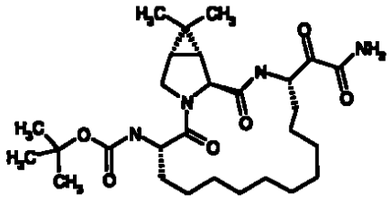


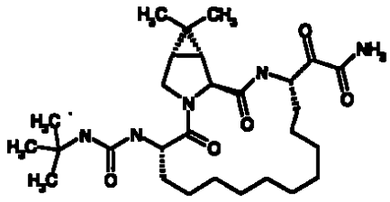




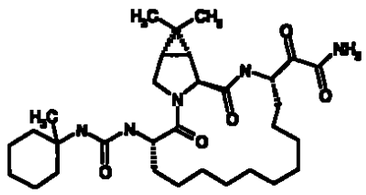


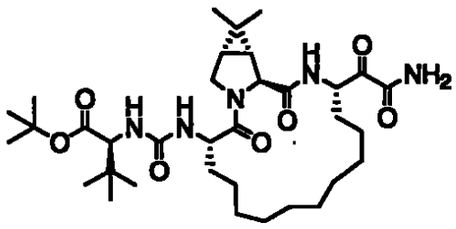


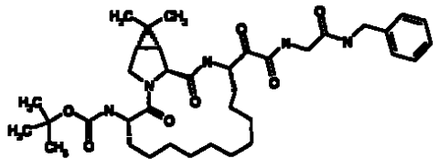


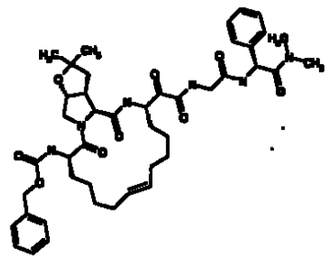


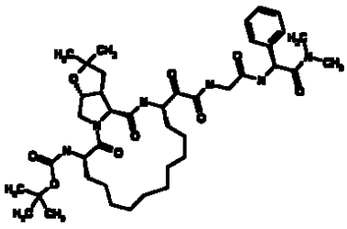
684
682

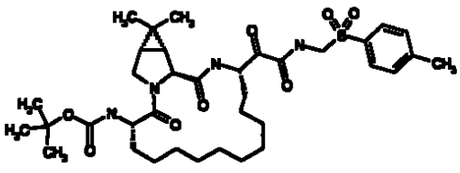


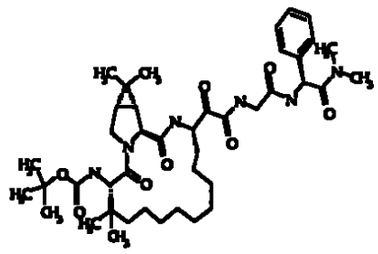


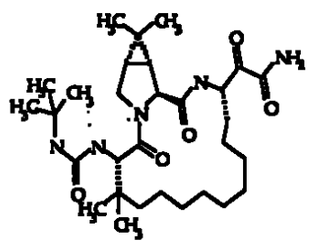


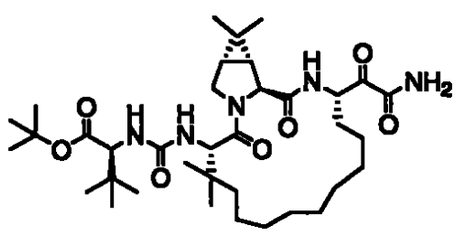


