CSA229901

Organizacion CSA Ltda

"SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO"
INVENTARIO

Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

08 - 10100

SOLICITUD DE PATENTE DE INVENCIÓN

PTIDOS MACROCICLÍCOS COMO INHIBIDORES DEL LA
3 DEL VHC

"SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO"
INVENTARIO

INC.

e, Rahway, New Jersey 07065-0907.

K 34/06

OLARTERAIS

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-010100- -00000-0000
Fecha: 2008-02-01 17:08:26 Dep: 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 342

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-010100- -00000-0000
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PETITORIO - FORMULARIO ÚNIC
PATENTE PCT
ENTRADA EN FASE NA
SOLICITUD D

(1) [X] Patente de Invención. [ ]

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**	**Nombre:** MERCK & CO., INC. **Dirección:** 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 E.U.A. **Nacionalidad o Domicilio:** ESTADOS UNIDOS **Lugar de Constitución:** ESTADOS UNIDOS **Teléfono:** **Fax:** **E-mail:**	**IDENTIFICACIÓN** **C.C.** [ ] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** **Número**
REPRESENTANTE O 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** 79782747Bta **TP** 74.295
INVENTOR (ES) (72)	**Nombre:** VER PAGINA ADJUNTA **Dirección:** VER PAGINA ADJUNTA **Nacionalidad o Domicilio:** VER PAGINA ADJUNTA	

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2006/029635 Fecha Julio 28, 2006

Publicación Internacional No. WO 2007/016441 Fecha Febrero 8, 2007

(6) **Título (54)** PEPTIDOS MACROCICLÍCOS COMO INHIBIDORES DE LA PROTEASA NS3 DEL VHC

(7) **Clasificación Internacional (51)** C07K 5/08, C07K 5/10, C07K 7/06, A61K 38/06, A61K 38/07, A61K 38/08, A61P 31/14

(8) **Prioridad** **SI** [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Agosto 1, 2005	60/704.256
US	Octubre 7, 2005	60/724.509

(9) **Comprobante de pago No.** 08-8,805 **Fecha** Febrero 1, 2008

(10) **ANEXOS**

[x]	Comprobante de pago de la tasa de presentación de la solicitud.
[x]	Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
[x]	Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 07-055.540
[ ]	Documento de cesión del inventor al solicitante o a su causante.
[ ]	Declaraciones.
[x]	Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
[x]	Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
[ ]	Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
[ ]	Traducción del examen preliminar internacional efectuado por la IPEA.
[ ]	De ser el caso, copia del contrato de acceso.
[ ]	De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
[ ]	De ser el caso, certificado de depósito del material biológico.
[ ]	Arte final 12 x 12.
[ ]	De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
[ ]	De ser el caso, modificaciones efectuadas a la solicitud internacional.
[x]	Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

( ) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

C.C. 79782747Bta T.P. 74.295

LISTA DE INVENTORES **PCT/US2006/029635**

KATHARINE HOLLOWAY M,
126 East Lincoln Avenue, Rahway,
New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estadounidense

NIGEL LIVERTON J,
126 East Lincoln Avenue, Rahway,
New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Británica

JOHN MCCAULEY A,
126 East Lincoln Avenue, Rahway,
New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estadounidense

MICHAEL RUDD T,
126 East Lincoln Avenue, Rahway,
New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estadounidense

JOSEPH VACCA P,
126 East Lincoln Avenue, Rahway,
New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estadounidense

STEVEN LUDMERER W,
126 East Lincoln Avenue, Rahway,
New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estadounidense

5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-010100- -00000-0000

Fecha: 2008-02-01 17:08:26 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 342

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 8,805
FECHA : FEBRERO 1 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-010100- -00000-0000

Fecha: 2008-02-01 17:08:26 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 342

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	2661940	01/02/2008	11,577,000.00

***** 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	501,000.00
		TOTAL : $	501,000.00

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

PODER ESPECIAL

Yo el abajo firmante, J. Ian Raisbeck, identificado con cédula de ciudadanía No. 79.376.996 de Bogotá, representante legal de OLARTE RAISBECK & FRIERI LTDA., sociedad limitada constituida en la República de Colombia, y obrando bajo las facultades otorgadas por el Poder General adjunto por la sociedad MERCK & Co. Inc., constituida de acuerdo a las leyes de New Jersey, Estados Unidos de América domiciliada en 126 East Lincoln Avenue, Rahway, NJ 07065-0907, Estados Unidos de América, nombro por el presente a los Doctores CARLOS R. OLARTE y/o ANA MARIA FRIERI DEL CASTILLO y/o JUAN GUILLERMO MOURE PEREZ y/O NATALIA CASTRO VELEZ, para que representen a la sociedad MERCK & Co. Inc., en la Republica de Colombia, en materia de patentes, y ante las autoridades ya sean administrativas, judiciales o de policía, para iniciar ante dichas autoridades todas las acciones necesarias para cumplir con el objeto indicado e intervenir en todas las instancias, grados o etapas procesales; elevar y tramitar solicitudes, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y reconvenciones; formular descripciones, enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento, allanarse a la pretensión, percibir, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal y los demás actos que exprese la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestros intereses. Por el presente instrumento se revoca todo poder anteriormente otorgado por mi representada para realizar las gestiones antes mencionadas.

Dado y firmado el 28 de Mayo de 2007

J. IAN RAISBECK

DILIGENCIA DE PRESENTACION PERSONAL Y
RECONOCIMIENTO DE CONTENIDO Y FIRMA.
NOTARIA EL ARTICULO ESCRITO ANTECEDE A:

27

FUE PRESENTADO PERSONALMENTE
ANTE EL SUSCRITO NOTARIO POR EL SEÑOR(A)
DE APELLIDO [illegible]

Con C.C. 79376996 Bta

Y ANTE LA EXHIBICION DEL DOCUMENTO DE IDENTIDAD
DECLARO QUE RECONOCE COMO SUYA LA FIRMA QUE
APARECE PUESTA POR EL

EL DECLARANTE:

HOY: 21 MAY 2001

HUELLA

MARIA EUGENIA ROJAS DE URUETA
NOTARIA VEINTISIETE
REPUBLICA DE COLOMBIA

REPÚBLICA DE COLOMBIA

MARÍA EUGENIA ROJAS DE URUETA
NOTARIA

Notaría 27 Bogotá D.C.

WK 4682369

ESCRITURA PUBLICA NUMERO - - - - - -
TRESCIENTOS DOCE (312).- - - - - - - - - - - -
En la ciudad de Bogotá, Distrito Capital, República de Colombia, a los Veintidos - - - (22) días del mes de Marzo - - - - - de dos mil siete (2007), ante mi, MARIA EUGENIA ROJAS DE URUETA - - - - - - - - - - - - - - - - NOTARIA(O) VEINTISIETE (27) DEL CIRCULO DE BOGOTA, - - - se otorgó la escritura pública que se consigna en los siguientes términos: ----------
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CLASE(S) DE ACTO: PROTOCOLIZACION: ----------
OLARTE RAISBECK & FRIERI LTDA----------
NIT: 830122870-6.----------

Compareció **CARLOS REINALDO OLARTE GARCIA** mayor de edad, vecino de ésta ciudad, identificado con la cédula de ciudadanía número 79.782.747, obrando en nombre y representación **OLARTE RAISBECK & FRIERI LTDA**, con número de identificación tributaria (NIT) 830122870-6 entidad legalmente constituida mediante escritura pública número mil ciento diecinueve (1119) de la notaría treinta y nueve (39) de Bogotá del diez (10) de junio de dos mil tres (2003), como lo acredita con el certificado de constitución y gerencia expedido por la Cámara de Comercio de Bogotá que presenta para su protocolización y declaró ----------

PRIMERO.- Que presenta para su protocolización y custodia en los archivos de ésta notaría, bajo el número y lugar que a ésta escritura corresponda, en cinco (5) folios autenticados, un poder con su traducción la cual es del siguiente tenor:----------

PODER GENERAL ----------

NOTARIA VEINTISIETE
María Eugenia Rojas de Urueta

El suscrito, MERCK & CO., INC, domiciliado en 126 EAST LINCOLN AVENUE, RAHWAY, NJ 07065-0907, USA.---------- nombramos por el presente a Olarte Raisbeck & Frieri Ltda. con Oficinas en el World Trade Center Torre A, Calle 100 No. 8A-37, piso 10, Bogotá D.C. nuestro representantes legales con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales en materia de patentes, los cuales quedan a su vez facultados para representarnos ante las autoridades de cualquier jerarquía de la República de Colombia y la República del Ecuador, la Republica del Perú y la República Bolivariana de Venezuela, ya sean administrativas, judiciales o de Policía, para iniciar ante dichas autoridades todas las acciones necesarias para cumplir con el objeto indicado e intervenir en todas las instancias, grados o etapas procesales, elevar y tramitar solicitudes, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y reconvenciones; formular descripciones, enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento allanarse a la pretensión, recibir, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal y los demás actos que exprese la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyerén conducentes al resguardo de nuestros intereses.- ----------

Firma: Donna L. Margiotto, Senior Manager, "Patent----------

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CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

1 DE FEBRERO DE 2007 HORA 09:15:34

02C25020105804PCT0708 HOJA : 001

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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O INSCRIPCION DE DOCUMENTOS.
LA CAMARA DE COMERCIO DE BOGOTA, CON FUNDAMENTO EN LAS MATRICULAS E INSCRIPCIONES DEL REGISTRO MERCANTIL,

CERTIFICA :

NOMBRE : OLARTE RAISBECK & FRIERI LTDA PERO PARA TODOS LOS EFECTOS PODRA OPERAR BAJO EL NOMBRE OLARTERAISBECK
N.I.T. : 830122870-6 ADMINISTRACION: BOGOTA PERSONAS JURIDICAS, REGIMEN COMUN.
DOMICILIO : BOGOTA D.C.

CERTIFICA :

MATRICULA NO. 01284164

CERTIFICA :

CONSTITUCION : QUE POR ESCRITURA PUBLICA NO. 0001119 DE NOTARIA 39 DE BOGOTA D.C. DEL 10 DE JUNIO DE 2003 , INSCRITA EL 25 DE JUNIO DE 2003 BAJO EL NUMERO 00885810 DEL LIBRO IX, SE CONSTITUYO LA SOCIEDAD COMERCIAL DENOMINADA: OR LEGAL LTDA

CERTIFICA :

QUE POR ESCRITURA PUBLICA NO. 0001328 DE NOTARIA 39 DE BOGOTA D.C. DEL 4 DE JULIO DE 2003 , INSCRITA EL 9 DE JULIO DE 2003 BAJO EL NUMERO 00887749 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE : OR LEGAL LTDA POR EL DE : OLARTE RAISBECK & FRIERI LTDA PERO PARA TODOS LOS EFECTOS PODRA OPERAR BAJO EL NOMBRE OLARTERAISBECK

CERTIFICA :

REFORMAS:

ESCRITURA	FECHA	NOTARIA	CIUDAD	INSCRIPCION	FECHA
0001328	2003/07/04	00039	BOGOTA D.C.	00887749	2003/07/09

CERTIFICA :

VIGENCIA: QUE LA SOCIEDAD NO SE HALLA DISUELTA. DURACION HASTA EL 10 DE JUNIO DE 2103 .

CERTIFICA :

OBJETO SOCIAL : LA SOCIEDAD TENDRA POR OBJETO PRINCIPAL LA PRESTACION DE SERVICIOS DE ASESORIA EN EL AREA SOCIAL, TECNICA, COMERCIAL Y JURIDICA, DE PERSONAS NATURALES O JURIDICAS, NACIONALES O EXTRANJERAS, PUBLICAS O PRIVADAS. EN DESARROLLO DE SU OBJETO SOCIAL PODRA : A. PRESTAR ASESORIA Y EJERCER LA REPRESENTACION JUDICIAL DE PERSONAS NATURALES O JURIDICAS ANTE LAS DIFERENTES JURISDICCIONES Y PARTICIPAR EN SU NOMBRE Y REPRESENTACION EN TRIBUNALES DE ARBITRAMENTO, AMIGABLE COMPOSICION, CONCILIACION Y MEDIACION. B. CONFORMAR Y PARTICIPAR EN CENTROS DE ARBITRAJE Y CONCILIACION. C. CELEBRAR Y EJECUTAR TODAS LAS OPERACIONES DE CAMBIO Y COMERCIO EXTERIOR QUE REQUIERA EL BUEN FUNCIONAMIENTO DE LA COMPAÑIA ; D. ADQUIRIR, ENAJENAR, GRAVAR, DAR O TOMAR EN ARRENDAMIENTO TODA CLASE DE BIENES, DANDO O RECIBIENDO LAS GARANTIAS DEL CASO CUANDO HAYA LUGAR A ELLAS ;