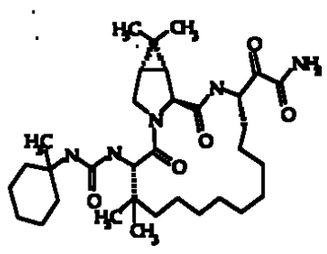




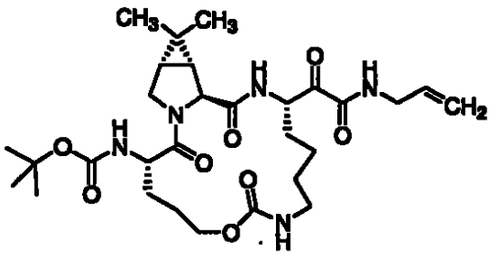


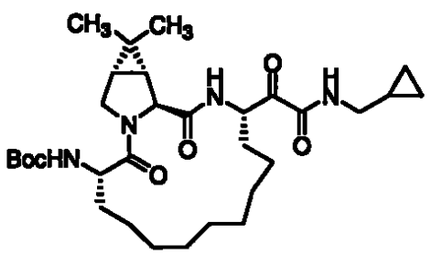


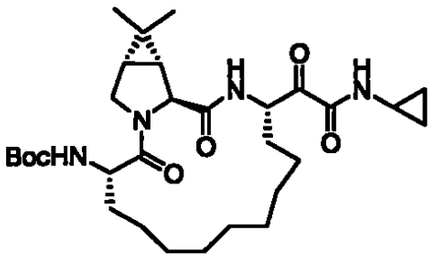


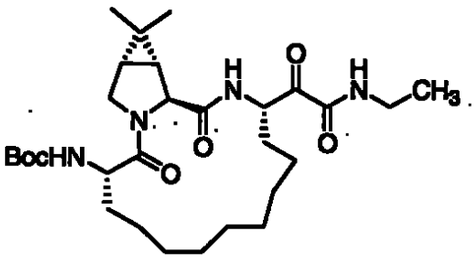


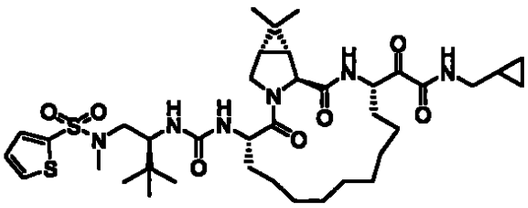
686
684

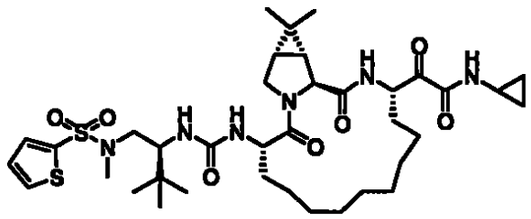


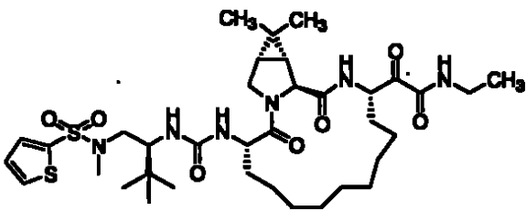


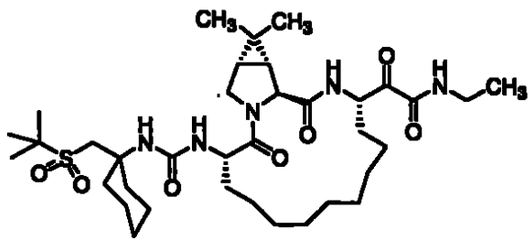


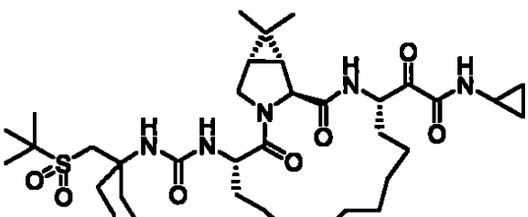


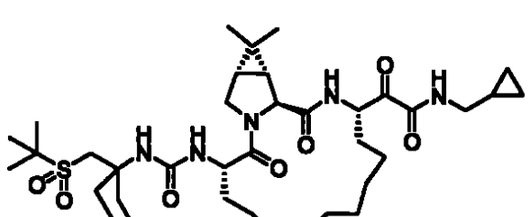