NOTARIA VEINTISIETE
María Eugenia Rojas de Urueta

E. INTERVENIR COMO DEUDORA O ACREEDORA EN TODA CLASE DE OPERACIONES DE CREDITO, DANDO O RECIBIENDO LAS GARANTIAS DEL CASO CUANDO HAYA LUGAR A ELLAS ; F. CELEBRAR CON ESTABLECIMIENTOS DE CREDITO NACIONALES O EXTRANJEROS Y CON COMPAÑIAS ASEGURADORAS TODAS LAS OPERACIONES QUE SE RELACIONEN CON LOS NEGOCIOS Y BIENES SOCIALES. G. ABRIR, OPERAR Y CERRAR CUALQUIER TIPO DE CUENTAS BANCARIAS ; H. GIRAR, ACEPTAR, ENDOSAR, ASEGURAR, COBRAR, RECHAZAR, PROTESTAR, AVALAR GARANTIZAR Y NEGOCIAR EN GENERAL TODA CLASE DE INSTRUMENTOS NEGOCIABLES Y CUALQUIER OTRA CLASE DE TITULOS DE CREDITO ; I. ORGANIZAR, PROMOVER, FORMAR Y FINANCIAR SOCIEDADES O EMPRESAS NACIONALES O EXTRANJERAS QUE TIENDAN A FACILITAR, ENSANCHAR, O COMPLEMENTAR LOS NEGOCIOS SOCIALES DENTRO Y FUERA DEL PAIS Y SUSCRIBIR ACCIONES O CUOTAS EN ELLAS, Y EJERCER TODOS LOS DERECHOS Y OBLIGACIONES ECONOMICOS Y CORPORATIVOS QUE SURJAN DE DICHA PARTICIPACION. J. CREAR CONSORCIOS Y UNIONES TEMPORALES. K. SERVIR DE COMISIONISTA O INTERMEDIARIO COMERCIAL A TITULO DE CORRETAJE O A CUALQUIER OTRO TITULO ; I. SER CORRESPONSAL Y TENER CORRESPONSALES INTERNACIONALES ; M. EFECTUAR AVALUOS COMERCIALES DE TODA CLASE DE BIENES. N. ADQUIRIR Y CONSTRUIR TODA CLASE DE INSTALACIONES INDUSTRIALES O COMERCIALES COMO FABRICAS, TALLERES, ALMACENES DE DISTRIBUCION O VENTA ESTABLECIMIENTOS DE COMERCIO, ETC. O. DISTRIBUIR O VENDER TODO TIPO DE PRODUCTOS Y ABRIR Y ADMINISTRAR, DIRECTA O INDIRECTAMENTE, LOS ESTABLECIMIENTOS DE COMERCIO QUE SEAN NECESARIOS PARA ELLO. P. ENAJENAR, ARRENDAR, GRAVAR Y ADMINISTRAR EN GENERAL LOS BIENES QUE COMPONEN EL PATRIMONIO SOCIAL. Q. APORTAR SUS BIENES, EN TODO O EN PARTE, A OTRA U OTRAS SOCIEDADES A QUE LE CONVENGA VINCULARSE PARA UN MEJOR DESARROLLO DE SUS NEGOCIOS. R. TRANSIGIR, DESISTIR O SOMETER A DECISIONES ARBITRALES LAS CUESTIONES EN QUE TENGA INTERES FRENTE A TERCEROS. ; S. SOLICITAR, CONSEGUIR LOS REGISTROS RESPECTIVOS ANTE LA AUTORIDAD COMPETENTE Y EXPLOTAR EL DERECHO SOBRE MARCAS, NOMBRES COMERCIALES O CUALQUIER SIGNO DISTINTIVO, DIBUJOS, INSIGNIAS, PATENTES Y CUALQUIER OTRO DERECHO DE PROPIEDAD INDUSTRIAL O INTELECTUAL YA SEA A NOMBRE DE LA SOCIEDAD O DE UN TERCERO. T. HACER PUBLICACIONES Y COMUNICACIONES RELACIONADAS CON EL OBJETO SOCIAL. U. CELEBRAR Y EJECUTAR CON SU PROPIO NOMBRE Y POR CUENTA DE TERCEROS O EN PARTICIPACION CON ELLOS, ACTOS O CONTRATOS Y OPERACIONES EN GENERAL, TODO ACTO O CONTRATO QUE SEA NECESARIO O CONVENIENTE PARA CUMPLIR O FACILITAR LOS ACTOS Y OPERACIONES PREVISTAS EN LOS ESTATUTOS Y QUE DE MANERA DIRECTA SE RELACIONEN CON EL OBJETO SOCIAL, TAL COMO QUEDA DETERMINADO.

CERTIFICA :

CAPITAL Y SOCIOS : $ 120,000,000.00 DIVIDIDO EN 12,000.00 CUOTAS CON VALOR NOMINAL DE $ 10,000.00 CADA UNA, DISTRIBUIDO ASI :

- SOCIOS CAPITALISTA(S)

FRIERI DEL CASTILLO ANA MARIA C.C. 00045483209
NO. CUOTAS: 4,000.00 VALOR:$40,000,000.00
RAISBECK LLINAS JAMES IAN C.C. 00079376996
NO. CUOTAS: 4,000.00 VALOR:$40,000,000.00
OLARTE GARCIA CARLOS REINALDO C.C. 00079782747
NO. CUOTAS: 4,000.00 VALOR:$40,000,000.00
TOTALES
NO. CUOTAS: 12,000.00 VALOR :$120,000,000.00

CERTIFICA :

REPRESENTACION LEGAL : LA SOCIEDAD TENDRA UN GERENTE GENERAL, EL CUAL TENDRA UN PRIMER SUPLENTE Y UN SEGUNDO SUPLENTE QUE LO

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56471812

CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

1 DE FEBRERO DE 2007 HORA 09:15:35

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* *

REEMPLAZARA EN SUS FALTAS ABSOLUTAS, TEMPORALES O ACCIDENTALES, Y CUYA DESIGNACION Y REMOCION CORRESPONDERA TAMBIEN A LA JUNTA DE SOCIOS.

CERTIFICA :

** NOMBRAMIENTOS : **

QUE POR ESCRITURA PUBLICA NO. 0001119 DE NOTARIA 39 DE BOGOTA D.C. DEL 10 DE JUNIO DE 2003 , INSCRITA EL 25 DE JUNIO DE 2003 BAJO EL NUMERO 00885810 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

NOMBRE	IDENTIFICACION
GERENTE	
OLARTE GARCIA CARLOS REINALDO	C.C.00079782747
PRIMER SUPLENTE DEL GERENTE	
RAISBECK LLINAS JAMES IAN	C.C.00079376996
SEGUNDO SUPLENTE DEL GERENTE	
FRIERI DEL CASTILLO ANA MARIA	C.C.00045483209

CERTIFICA :

FACULTADES DEL REPRESENTANTE LEGAL : EL GERENTE GENERAL ES EL REPRESENTANTE LEGAL DE LA SOCIEDAD, Y EN CASO DE FALTA TEMPORAL O ABSOLUTA HARA SUS VECES EL PRIMER SUPLENTE O EN SU DEFECTO EL SEGUNDO SUPLENTE, TAMBIEN ELEGIDOS POR LA JUNTA DE SOCIOS. EL GERENTE REPRESENTARA Y COMPROMETERA A LA SOCIEDAD FRENTE A TERCEROS, SEAN PERSONAS O ENTIDADES PARTICULARES, OFICIALES O JUDICIALES. ASI MISMO, PODRA CELEBRAR EN SU NOMBRE CONTRATO DE ARRENDAMIENTO COMO ARRENDADOR O ARRENDATARIO. CONSTITUIR APODERADOS DE LA SOCIEDAD, DESISTIR, INTERPONER TODA CLASE DE RECURSOS RECIBIR DINERO EN MUTUO, HACER DEPOSITOS BANCARIOS O DE CUALQUIER OTRA INDOLE, FIRMAR TITULOS VALORES Y NEGOCIARLOS, TENERLOS, CONTRATARLOS, PAGARLOS, ENDOSARLOS, DESCARGARLOS, CELEBRAR CONTRATOS COMERCIALES, EJECUTAR LOS ACUERDOS DE LA JUNTA DE SOCIOS Y CONVOCARLA A REUNIONES ORDINARIAS O EXTRAORDINARIAS, SUSCRIBIR CONTRATOS LABORALES A NOMBRE DE LA SOCIEDAD, Y EN GENERAL TODAS LAS GESTIONES QUE OBEDEZCAN A LA NATURALEZA DE SU ENCARGO Y QUE SE RELACIONEN DIRECTAMENTE CON EL GIRO ORDINARIO DE LOS NEGOCIOS SOCIALES. EL GERENTE REQUERIRA APROBACION DE LA JUNTA DE SOCIOS PARA CELEBRAR ACTOS CUYA CUANTIA SEA O EXCEDA LA SUMA DE DIEZ MILLONES DE PESOS ($10,000,000) MONEDA CORRIENTE.

CERTIFICA :

** REVISOR FISCAL: **

QUE POR ACTA NO. 0000006 DE JUNTA DE SOCIOS DEL 5 DE MARZO DE 2004 , INSCRITA EL 8 DE JULIO DE 2004 BAJO EL NUMERO 00942232 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL	
LACHE NUÑEZ JOSE LUCIO	C.C.00006763005

CERTIFICA :

DIRECCION DE NOTIFICACION JUDICIAL : CLL 100 NO 8A-37 P 10 W.T.C.

NOTARIA VEINTISIETE
María Eugenia Rojas de Urrea

T A
MUNICIPIO : BOGOTA D.C.
DIRECCION COMERCIAL : CLL 100 NO 8A-37 P 10 W.T.C. T A
MUNICIPIO : BOGOTA D.C.
E-MAIL : ELIZABETH.BARBOSA@OLARTERAISBECK.COM

CERTIFICA :

QUE LA SOCIEDAD TIENE MATRICULADOS LOS SIGUIENTES ESTABLECIMIENTOS :
NOMBRE : OR LEGAL LIMITADA
MATRICULA NO. 01284255
RENOVACION DE LA MATRICULA : EL 27 DE MARZO DE 2006
ULTIMO AÑO RENOVADO : 2006

CERTIFICA :

DE CONFORMIDAD CON LO ESTABLECIDO POR LA LEY 962 DE 2005, LOS ACTOS DE REGISTRO AQUI CERTIFICADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE INSCRIPCION, SIEMPRE QUE NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

INFORMACION COMPLEMENTARIA

LOS SIGUIENTES DATOS SOBRE RIT Y PLANEACION DISTRITAL SON INFORMATIVOS
CONTRIBUYENTE INSCRITO EN EL REGISTRO RIT DE LA DIRECCION DISTRITAL DE IMPUESTOS, FECHA DE INSCRIPCION 2003/06/24
FECHA DE ENVIO DE INFORMACION A PLANEACION DISTRITAL: 10 DE JULIO DE 2004

EL SECRETARIO DE LA CAMARA DE COMERCIO,

VALOR : $ 3,000.00

DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, MEDIANTE EL OFICIO DEL 18 DE NOVIEMBRE DE 1996, LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.

TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS

El documento de Poder de Merck & Co., Inc. a Olarte Raisbeck & Frieri Ltda. lleva una certificación notarial con el siguiente sello en inglés:

(Firmado)

Sello: "Barbara Ann Cozzi, Notario Público de New Jersey – Mi comisión vence el 30 de Noviembre de 2008".

MINISTERIO DE RELACIONES EXTERIORES
LEGALIZACIÓN
513217
COTEJA FIRMA ANTERIOR
DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

Apostilla adjunta:

APOSTILLA:

(Convention de La Haye du 5 octobre 1961)

1. País:	Estados Unidos de Amé
	El presente documento público
2. Ha sido firmado por:	Barbara Ann Cozzi
3. Actuando en calidad de:	Notario Público de New Jersey
4. Lleva el sello/estampilla de:	Barbara Ann Cozzi, Notario
	Certificado
5. En:	Trenton, New Jersey
6. El:	6 de February de 2007
7. Por:	Bradley Abelow, Tesorero de New Jersey
8. Bajo el No.:	A282565
9. Sello / estampilla:	El Estado de New Jersey – Sello del Estado
10. Firma:	Bradley Abelow

2007 MAR 1 A 8:49
JEFE DE LEGALIZACIONES
BOGOTA D.C.

NO SE ASUME RESPONSABILIDAD DEL TEXTO

María Estefanía Rojas de Prieto

Traductor Oficial
JORGE E. SIERRA REYES
Decreto 376 - 1993 Minjusti

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Merck & Co.Inc. - Apost."

Fecha: 15 de Febrero de 2007.

Traductor: Jorge Enrique Sierra Reyes.

Licencia No. 376 de 1993, del Ministerio de Justicia.

Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.

Teléfono: (57-1) 2182308, (57-1) 6232925.

E-mail: treseser1@yahoo.com. No. 9508

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

11

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
BARBARA ANN COZZI

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

4. BEARS THE SEAL/STAMP OF:
BARBARA ANN COZZI, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

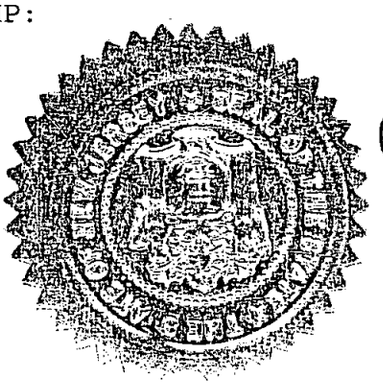
6. THE 6TH DAY OF FEBRUARY 2007

7. BY: Bradley Abelow, NEW JERSEY TREASURER

8. NO. A282565

9. SEAL/STAMP:

10. SIGNATURE



Bradley Abelow

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro

Zayde Chahin
José Luis Londoño
Felipe Mendoza
Simón Salinas
Alexander Agudelo
Camilo A. Rodríguez

Of Counsel
Guillermo Chahin
Graciela Melo
Jacqueline Chaparro
Cruz E. de Moncaleano

General Power

The undersigned,

domiciled in

hereby appoint Olarte Raisbeck & Frieri Ltda. with offices in the World Trade Center – Torre A, Calle 100 No. 8A-37, Piso 10, Bogota D.C., legal representatives with authority to receive notifications and to appoint judicial or extrajudicial agents in patent matters, who at the same time have the authority to represent us before the administrative, judicial or police authorities of any hierarchy of the Republic of Colombia, the Republic of Bolivia, the Republic of Ecuador, the Republic of Peru, and the Bolivarian Republic of Venezuela, to initiate before said authorities all the necessary actions to accomplish said purposes and to intervene in all instances, grades and procedural levels; to file and prosecute applications, declarations, complaints, to claim, counterclaim, answer claims and counterclaims; to draw up specifications; to make amendments; oppositions and all types of objections and writings of any nature; cancellations and administrative injunction proceedings; to pay all installments and effect all other payments prescribed by law; to receive documents and monies; act as complainants as well as defendants, before the competent judges, with full powers to request preliminary injunctions of any nature, settle, make arrangements, to submit to arbitrators, to desist from claims or procedures, to accept claims, to collect, to ratify legal proceedings subscribed before the appointment and/or presentation of this Power, substitute or delegate the legal representation and other acts prescribed by law, in short, with all such further powers as may be required; to comply with all other requirements and, to take all those measures which they may deem fit for the protection of our interests.