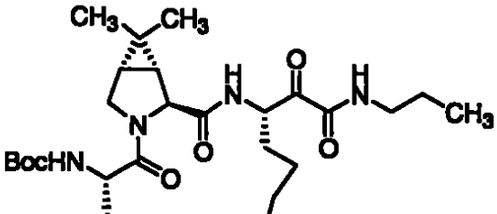


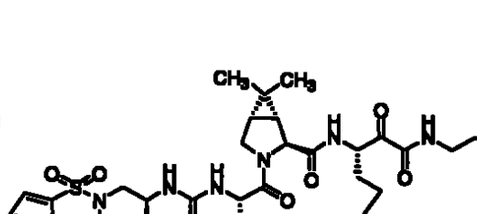


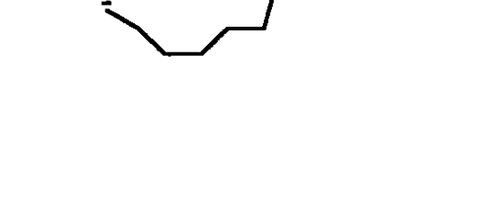


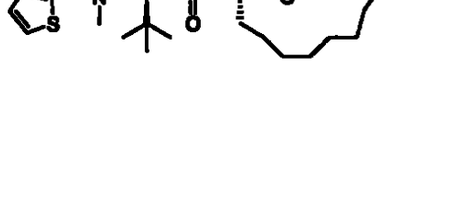


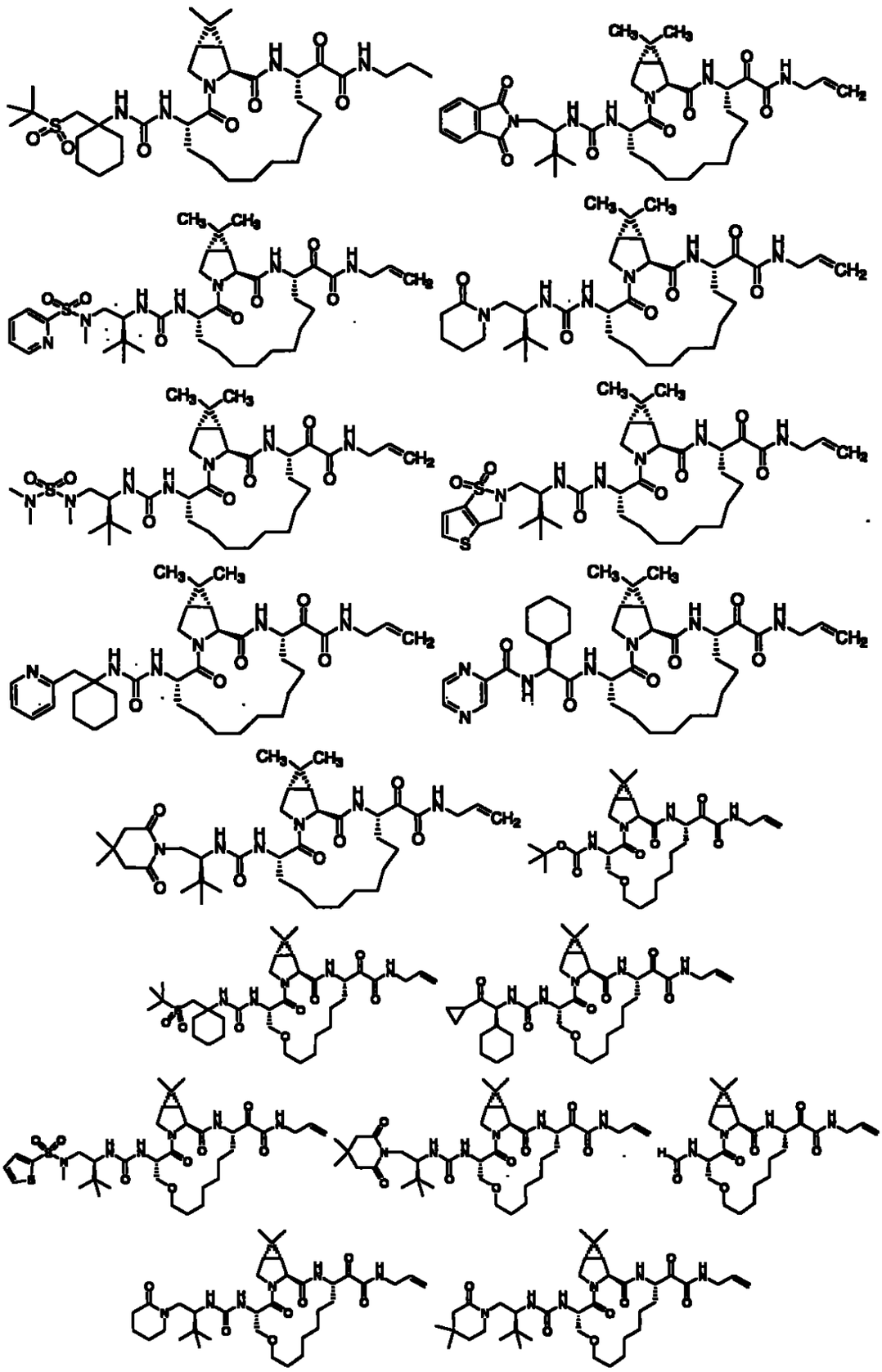




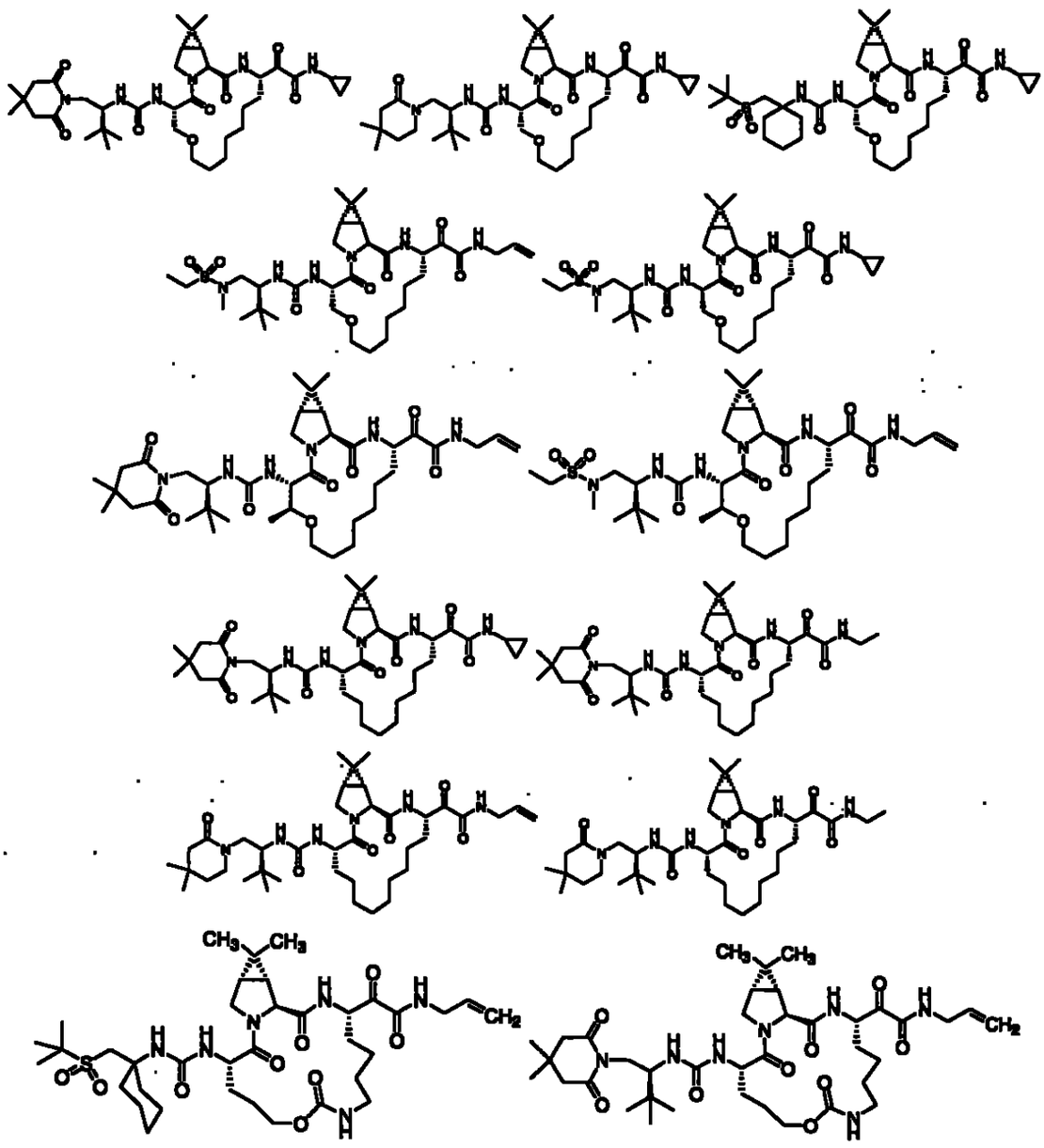




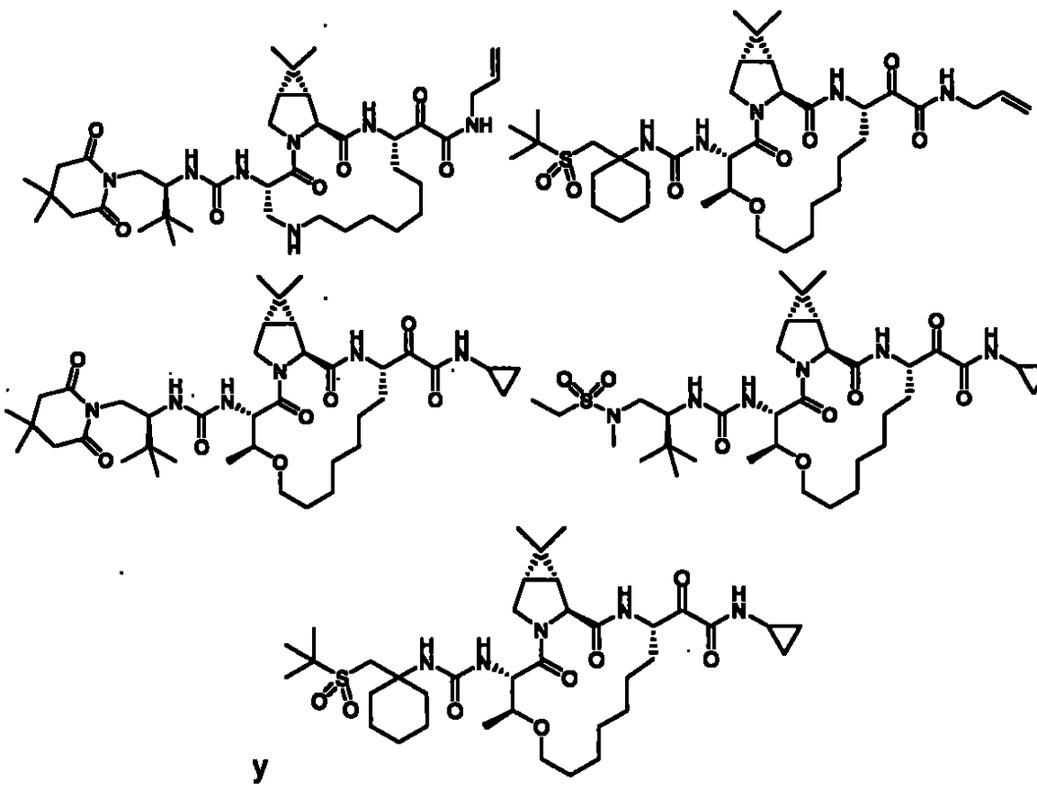




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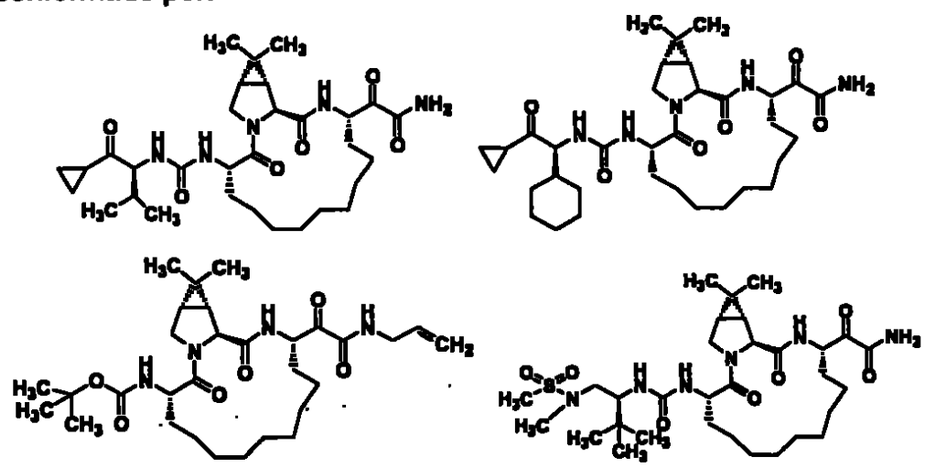
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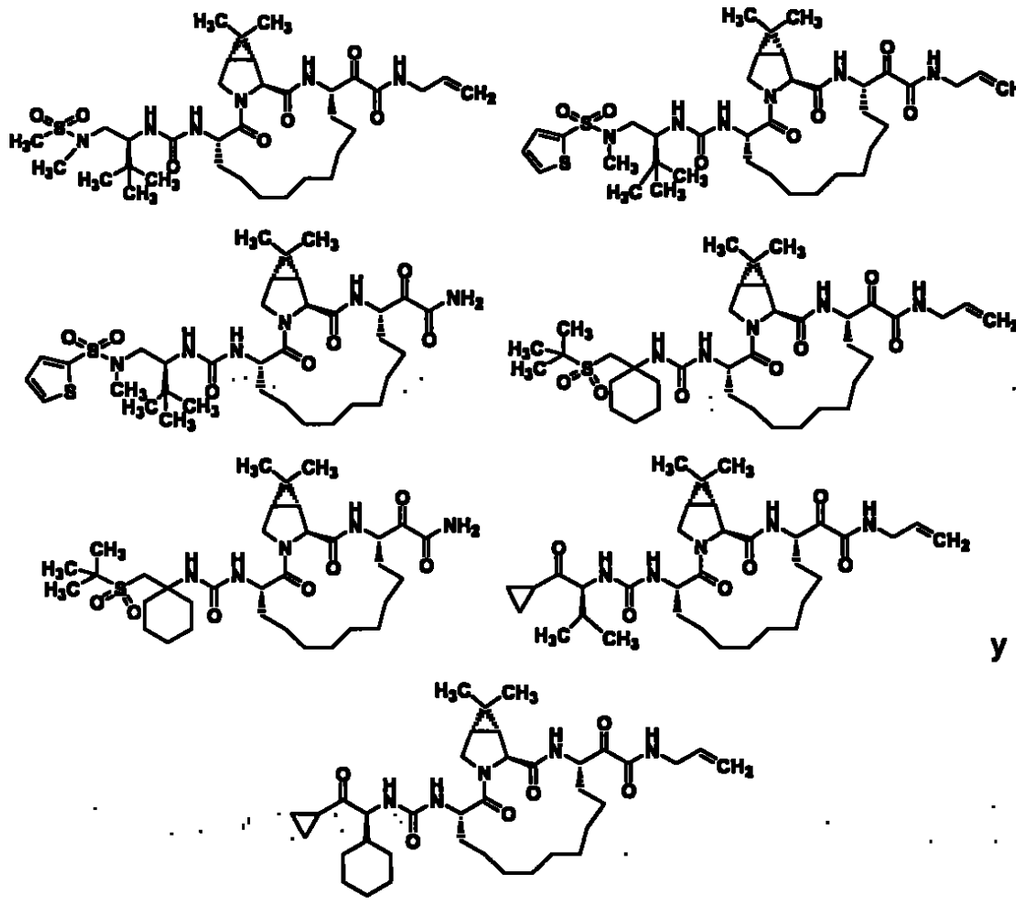


y

o sales, solvatos o ésteres aceptables para uso farmacéutico de dicho compuesto

40. El compuesto de acuerdo con la Reivindicación 39, seleccionado del grupo conformado por:





y

o sales, solvatos o ésteres aceptables para uso farmacéutico de dicho compuesto.

41. El compuesto de la Reivindicación 1, en el cual R^1 es cetoamida, ácido, cetoácido, cetoéster, cetoaldehído, dicetona, ácido bórico o trifluorocetona.

42. Una composición farmacéutica que comprende como ingrediente activo un compuesto de acuerdo con la Reivindicación 1.

43. La composición farmacéutica de acuerdo con la Reivindicación 42 adecuada para el uso en el tratamiento de trastornos relacionados con el VHC.

44. La composición farmacéutica de acuerdo con la Reivindicación 42, que además comprende un vehículo aceptable para uso farmacéutico.

45. La composición farmacéutica de acuerdo con la Reivindicación 46, que además contiene un agente antiviral.

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46. La composición farmacéutica de acuerdo con la Reivindicación 45, que además contiene un interferón o un interferón pegilado.

47. La composición farmacéutica de acuerdo con la Reivindicación 46, donde dicho egente antiviral es ribavirin y dicho interferón es α-interferón.

48. Un método para tratar trastornos asociados con la proteasa del VHC, comprendiendo dicho método administrar a un paciente que necesita dicho tratamiento cantidades terapéuticamente efectivas de un compuesto de acuerdo con la Reivindicación 1.

49. Un método para el tratamiento de trastornos relacionados con la proteasa del VHC, comprendiendo dicho método administrar a un paciente que necesita dicho tratamiento una composición farmacéutica que comprende cantidades terapéuticamente efectivas de un compuesto de acuerdo con la Reivindicación 1.

50. El método de acuerdo con la Reivindicación 49, en el cual dicha administración es subcutánea.

51. El uso de un compuesto de acuerdo con la Reivindicación 1 para la fabricación de un medicamento para tratar trastornos asociados con la proteasa del VHC.

52. Una composición farmacéutica para tratar trastornos asociados con la proteasa del VHC, comprendiendo dicha composición una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 40 y un vehículo aceptable para uso farmacéutico.

53. La composición farmacéutica de acuerdo con la Reivindicación 52, que además contiene un agente antiviral.

54. La composición farmacéutica de acuerdo con la Reivindicación 53, que aun contiene además un interferón o un interferón pegilado.

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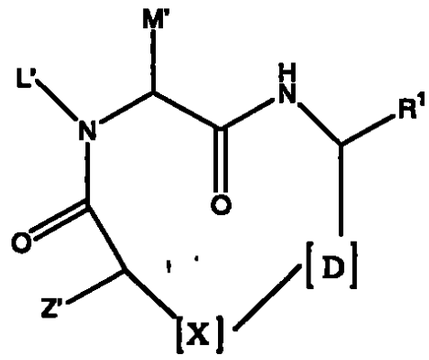
55. La composición farmacéutica de acuerdo con la Reivindicación 54, en la cual dicho agente antiviral es ribavirin y dicho interferón es α-interferón.

p.p. de: SCHERING CORPORATION

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Resumen de la Invención

La presente invención revela compuestos novedosos que poseen actividad inhibidora de la proteasa del VHC al igual que composiciones farmacéuticas que comprenden dichos compuestos y métodos para usarlos para tratar trastornos asociados con la proteasa del VHC. Los compuestos novedosos típicamente incluyen un macrociclo de 15–20 miembros y poseen la estructura general de la Fórmula estructural 1:



Fórmula 1

en la cual Z', L', M', R_1, X y D se definen en la presente.

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TRATADO DE C OPERACIÓN DE PATENTES
PCT
INFORME PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD
(Capítulo II del Tratado de Cooperación en materia de Patentes)
(PCT Artículo 36 y Regla 70)

Referencia del expediente del solicitante o mandatario: IN06005
Solicitud Internacional No.: PCT/US2004/031136
Fecha de presentación internacional: 23.09.2004
Fecha de prioridad: 26.09.2003
Clasificación Internacional de Patentes (IPC) o la vez clasificación nacional e IPC: C07K 5/12, C07D 245/00, A61K 38/12.
Solicitante: SCHERING CORPORATION et. al.

1. El presente informe preliminar internacional sobre patentabilidad, se establece por esta Administración encargada del examen preliminar internacional según el Artículo 35 y se transmite al solicitante conforme el Artículo 36.

2. Este INFORME consta de un total de 9 hojas, incluida la presente hoja de portada.

3. Este informe también contiene ANEXOS, que comprenden.

a. ☐ (*remitido al solicitante y a la oficina internacional*) un total de ___ hojas, descritas a continuación:

☐ hojas de la descripción, las reivindicaciones y/o los dibujos que han sido modificadas y que sirven de base al presente informe, y/o de hojas que contienen rectificaciones autorizadas por esta Administración (véase la Regla 70.16 y la Instrucción Administrativa 607 del PCT).

☐ hojas que reemplazan a otras hojas anteriores, pero que esta Administración considera que contienen modificaciones que se extienden más allá de la divulgación de la invención tal como fue originalmente presentada, según se indica en el punto 4 del Reglamento I y en el Recuadro Suplementario.

b. ☐ (remitido únicamente a la Oficina Internacional) un total de (indicar tipo y soporte(s) electrónico(s)) , que contienen una lista de secuencias y/o tabla(s) relativa(s), solo en formato legible por ordenador, como se indica en el Recuadro Suplementario relativo a Listas de Secuencias (ver Instrucción Administrativa 802).