Poder General

El suscrito,

MERCK & CO., INC.

domiciliado en

126 EAST LINCOLN AVENUE, RAHWAY, NJ 07065-0907, USA.

nombramos por el presente a Olarte Raisbeck & Frieri Ltda. con oficinas en el World Trade Center – Torre A, Calle 100 No. 8A-37, Piso 10, Bogotá D.C., nuestros representantes legales con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales en materia de patentes, los cuales quedan a su vez facultados para representarnos ante las autoridades de cualquier jerarquía de la República de Colombia, la República del Ecuador, la República del Perú y la República Bolivariana de Venezuela, ya sean administrativas, judiciales o de policía, para iniciar ante dichas autoridades todas las acciones necesarias para cumplir con el objeto indicado e intervenir en todas las instancias, grados o etapas procesales; elevar y tramitar solicitudes, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y reconvenciones; formular descripciones, enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento, allanarse a la pretensión, percibir, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal y los demás actos que exprese la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestros intereses.

Signature/Firma:X Donna L. Margiotto

Donna L. Margiotto, Senior Manager, Patent Administration

Date/Fecha: February 1, 2007

City,Country/Ciudad,País: Rahway, NJ, USA.

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification	**Certificación Notarial**
On this date, February 1, 2007	En esta fecha,
The undersigned Notary Public certifies:	el Notario Público suscrito certifica:
1. That	1. Que
Donna L. Margiotto	
of legal age and domiciled in	mayor de edad y domiciliado
126 East Lincoln Avenue, Rahway, NJ 07065-0907, USA.	
signed the foregoing document.	suscribió el documento que antecede.
2. That the grantor has executed the foregoing document as Senior Manager, Patent Administration of MERCK & CO., INC.	2. Que el otorgante ha suscrito el referido documento en su carácter de de
3. That MERCK & CO., INC., having its principal place of business located in New Jersey, USA. is duly incorporated, is currently in existence, and that the purposes for which the General Power is granted are within the scope of its corporate purposes.	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. That the grantor has the authority to execute the General Power and that his/her representation is legal.	4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legitima.
5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s): Corporate Resolution No. 5 – Patent Matters, amended October 24, 2006 by the Board of Directors of Merck & Co., Inc. at a meeting held on October 24, 2006.	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):

NOTARIA VEINTISIETE
María Eugenia Rojas de Urueta

NOTARY PUBLIC (Signature):X Barbara Ann Cozzi

BARBARA ANN COZZI
Notary Public of New Jersey
My Commission Expires Nov. 30, 2008

13

WK 4682370

Aministration. ----------

Fecha febrero 2007 ----------

Ciudad País: Rahway, NJ, USA----------

CERTIFICACION NOTARIAL .----------

En esta fecha, ----------

El notario público suscrito certifica: ------

1. Que Donna L. Margiotto mayor de edad, y domiciliado 126 East Lincoln Avenue, Rahway, NJ 07065-0907, USA. Suscribió el documento que antecede. ----------

2. Que el otorgamiento 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 que los propósitos para los cuales se otorga el poder se encuentran dentro de los que comprenden su objeto social.----------

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

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): ----------

NOTARIA VEINTISIETE María Eugenia Rojas de Urueta

NOTARY PUBLIC (fdo. ilegible) BARBARA ANN COZZI Notary Public Of New Jersey My Comisión Expires Nov. 30, 2006 -------

TRADUCCION OFICIAL DE UN DOCUMENTO QUE ESTA ORIGINALMENTE EN INGLES ----------

El documento de Poder de Merck & Co., Inc. a Olarte Raisbeck & Frieri Ltda. lleva una certificación notarial con el siguiente sello en inglés:----------

(Firmado) ----------

Sello: " Barbara Ann Cozzi, Notario Público de New Jersey- Mi comisión vence el 30 de Noviembre de 2008".----------

APOSTILLA

(Convention de La Haye Du 5 octobre 1961)

1. País: Estados Unidos de América ----------

El presente documento público ----------

2. Ha sido firmado por: Barbara Ann Cozzi----------

3. Actuando en calidad de: Notario Público de New Jersey.--------

4 Lleva el sello/ estampilla de: Barbara Ann Cozzi, notario ------

Certificado

5. En: Trenton, New Jersey} ----------

6) El 6 de February de 2007 ----------

7. Por: Bradley Abelow, Tesorero de New Jesery. ----------

8 Bajo el No. A282565 ----------

9. Sello/ estampilla: El Estado de New Jesery- Sello del Estado--

10. Firma: Bradley Abelow ----------

Certificación: ----------

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Merck & Co. Inc.- Apost"----------

Fecha: 15 de Febrero de 2007.----------

Traductor: Jorge Enrique Sierra Reyes.- ----------

Licencia No. 376 de 1993, del Ministerio de Justicia.- ----------

Dirección Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia. ---

Teléfono: (57-1) 2182308, (57-1) 6232925.- ----------

E-mail: treseser1@yahoo.com 9508- ----------

SEGUNDO.- Que solicita a la señora Notaria la incorporación de dicho documentos al protocolo de ésta notaría para que de su tenor se expidan las copias que más adelante se soliciten ----------

---

El(los) compareciente(s) hace(n) constar que han verificado cuidadosamente sus nombres completos, estado(s) civil(es), los número(s) de sus documentos de identidad; Declara(n) que todas las informaciones consignadas en el presente instrumento son correctas y, en consecuencia, asumen la responsabilidad que

WK 4682371

se derive de cualquier inexactitud en los mismos. Conocen la ley y saben que el Notario responde de la regularidad formal de los instrumentos que autoriza, pero no de la veracidad de las declaraciones de los interesados.

ADVERTENCIA, OTORGAMIENTO Y AUTORIZACION.- Leído el presente instrumento por el (los) compareciente (s) y advertido (s) sobre las formalidades legales, lo aprueban y firman conmigo y ante mí la(el) Notaria(o) quién lo autoriza. A los otorgantes se les advirtió finalmente que una vez firmado el presente instrumento, La(el) Notaria(o) no aceptará correcciones o modificaciones sino en la forma y casos previstos por la Ley. --Se utilizaron las hojas de papel Notarial Nos : WK 4682369, WK 4682370, WK 4682371.- - - - - - - - - - - - - - - - - -

NOTARIA VEINTISIETE

DERECHOS LEGALES: $ 38.110.oo

RESOLUCION 7880 DE 2006

IVA $ 14.642.oo

CARLOS REINALDO OLARTE GARCIA

C.C.No. 79'782.747 Bogotá

TEL: 601-7700

ESTE PAPEL NO TIENE COSTO PARA EL USUARIO

MARIA EUGENIA ROJAS DE URUETA

NOTARIA(O) VENTISIETE (27) DE BOGOTA

REPUBLICA DE COLOMBIA
27
María Eugenia Rojas
de Urueta
NOTARIa
Notaría Veintisiete de Santafé de Bogotá