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4. El presente informe contiene indicaciones relativas a los siguientes puntos:

☒	Recuadro I	Base de este informe
☐	Recuadro II	Prioridad
☒	Recuadro III	Ninguna formulación de opinión sobre la novedad, la actividad inventiva y la aplicación industrial
☐	Recuadro IV	Falta de unidad de Invención
☒	Recuadro V	Declaración motivada según el Artículo 35(2) sobre la novedad, la actividad inventiva y la aplicación industrial, citas y explicaciones en apoyo de esta declaración
☒	Recuadro VI	Ciertos documentos citados
☐	Recuadro VII	Defectos en la Solicitud Internacional
☒	Recuadro VIII	Observaciones relativas a la solicitud internacional

Fecha de radicación de la demanda: 15.04.2005
Fecha de elaboración de este reporte: 01.09.2005

Nombre y dirección postal de la Administración encargada del Examen Preliminar Internacional:
Oficina de Patentes Europea
D-80298 – Munich
Tel: +49-89 2399 - 0, Tx: 523656 epmu d
Fax: +49-89 2399 – 4465.

Funcionario Autorizado: Vogt, T
Tel: + 49 89 2399-8477

Recuadro I. Base de este informe

1. Por lo que respecta al **idioma**, este informe se ha establecido sobre la base de la solicitud internacional en el idioma en el cual se depositó, salvo indicación en contra señalada a continuación.

☐ Este informe está basado en una traducción del idioma original al siguiente idioma , que es el de una traducción proporcionada a los fines de:
- ☐ búsqueda internacional (según Reglas 12.3 y 23.1 (b))
- ☐ publicación de la solicitud internacional (según Regla 12.4)
- ☐ examen preliminar internacional (según Reglas 55.2 y/o 55.3)

2. Por lo que respecta a los **elementos*** de la solicitud internacional, esta opinión se ha establecido sobre la base de (*las hojas de reemplazo que hayan sido enviadas a la Oficina receptora en respuesta a un requerimiento según el Artículo 14 se las denomina en este informe como "inicialmente presentadas" y no se anexan al informe):*

Descripción, Páginas

1 – 259 tal como se presentaron inicialmente

Reivindicaciones, Números

1 – 55 tal como se presentaron inicialmente

☐ una lista de secuencias y/o tabla(s) relativa(s) – ver Recuadro Suplementario relativo a Listas de Secuencias

3. Las modificaciones ha ocasionado la cancelación de:

- ☐ la descripción, páginas
- ☐ las reivindicaciones, Nos.
- ☐ los dibujos, hojas/fig.
- ☐ la lista de secuencias (especificar):
- ☐ tabla(s) relativa(s) a la lista de secuencias (especificar):

4. ☐ El presente informe ha sido establecido como si no se hubiesen presentado (algunas de) las modificaciones anexadas a este informe y listadas abajo, ya que se ha considerado que iban más allá de la divulgación de la invención tal como fue presentada, como se indica en el Recuadro Suplementario (Regla 70.2(c)).

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☐ la descripción, páginas
☐ las reivindicaciones, Nos.
☐ los dibujos, hojas/fig.
☐ la lista de secuencias (especificar):
☐ tabla(s) relativa(s) a la lista de secuencias (especificar):

* Si se utiliza el punto 4, algunas o todas estas páginas pueden llevar el sello de "sustituida".

Recuadro No. III. Ninguna formulación de opinión sobre la novedad, la actividad inventiva y la aplicación industrial

1. Las preguntas con respecto a si el invento reivindicado parece ser novedoso, implica una actividad inventiva (no ser evidente), o ser susceptible de aplicación industrial, por lo que respecta.

☐ al conjunto de la solicitud internacional,
☒ a las reivindicaciones Nos. 1-38, 41-55 (incompleta)

debido a que:

☒ la solicitud internacional, o las reivindicaciones Nos. 48-50 (IA) en cuestión se refieren al objeto, respecto del cual no requiere examen preliminar internacional (especifique):

Ver hoja separada

☐ a descripción, reivindicaciones, o los dibujos (indíquese cuales a continuación) o tales reivindicaciones Nos. en cuestión no son claras, de manera que no es posible formular una opinión significativa (especifique):

☐ las reivindicaciones, o las reivindicaciones Nos. en cuestión no son claras, de manera que no es posible formular una opinión significativa.

☒ no se ha emitido informe de búsqueda internacional para dichas reivindicaciones Nos. 1-38, 41-55 (búsqueda incompleta)

☐ la lista de de secuencias nucleótidas y/o de aminoácidos no cumplen la norma estándar prevista en el Anexo C de las Instrucciones Administrativas por que:

La lista en papel ☐ no se presentó

☐ no cumple con la norma estándar

La lista en formato legible por ordenador

☐ no se presentó

☐ no cumple con la norma estándar

☐ las tablas relativas a las listas de secuencias de nucleótidas y/o de aminoácidos, si únicamente se han presentado en formato legible por ordenador, no cumplen con los requisitos técnicos previstos en el Anexo C-*bis* de las Instrucciones Administrativas.

☐ Ver recuadro suplementario para más detalles.

Recuadro No. V Declaración razonada según el Artículo 35(2) con respecto a la novedad, nivel inventivo o aplicación industrial: anterioridades y explicaciones que soportan tal declaración

1. Declaración

Novedad (N)	Si:	Reivindicaciones 39, 10
	No:	Reivindicaciones 1-38, 41-55
Nivel Inventivo (NI)	Si:	Reivindicaciones 39, 40
	No:	Reivindicaciones 1-38, 41-55
Aplicación Industrial (AI)	Si:	Reivindicaciones 1-47, 51-55
	No:	Reivindicaciones 48-50

2. Citas y explicaciones (Regla 70.7)

ver hoja separada.

Recuadro No. VI Ciertos documentos citados

1. Ciertos documentos publicados (Regla 70.10)

y/o

2. Divulgaciones no escritas (Regla 70.9)

Ver hoja adjunta

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 descripción:

ver hoja adjunta

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III. Ningún concepto.

El reporte de búsqueda internacional (ISR) solamente fue parcialmente establecido para las reivindicaciones 1-38, 41-55. El reporte de evaluación preliminar internacional (IPER) por lo tanto no tendrá en cuenta dichas reivindicaciones (Regla 66(1)e del PCT).

Las reivindicaciones 48-50 se relacionan con materia, considerada por esta Autoridad, estar cubierta por la Regla 67.1 (iv) del PCT. De manera que no se formulará ningún concepto con respecto a la aplicación industrial de los temas encontrados en estas reivindicaciones (Artículo 34(a)(i) del PCT).

Por lo tanto, el IPER solamente tendrá en cuenta la materia de las reivindicaciones 39 y 40, y las reivindicaciones 1-38 y 41-55 solo si se relacionan con las reivindicaciones 39 y 40.

VII. Claridad y soporte de las reivindicaciones (Artículo 6 del PCT).

Las presentes reivindicaciones 1-38 y 41-55 se relacionan con un número extremadamente grande de posibles compuestos. De hecho, las reivindicaciones contienen tantas opciones, variables y posibles permutaciones que existe una falta de claridad dentro del marco del Artículo 6 del PCT de tal modo que vuelve imposible una búsqueda significativa de las reivindicaciones. Adicionalmente, dichas reivindicaciones carecen se soporte puesto que solo una pequeña porción de los compuestos realizados son realmente sintetizados, y no es obvio una generalización de la enseñanza obtenida de las mismas con respecto al alcance total de la presente fórmula 1. Además, el esqueleto de los compuestos de fórmula 1 carece de un único elemento estructural que se encuentre en todos los compuestos de ejemplo y a los cuales se les pueda asignar de manera única la función.

Adicionalmente, el alcance de las reivindicaciones no presenta claridad puesto que algunos de los compuestos de ejemplo no están dentro del alcance de las mismas. Estos compuestos están en conflicto con la definición de las variables [X] y [D] las cuales dictan que por lo menos dos grupos CHR_{29} deben estar presentes para el fragmento [X] (a=2-9) y un grupo CHR_{32} (g=1-9) para el fragmento [D]. Estos requisitos excluyen cualquier compuesto en donde el fragmento [X]-[D] empiece con $CR_{29}R_{29}$, CHR_{29}-O/N/S/C(O) o C_5H_4N-C(O), ó [D] empiece con C(O) o C=C. Los ejemplos en cuestión son: 14, 16-19, 52-66, 73-77 y 79-82 (compare con las reivindicaciones 17, 18, 30, 31, 38, y 39).

También se llama la atención de los solicitantes a los últimos cinco compuestos de la reivindicación 31. Estos compuestos solo tiene dos lugares de conectividad, en vez de 3 (ver también la reivindicación 38).

V. Declaración Razonada.
Materia de la presente solicitud.

Proporcionar inhibidores macrocíclicos de la serina proteasa NS3 del virus de la hepatitis C.

Documentos del estado de la técnica anterior (antecedentes) citados (Regla 64(1) del PCT).

D1: WO 00/09543 A.
D2: WO 00/59929 A.
D3: WO 01/81325 A.
D4: TSANTRIZOS ET AL. (03.2003) ANGEWANDTE CHEMIE 42, 356-1360.
D5: WO 03/062228 A (2003-07-31)
D6: GOUDREAU ET AL. (17.09.2004) J. ORG. CHEM. 69, 6185-6201.
D7: WO 2004/072243 A.
D8: WO 2004/093798 A.

Los antecedentes D6-D8 no forman parte del estado de la técnica anterior según la Regla 64(1) del PCT.

Novedad (Artículo 33(2) del PCT).

D1 y D2 divulgan tripéptidos lineales (D1) y P1-P3 ciclizados para usarse como inhibidores de la serina proteasa NS3. Los compuestos se caracterizan en que ellos comprenden una prolina sustituida sobre la posición P2, y un grupo ciclopropilo sobre la posición P1. Los compuestos de la presente solicitud no pueden tener un grupo ciclopropilo sobre la posición P1. De manera curiosa, D6 ilustra que compuestos macrocíclicos que comprenden un grupo ciclopropilo sobre la posición P1 son significativamente más potentes (D6, p. 6192). BILN2061, uno de los inhibidores más potentes de la serina proteasa NS3 del virus de la hepatitis C en el mercado hoy en día está dentro del alcance de D2.

D4 divulga como los inventores de D1 obtuvieron las estructuras macrocíclicas de D2. Se manifiesta lo siguiente:
"... *especulamos que enlazamientos intra moleculares de la cadena lateral P1 a la cadena lateral P3 con un puente de hidrocarbonos conllevaría a un inhibidor macrocíclico que, en estado libre, adoptaría de manera preferencial la conformación del péptido enlazado a NS3.*", y *"Sin embargo, se observó una caída en potencia de más de 36 veces al cortar el puente del inhibidor 4c para producir el análogo 3b de cadena abierta correspondiente (Tabla 1), lo cual confirma la importancia de la macrociclización."* (páginas 1356 y 1357).

Los inhibidores macrocíclicos de la serina proteasa NS3 del virus de la hepatitis C descritos en la reivindicación 1 de D3 parece ser que coinciden parcialmente con los compuestos de la presente reivindicación 1. Sin embargo, ninguno de los compuestos de ejemplo realmente está dentro del alcance de la presente reivindicación 1. Por ejemplo, el compuesto 54 d D3 difiere únicamente en la definición de R1. D3 parece no anticipar la presencia de una prolina sustituida (por ejemplo, cuando R3 y R4 juntos con Z forman una estructura cíclica). Puesto que los compuestos definidos en la reivindicación 1 de D3 tienen la misma función que aquellos de la presente solicitud y son igualmente definidos de manera amplia que aquellos de la reivindicación 1 de la presente solicitud, el examinador considera que la materia de las presente reivindicaciones 1-19, 25-29, 33-37, 41-55 carecen de novedad con respecto a D3. Se

observa que aunque algunas de las presentes reivindicaciones se refieren a una estructura de fórmula 2, no restringen realmente el alcance de la reivindicación 1.

D5 divulga inhibidores de la proteasa NS3 del virus de la hepatitis C que difieren de la presente solicitud en que son lineales (por ejemplo, D5 no anticipa enlazar R2 y R3 por medio de un puente molecular). D5 divulga las prolinas sustituidas sobre la posición P2, el grupo resistente a la proteasa, C(O)-C(O)-NH (por ejemplo, la sustitución R1 más preferida de la presente solicitud) y el grupo ZWY que parece coincidir con la definición del mismo encontrado en la presente solicitud.

Los compuestos descritos en las reivindicaciones 1 de D7 y D8 coinciden con aquellos de la reivindicación 1 de la presente solicitud cuando s=0. Sin embargo, ni D7 ni D8 divulgan de manera específica ningún compuesto en donde s=0.

Resumiendo: la materia de las reivindicaciones 1-19, 25-29, 33-37, 41-55 carecen de novedad con respecto a los antecedentes citados (Artículo 33(2) del PCT).

Las reivindicaciones 39 y 40 contienen características las cuales por si solas o en combinación con las reivindicaciones a las cuales se refieren, parecen no haberse divulgado en los antecedentes citados. La materia de dichas reivindicaciones por lo tanto parece ser novedosa (Artículo 33(2) del PCT).

Nivel Inventivo (Artículo 33(3) del PCT)
El estado de la técnica más cercano para los compuestos de la presente solicitud es el documento D3.

El problema a resolverse con la presente solicitud puede por lo tanto verse como el proporcionar inhibidores adicionales de la serina proteasa NS3 del virus de la hepatitis C.

La solución del solicitante parece carecer de nivel inventivo con respecto a una combinación de documentos D3 y D5, en vista de D4. Al examinador le parece que el solicitante siguió el incentivo encontrado en D4, a saber que la ciclización P1-P3 potencializa la actividad de inhibidores peptídicos lineales de la serina proteasa NS3 del virus de la hepatitis C.
Por lo tanto parece que el solicitante ha modificado los compuestos de D3 al insertar los péptidos de D5.

De manera consecuente, el examinador considera que la definición amplia de los compuestos presentemente encontrados en las reivindicaciones 1-38 y 41 carecen de nivel inventivo.

Se puede reconocer un nivel inventivo para los compuestos específicos de las reivindicaciones 39 y 40, puesto que la mayoría de estos compuestos tienen una actividad de enlazamiento por debajo de 100 nM, y algunos de éstos tienen una actividad inhibitoria en el rango nanomolar.

El nivel inventivo de las reivindicaciones relacionadas con el uso médico de los compuestos reivindicados solo puede reconocerse para compuestos inventivos.

Resumiendo: la materia de las reivindicaciones 1-38, 41 y reivindicaciones 42-55, siempre y cuando se relacionen con dichas reivindicaciones, carecen de nivel inventivo.

Las reivindicaciones 39-40 y 42-55, siempre y cuando se relacionen con dichas reivindicaciones, parecen ser inventivas, puesto que contienen características las cuales por si solas o en combinación con las reivindicaciones a las cuales se refieren, no parecen haber sido sugeridas por ninguna combinación de los antecedentes citados.