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de fecha 22 de Marzo de 2007
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Interesado

Dado en Santafé de Bogotá D.C., a 29 MAR. 2007
El Notario Veintisiete de Santafé de Bogotá,

REPUBLICA DE COLOMBIA
27
María Eugenia Rojas
de Urueta
NOTARIa
Notaría Veintisiete de Santafé de Bogotá

ESTADO EN BLANCO

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

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(71) Applicant *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HOLLOWAY, M., Katharine** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **LIVERTON, Nigel, J.** [GB/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **MCCAULEY, John, A.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **RUDD, Michael, T.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **VACCA, Joseph, P.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **LUDMERER, Steven, W.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **OLSEN, David, B.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

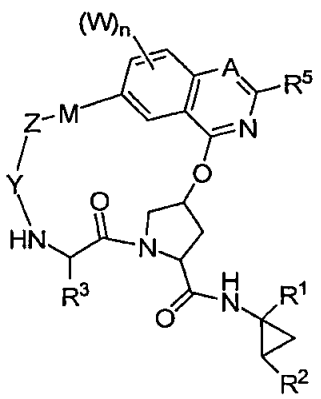
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ,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

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

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(54) Title: MACROCYCLIC PEPTIDES AS HCV NS3 PROTEASE INHIBITORS



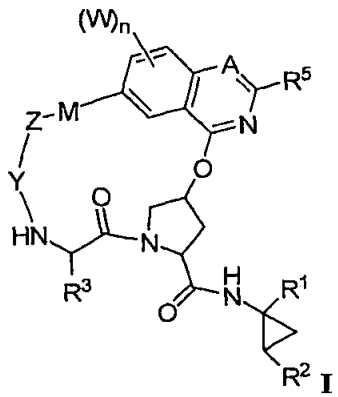
(I)

(57) Abstract: The present invention relates to macrocyclic compounds of formula (I) that are useful as inhibitors of the hepatitis C virus (HCV) NS3 protease, their synthesis, and their use for treating or preventing HCV infections. Formula (I).

WO 2007/016441 A1

ABSTRACT OF THE DISCLOSURE

The present invention relates to macrocyclic compounds of formula (I) that are useful as inhibitors of the hepatitis C virus (HCV) NS3 protease, their synthesis, and their use for treating or preventing HCV infections.



I

TITLE OF THE INVENTION

MACROCYCLIC PEPTIDES AS HCV NS3 PROTEASE INHIBITORS

The present invention relates to macrocyclic compounds that are useful as inhibitors of the hepatitis C virus (HCV) NS3 protease, their synthesis, and their use for treating or preventing HCV infection.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals, estimated to be 2-15% of the world's population. There are an estimated 3.9 million infected people in the United States alone, according to the U.S. Center for Disease Control, roughly five times the number of people infected with the human immunodeficiency virus (HIV). According to the World Health Organization, there are more than 170 million infected individuals worldwide, with at least 3 to 4 million people being infected each year. Once infected, about 20% of people clear the virus, but the rest harbor HCV the rest of their lives. Ten to twenty percent of chronically infected individuals eventually develop liver-destroying cirrhosis or cancer. The viral disease is transmitted parenterally by contaminated blood and blood products, contaminated needles, or sexually and vertically from infected mothers or carrier mothers to their off-spring.

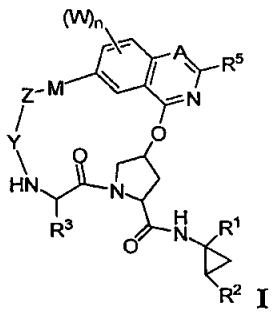
Current treatments for HCV infection, which are restricted to immunotherapy with recombinant interferon-α alone or in combination with the nucleoside analog ribavirin, are of limited clinical benefit. Moreover, there is no established vaccine for HCV. Consequently, there is an urgent need for improved therapeutic agents that effectively combat chronic HCV infection. The current state of the art in the treatment of HCV infection has been discussed in the following references: B. Dymock, et al., "Novel approaches to the treatment of hepatitis C virus infection," Antiviral Chemistry & Chemotherapy, 11: 79-96 (2000); H. Rosen, et al., "Hepatitis C virus: current understanding and prospects for future therapies," Molecular Medicine Today, 5: 393-399 (1999); D. Moradpour, et al., "Current and evolving therapies for hepatitis C," European J. Gastroenterol. Hepatol., 11: 1189-1202 (1999); R. Bartenschlager, "Candidate Targets for Hepatitis C Virus-Specific Antiviral Therapy," Intervirology, 40: 378-393 (1997); G.M. Lauer and B.D. Walker, "Hepatitis C Virus Infection," N. Engl. J. Med., 345: 41-52 (2001); B.W. Dymock, "Emerging therapies for hepatitis C virus infection," Emerging Drugs, 6: 13-42 (2001); and C. Crabb, "Hard-Won Advances Spark Excitement about Hepatitis C," Science: 506-507 (2001).

Several virally-encoded enzymes are putative targets for therapeutic intervention, including a metalloprotease (NS2-3), a serine protease (NS3), a helicase (NS3), and an RNA-dependent

RNA polymerase (NS5B). The NS3 protease is located in the N-terminal domain of the NS3 protein, and is considered a prime drug target since it is responsible for an intramolecular cleavage at the NS3/4A site and for downstream intermolecular processing at the NS4A/4B, NS4B/5A and NS5A/5B junctions. Previous research has identified classes of peptides, such as hexapeptides as well as tripeptides discussed in U.S. patent applications US2005/0020503, US2004/0229818, and US2004/00229776, showing degrees of activity in inhibiting the NS3 protease. The aim of the present invention is to provide further compounds which exhibit activity against the HCV NS3 protease.

SUMMARY OF THE INVENTION

The present invention relates to novel macrocyclic compounds of formula (I) and/or pharmaceutically acceptable salts and/or hydrates thereof. These compounds are useful in the inhibition of HCV (hepatitis C virus) NS3 (non-structural 3) protease, the prevention or treatment of one or more of the symptoms of HCV infection, either as compounds or their pharmaceutically acceptable salts and/or hydrates (when appropriate), or as pharmaceutical composition ingredients, whether or not in combination with other HCV antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. More particularly, the present invention relates to a compound of formula (I) and/or a pharmaceutically acceptable salt and/or hydrate thereof:



I

wherein:

n is 1 or 2;

R^1 is CO_2R^{10}, $CONR^{10}SO_2R^6$, $CONR^{10}SO_2NR^8R^9$, or tetrazolyl;

R^2 is C_1-C_6 alkyl, C_2-C_6 alkenyl or C_3-C_8 cycloalkyl, wherein said alkyl, alkenyl or cycloalkyl is optionally substituted with 1 to 3 halo;