Aplicación Industrial (Artículo 33(4) del PCT).
La materia de las reivindicaciones 1-47, 51-55 cumplen con los requisitos de aplicación industrial.

Para la evaluación de las presentes reivindicaciones 48-50 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.

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 IN06005	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US2004/031136	International filing date *(day/month/year)* 23.09.2004	Priority date *(day/month/year)* 26.09.2003
International Patent Classification (IPC) or national classification and IPC C07K5/12, C07D245/00, A61K38/12		
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 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.04.2005	01.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Vogt, T Telephone No. +49 89 2399- 8477

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

INTERNATIONAL PRELIMINARY REPORT N PATENTABILITY

International application No. PCT/US2004/031136

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

   1-259 as originally filed

   Claims, Numbers

   1-55 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/US2004/031136

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. 1-38, 41-55 (incomplete)

because:

☒ the said international application, or the said claims Nos. 48-50 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-38, 41-55 (incomplete search)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/031136

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	39,40
	No:	Claims	1-38, 41-55
Inventive step (IS)	Yes:	Claims	39,40
	No:	Claims	1-38, 41-55
Industrial applicability (IA)	Yes:	Claims	1-47, 51-55
	No:	Claims	48-50

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

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

III No opinion.

The international search report (ISR) was only partially established for claims 1-38, 41-55. The international preliminary examination report (IPER) will therefore not cover said claims (Rule 66(1)e PCT).

Claims 48-50 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).

Hence, the IPER will only relate to the subject matter of claims 39 and 40, and claims 1-38 and 41-55 insofar as they relate to claims 39 and 40.

VII Clarity and support of the claims (Art. 6 PCT).

Present claims 1-38 and 41-55 relates to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, and possible permutations that a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Moreover said claim lacks support, because only a small portion of the embodied compounds is actually synthesized and a generalisation of the teaching obtained therefrom to the full scope of present formula 1 is not obvious. Furthermore, the backbone of the compounds of formula 1 lacks a single structural element that is found in all exemplified compounds and to which the function can be uniquely assigned.

In addition, the scope of the claims is rendered unclear because some of the exemplified compounds do not fall within the scope thereof. These compounds are in conflict with the definition of the variables [X] and [D] which dictate that at least two CHR_{29} groups must be present for the fragment [X] (a=2-9) and one CHR_{32} (g=1-9) for the fragment [D]. These requirements exclude any compounds wherein the fragment [X]-[D] starts with $CR_{29}R_{29}$, CHR_{29}-O/N/S/C(O) or C_5H_4N-C(O), or [D] starts with C(O) or C=C. The examples in question are: 14, 16-19, 52-66, 73-77 and 79-82 (cf. claims 17, 18, 30, 31, 38 and 39).

The applicants attention is also directed to the last five compounds of claim 31. These compounds only have two places of connectivity, instead of 3 (see also claim 38).

V Reasoned Statement.

Subject matter of the present application.

The provision of macrocyclic inhibitors of hepatitis C virus NS3 serine protease.

Cited prior art documents (Rule 64(1) PCT).

D1: WO 00/09543 A.
D2: WO 00/59929 A.
D3: WO 01/81325 A.
D4: TSANTRIZOS ET AL. (03.2003) ANGEWANDTE CHEMIE 42, 356-1360.
D5: WO 03/062228 A (2003-07-31).
D6: GOUDREAU ET AL. (17.09.2004) J. ORG. CHEM. 69, 6185-6201.
D7: WO 2004/072243 A.
D8: WO 2004/093798 A.

D6-D8 do not form part of the prior art under Rule 64(1) PCT.

Novelty (Art. 33(2) PCT).

D1 and D2 disclose linear (D1) and P1-P3 cyclized (D2) tripeptides for use as inhibitors of the NS3 serine protease. The compounds are characterised in that they comprise a substituted proline at the P2 position, and a cyclopropyl group at the P1 position. The compounds of the present application can not have a cyclopropyl group at the P1 position. Interestingly, D6 shows that macrocyclic compounds comprising a cyclopropyl group in the P1 position are significantly more potent (cf. D6, p. 6192).
BILN2061, which is one of the most potent inhibitors of HCV NS3 serine protease on the market today falls within the scope of D2.

D4 discloses how the inventors of D1 arrived at the macrocyclic structures of D2. It is stated:
"*... we speculated that intra molecular linking of the P1 side chain to the P3 side chain with a hydrocarbon bridge would lead to a macrocyclic inhibitor which would, in the free state, preferentially adopt the conformation of NS3-bound peptide.*"., and "*However, a more then 36-fold drop in potency was observed upon cleaving the bridge of inhibitor 4c to produce the corresponding open-chain analogue 3b (Table 1), which confirms the*

importance of macrocyclization." (cf. pp. 1356 and 1357).

The macrocyclic inhibitors of HCV NS3 serine protease described in claim 1 of D3 appear to partly overlap with the compounds of present claim 1. However, none of the exemplified compounds actually falls within the scope of present claim 1. Compound 54 of D3, for instance, differs only in the definition of R1. D3 does not appear to anticipate the presence of a substituted proline (eg. when R3 and R4 together with Z form a ring structure). Since the compounds defined in claim 1 of D3 have the same function as those of the present application and are equally broadly defined as those of claim 1 of the present application, the examiner considers that the subject matter of present claims 1-19, 25-29, 33-37, 41-55 lacks novelty over D3. It is noted that although some of the present claims refer to a structure of formula 2, they do not actually restrict the scope of claim 1 thereto.

D5 discloses HCV NS3 protease inhibitors, which differ from the present application in that they are linear (eg. D5 does not anticipate to connect R2 and R3 via a bridge molecule). D5 discloses the substituted prolines at the P2-position, the protease resistant group C(O)-C(O)-NH (eg. the most preferred R1 substitution of the present application) and the ZWY group which appears to overlap with the definition thereof found in the present application.

The compounds described in claims 1 of D7 and D8 overlap with those of claim 1 of the present application when s=0. However, neither D7 nor D8 specifically disclose any compounds wherein s=0.

To summarize: the subject matter of claims 1-19, 25-29, 33-37, 41-55 lacks novelty over the cited prior art documents (Art. 33(2) PCT).

Claims 39 and 40 contain features which alone or in combination with the claims to which they refer do not appear to have been disclosed in the cited prior art. The subject matter of said claims therefore appears to be novel (Art. 33(2) PCT).

Inventive step (Art. 33(3) PCT).

Closest prior art for the compounds of the present application is D3.

The problem to be solved with the present application can therefore be seen as the provision of further inhibitors of HCV NS3 serine protease.

The solution of the applicant appears to lack an inventive step over a combination of documents D3 and D5, in view of D4. The examiner is of the opinion that the applicant followed the incentive found in D4, namely that P1-P3 cyclization potentiates the activity of linear peptidic inhibitors of HCV NS3 serine protease.
It thus appears that the applicant has modified the compounds of D3 by inserting the peptides of D5.

It thus follows that the examiner considers that the broad definition of the compounds presently found in claims 1-38 and 41 lacks an inventive step.

An inventive step can be acknowledged for the specific compounds of claims 39 and 40, because most of these compounds have a binding activity below 100 nM, and some of these have an inhibitory activity in the nanomolar range.

The inventive step of claims directed to the medical use of the claimed compounds can only be acknowledged for inventive compounds.

To summarize: the subject matter of claims 1-38, 41 and claims 42-55, insofar as they relate to said claims, lack an inventive step.

Claims 39-40 and 42-55, insofar as they relate to said claims, appear to be inventive, because they contain features which alone or in combination with the claims to which they refer do not appear to have been suggested by any combination of the cited prior art documents.

Industrial applicability (Art. 33(4) PCT).

The subject matter of claims 1-47, 51-55 meets the requirement of industrial applicability.

For the assessment of the present claims 48-50 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.

PATENT COOPERATION TREATY

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711

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

KALYANARAMAN, Palaiyur, S.
Schering-Plough Corporation
2000 Galloping Hill Road
Mail Stop K-6-1 1990
Kenilworth, NJ 07033-0530
United States of America

Date of mailing (day/month/year)	
09 May 2005 (09.05.2005)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
IN06005	
International application No.	**International filing date (day/month/year)**
PCT/US2004/031136	23 September 2004 (23.09.2004)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
VELASQUEZ, Francisco 4 Alexandra Way Clinton, NJ 08809 United States of America	MX	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
VELAZQUEZ, Francisco 4 Alexandra Way Clinton, NJ 08809 United States of America	MX	US
TEAM 14 24. 05. 2005	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Juan CRUZ
Facsimile No. (41-22) 338.88.65	Telephone No. (41-22) 338 8238

\TENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
IN06005		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2004/031136	23/09/2004	26/09/2003
Applicant		
SCHERING CORPORATION		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. [X] Certain claims were found unsearchable (See Box II).

3. [ ] Unity of invention is lacking (see Box III).

4. With regard to the title,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,
   a. the figure of the drawings to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No
I-. ./US2004/031136

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K5/12 C07D245/00 A61K38/12

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 C07K C07D A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/09543 A (BOEHRINGER INGELHEIM CA LTD ; GOUDREAU NATHALIE (CA); GHIRO ELISE (CA)) 24 February 2000 (2000-02-24)	
A	WO 00/59929 A (BOEHRINGER INGELHEIM CA LTD ; GOUDREAU NATHALIE (CA); GHIRO ELISE (CA)) 12 October 2000 (2000-10-12) cited in the application the whole document	
X	WO 01/81325 A (SCHERING CORP) 1 November 2001 (2001-11-01) cited in the application the whole document	1-19, 25-29, 33-37, 41-55

-/--

[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
14 January 2005	02/02/2005

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	Vogt, T

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

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TSANTRIZOS Y S ET AL: "Macrocyclic inhibitors of the NS3 protease as potential therapeutic agents of hepatitis C virus infection" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, VERLAG CHEMIE. WEINHEIM, DE, vol. 42, no. 12, 28 March 2003 (2003-03-28), pages 1356-1360, XP002278992 ISSN: 0570-0833 the whole document	1-55
Y	WO 03/062228 A (SCHERING CORP) 31 July 2003 (2003-07-31) the whole document	1-55
P,A	GOUDREAU NATHALIE ET AL: "Potent inhibitors of the hepatitis C virus NS3 protease: design and synthesis of macrocyclic substrate-based beta-strand mimics." THE JOURNAL OF ORGANIC CHEMISTRY. 17 SEP 2004, vol. 69, no. 19, 17 September 2004 (2004-09-17), pages 6185-6201, XP002313531 ISSN: 0022-3263 the whole document	
P,A	WO 2004/072243 A (MIAO ZENWEI ; XU GUOYOU (US); NAKAJIMA SUANNE (US); OR YAT SUN (US); S) 26 August 2004 (2004-08-26) the whole document	
E,A	WO 2004/093798 A (TANG DATONG ; XU GOUYOU (US); MIAO ZHENWEI (US); NAKAJIMA SUANNE (US);) 4 November 2004 (2004-11-04) the whole document	1-55

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 48-50 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 1-38, 41-55 (incomplete)

Present claim 1 relates to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, and possible permutations that a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Moreover said claim lacks support, because only a small portion of the embodied compounds is actually synthesized and a generalisation of the teaching obtained therefrom to the full scope of present formula 1 is not obvious. Furthermore, the backbone of the compounds of formula 1 lacks a single structural element that is found in all exemplified compounds.

In addition, the scope of claim 1 is rendered unclear because some of the exemplified compounds do not fall within the scope thereof. These compouse are in conflict with the definition of the variables 'X! and 'D! which dictate that at least two CHR29 groups must be present for the fragment 'X! (a=2-9) and one CHR32 (g=1-9). This requirement excludes any compounds wherein the fragment 'X!-'D! starts with CR29R29 and CHR29-O/N/C(O) or C5H4N-C(O). The examples in question are 14, 16-19, 52-66, 73-77 and 79-82.

Consequently, the search has been carried out for those parts of the application which do appear to be clear (and concise), namely the compounds recited in the examples and claims 39 and 40. Specifically, the searched macrocyclic structure comprises the backbone structure depicted in formula 1, wherein:
Z'=NH-R;
L'-N-C(M')-C(O)= optionally substituted proline;
'X!-'D!=-CRR-A-A-B-'CRR!3-4-, wherein A=O, CRR or NR and B=O-C(O)-N, CRR-CRR-CRR or CRR-CR=CR;
R1= C(O)-R or B(OR)2;
wherein R always represents a position open for substitution.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/031136

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.: 1-38, 41-55 (incomplete)
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 48-50 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-38, 41-55 (incomplete)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box 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
P../US2004/031136

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0009543	A	24-02-2000	AU	769738 B2	05-02-2004
			AU	5273199 A	06-03-2000
			BG	105232 A	30-11-2001
			BR	9913646 A	05-06-2001
			CA	2338946 A1	24-02-2000
			CA	2445938 A1	24-02-2000
			WO	0009543 A2	24-02-2000
			CN	1323316 T	21-11-2001
			CZ	20010516 A3	15-08-2001
			EA	3906 B1	30-10-2003
			EE	200100081 A	15-08-2002
			EP	1105413 A2	13-06-2001
			HR	20010102 A1	28-02-2002
			HU	0105144 A2	29-04-2002
			ID	27839 A	26-04-2001
			JP	2002522554 T	23-07-2002
			NO	20010683 A	02-04-2001
			NZ	510396 A	27-02-2004
			PL	346626 A1	25-02-2002
			SK	2062001 A3	08-10-2001
			TR	200100432 T2	21-09-2001
			TR	200200129 T2	21-06-2002
			US	6534523 B1	18-03-2003
			US	6323180 B1	27-11-2001
			US	6268207 B1	31-07-2001
			US	6329379 B1	11-12-2001
			US	6329417 B1	11-12-2001
			US	2002016442 A1	07-02-2002
			US	2002037998 A1	28-03-2002
WO 0059929	A	12-10-2000	AT	277945 T	15-10-2004
			AU	778390 B2	02-12-2004
			AU	3548000 A	23-10-2000
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SUPERINDUSTRIA Y COMERCIO
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN (✓) MODELO DE UTILIDAD ( )	( )	( )
-Indicación de que se solicita la concesión de una patente.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Descripción de la invención.	( )	( )
-Dibujos de ser estos pertinentes.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )
DISEÑO INDUSTRIAL ( )		
-Indicación de que se solicita el registro de Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se 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 Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica del Esquema Trazado.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )

Firma Responsable: _____

Fecha: Marzo 24 de 2006

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

721

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2020
Bogotá D.C.,

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
SCHERING CORPORATION

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	Solicitud internacional	US2004/031136
	Fecha inicio fase nacional	26/04/2006
	Trámite	11
	Evento	379
	Actuación	416
	Oficio No.	895
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 14 JUL 2005

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

jramos