R^3 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8)alkyl, aryl(C_1-C_8)alkyl, or Het, wherein aryl is phenyl or naphthyl and said alkyl, cycloalkyl, or aryl is optionally substituted with 1 to 3 substituents

selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1\text{-}C_6$ alkyl)$O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, halo($C_1\text{-}C_6$ alkoxy), NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $S(O)(C_1\text{-}C_6$ alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$;

Het is a 5-6 membered saturated cyclic ring having 1, 2 or 3 heteroatoms selected from N, O and S, wherein said ring is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1\text{-}C_6$ alkyl)$O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, halo($C_1\text{-}C_6$ alkoxy), NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $S(O)(C_1\text{-}C_6$ alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$;

R^4 is H, $C_1\text{-}C_8$ alkyl, $C_3\text{-}C_8$ cycloalkyl($C_1\text{-}C_8$)alkyl, or aryl($C_1\text{-}C_8$)alkyl; wherein aryl is phenyl or naphthyl and said alkyl, cycloalkyl, or aryl is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1\text{-}C_6$ alkyl)$O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, halo($C_1\text{-}C_6$ alkoxy), NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $S(O)(C_1\text{-}C_6$ alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$;

R^5 is H, halo, OH, $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ alkyl, CN, CF_3, SR^{10}, $SO_2(C_1\text{-}C_6$ alkyl), $C_3\text{-}C_8$ cycloalkyl, $C_3\text{-}C_8$ cycloalkoxy, $C_1\text{-}C_6$ haloalkyl, $N(R^7)_2$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein said aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkoxy, alkyl or alkoxy is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^7)_2$, $N(C_1\text{-}C_6$ alkyl)$O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, halo($C_1\text{-}C_6$ alkoxy), $C_3\text{-}C_6$ cycloalkyl, $C_3\text{-}C_6$ cycloalkoxy, NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $S(O)(C_1\text{-}C_6$ alkyl), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$; wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

R^6 is $C_1\text{-}C_8$ alkyl, $C_3\text{-}C_8$ cycloalkyl, $C_3\text{-}C_8$ cycloalkyl($C_1\text{-}C_5$)alkyl, aryl, aryl($C_1\text{-}C_4$)alkyl, heteroaryl, heteroaryl($C_1\text{-}C_4$ alkyl), heterocyclyl, or heterocyclyl($C_1\text{-}C_8$ alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 W' substituents; and wherein each aryl is independently phenyl or naphthyl, each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and

each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen;

Y is C(=O), SO_2, or C(=N-CN);

Z is $C(R^{10})_2$, O, or $N(R^4)$;

M is C_1-C_{12} alkylene or C_2-C_{12} alkenylene or C_2-C_{12} alkynylene, wherein said alkylene or alkenylene is optionally substituted with 1, 2 or 3 substituents selected from the group consisting of C_1-C_8 alkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), and aryl(C_1-C_8 alkyl); wherein 2 substituents on adjacent carbon atoms of M are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S, or 2 substituents on the same carbon atom of M are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

A is $C(R^{11})$ or N;

when R^5 is other than H, R^{11} is H, C_1-C_6 alkyl, halo, OR^{10}, SR^{10}, or $N(R^{10})_2$;

when R^5 is H, R^{11} is H, C_1-C_6 alkyl, halo, OH, C_1-C_6 alkoxy, CN, CF_3, SR^{10}, $SO_2(C_1$-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, $N(R^7)_2$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein said aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkoxy, alkyl or alkoxy is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^7)_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), C_3-C_6 cycloalkyl, C_3-C_6 cycloalkoxy, NO_2, CN, CF_3, $SO_2(C_1$-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $S(O)(C_1$-C_6 alkyl), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$; wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

or R^5 and R^{11} are optionally taken together to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0-2 heteroatoms selected from N, O and S;

each R^7 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl(C_1-C_5)alkyl, aryl, aryl(C_1-C_4)alkyl, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl, or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 W' substituents; and wherein each aryl is independently phenyl or naphthyl, each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen;

each W is independently H, halo, OR^7, C_1-C_6 alkyl, CN, CF_3, NO_2, SR^7, CO_2R^7, $CON(R^7)_2$, $C(O)R^7$, $N(R^{10})C(O)R^7$, SO_2(C_1-C_6 alkyl), S(O)(C_1-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, $N(R^7)_2$, N(C_1-C_6 alkyl)O(C_1-C_6 alkyl), halo(C_1-C_6 alkoxy), $NR^{10}SO_2R^7$, $SO_2N(R^7)_2$, $NHCOOR^7$, $NHCONHR^7$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein 2 adjacent W moieties are optionally taken together with the atoms to which they are attached to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0-2 heteroatoms selected from N, O and S;

each W' is independently halo, OR^{10}, C_1-C_6 alkyl, CN, CF_3, NO_2, SR^{10}, CO_2R^{10}, $CON(R^{10})_2$, $C(O)R^{10}$, $N(R^{10})C(O)R^{10}$, SO_2(C_1-C_6 alkyl), S(O)(C_1-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, $N(R^{10})_2$, N(C_1-C_6 alkyl)O(C_1-C_6 alkyl), halo(C_1-C_6 alkoxy), $NR^{10}SO_2R^{10}$, $SO_2N(R^{10})_2$, $NHCOOR^{10}$, $NHCONHR^{10}$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein 2 adjacent W' moieties are optionally taken together with the atoms to which they are attached to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0-2 heteroatoms selected from N, O and S;

R^8 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), aryl, aryl(C_1-C_4 alkyl), heteroaryl, heterocyclyl, heteroaryl(C_1-C_4 alkyl), or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, halo(C_1-C_6 alkoxy), halo, OR^{10},

SR^{10}, $N(R^{10})_2$, $N(C_1\text{-}C_6$ alkyl$)O(C_1\text{-}C_6$ alkyl$)$, $C_1\text{-}C_6$ alkyl, $C(O)R^{10}$, $C_1\text{-}C_6$ haloalkyl, NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl$)$, $S(O)(C_1\text{-}C_6$ alkyl$)$, $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, and $C(O)N(R^{10})_2$; wherein each aryl is independently phenyl or naphthyl; each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

R^9 is $C_1\text{-}C_8$ alkyl, $C_3\text{-}C_8$ cycloalkyl, $C_3\text{-}C_8$ cycloalkyl$(C_1\text{-}C_8$ alkyl$)$, $C_1\text{-}C_8$ alkoxy, $C_3\text{-}C_8$ cycloalkoxy, aryl, aryl$(C_1\text{-}C_4$ alkyl$)$, heteroaryl, heterocyclyl, heteroaryl$(C_1\text{-}C_4$ alkyl$)$, or heterocyclyl$(C_1\text{-}C_8$ alkyl$)$, wherein said alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, $C_3\text{-}C_8$ cycloalkyl, heteroaryl, heterocyclyl, $C_1\text{-}C_6$ alkyl, halo$(C_1\text{-}C_6$ alkoxy$)$, halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1\text{-}C_6$ alkyl$)O(C_1\text{-}C_6$ alkyl$)$, $C_1\text{-}C_6$ alkyl, $C(O)R^{10}$, $C_1\text{-}C_6$ haloalkyl, NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl$)$, $S(O)(C_1\text{-}C_6$ alkyl$)$, $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, and $C(O)N(R^{10})_2$; wherein each aryl is independently phenyl or naphthyl; each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

or R^8 and R^9 are optionally taken together, with the nitrogen atom to which they are attached, to form a 4-8 membered monocyclic ring containing 0-2 additional heteroatoms selected from N, O and S; and

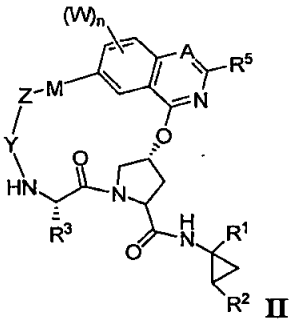
each R^{10} is independently H or $C_1\text{-}C_6$ alkyl.

The present invention also includes pharmaceutical compositions containing a compound of the present invention and methods of preparing such pharmaceutical compositions. The present invention further includes methods of treating or preventing one or more symptoms of HCV infection.

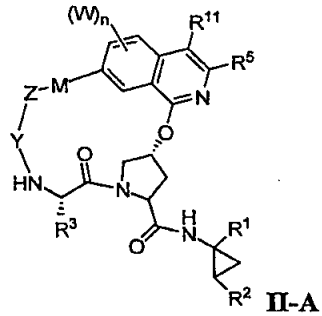
Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

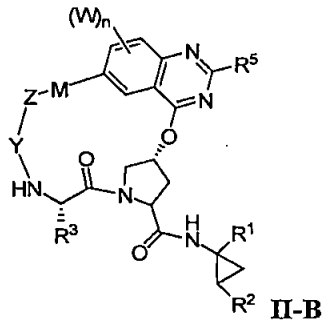
The present invention includes compounds of formula **I** above, and pharmaceutically acceptable salts and/or hydrates thereof. These compounds and their pharmaceutically acceptable salts and/or hydrates are HCV protease inhibitors (e.g., HCV NS3 protease inhibitors). The present invention also includes compounds of formulae **II**, **II-A**, **II-B**, **III**, **III-A** and **III-B** wherein variables n, R^1, R^2, R^3, Y, Z, M, W, A, R^5 and R^{11} are as defined for formula **I**.



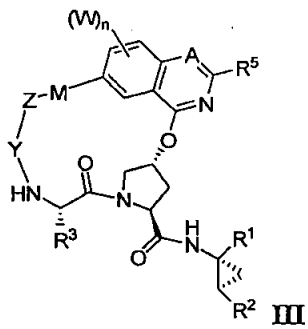
II



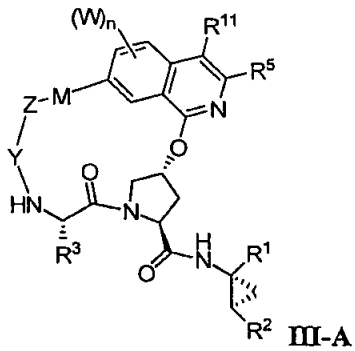
II-A



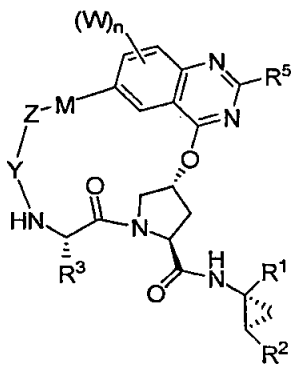
II-B



III



III-A



III-B

A first embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^1 is CO_2R^{10} or $CONR^{10}SO_2R^6$, and all other variables are as originally defined (i.e., as defined in the Summary of the Invention). In a first aspect of the first embodiment, R^1 is $CONR^{10}SO_2R^6$; and all other variables are as defined in the first embodiment. In a feature of the first aspect of the first embodiment, R^1 is $CONHSO_2R^6$ wherein R^6 is C_3-C_8 cycloalkyl, C_1-C_8 alkyl, aryl, aryl(C_1-C_4)alkyl, wherein said alkyl, cycloalkyl, or aryl is optionally substituted with 1 to 2 W' substituents; and all other variables are as defined in the first embodiment. In a second feature of the first aspect of the first embodiment, R^1 is $CONHSO_2R^6$ wherein R^6 is cyclopropyl; and all other variables are as defined in the first embodiment. In a third feature of the first aspect of the first embodiment, R^1 is $CONHSO_2R^6$ wherein R^6 is phenyl; and all other variables are as defined in the first embodiment. In a fourth feature of the first aspect of the first

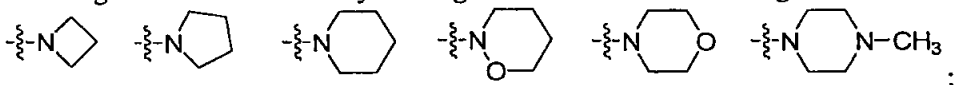
embodiment, R^1 is $CONHSO_2R^6$ wherein R^6 is benzyl; and all other variables are as defined in the first embodiment. In a fifth feature of the first aspect of the first embodiment, R^1 is $CONHSO_2R^6$ wherein R^6 is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl or t-butyl; and all other variables are as defined in the first embodiment. In a second aspect of the first embodiment, R^1 is CO_2R^{10}; and all other variables are as defined in the first embodiment. In a feature of the second aspect of the first embodiment, R^{10} is CO_2H; and all other variables are as defined in the first embodiment.

A second embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^1 is $CONHSO_2NR^8R^9$; and all other variables are as originally defined. In a first aspect of the second embodiment, R^8 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), aryl, aryl(C_1-C_4 alkyl), heteroaryl, or heteroaryl(C_1-C_4 alkyl); and R^9 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), C_1-C_8 alkoxy, aryl, aryl(C_1-C_4 alkyl), heteroaryl, or heteroaryl(C_1-C_4 alkyl), wherein said alkyl, cycloalkyl, alkoxy, aryl, or heteroaryl in both R^8 and R^9 is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, heteroaryl, C_1-C_6 alkyl, halo(C_1-C_6 alkoxy), halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, $C(O)R^{10}$, C_1-C_6 haloalkyl, NO_2, CN, CF_3, $SO_2(C_1$-C_6 alkyl), $S(O)(C_1$-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, and $C(O)N(R^{10})_2$, wherein each aryl is independently phenyl or naphthyl and each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and wherein the 2 adjacent substituents of said cycloalkyl, aryl, or heteroaryl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S; or R^8 and R^9 are optionally taken together, with the nitrogen atom to which they are attached, to form a 4-8 membered monocyclic ring containing 0-2 additional heteroatoms selected from N, O and S; and all other variables are as defined in the second embodiment.

In a second aspect of the second embodiment, R^8 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), aryl, aryl(C_1-C_4 alkyl), heteroaryl, or heteroaryl(C_1-C_4 alkyl); and R^9 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), C_1-C_8 alkoxy, aryl, aryl(C_1-C_4 alkyl), heteroaryl, or heteroaryl(C_1-C_4 alkyl), wherein said alkyl, cycloalkyl, alkoxy, aryl, or heteroaryl in both R^8 and R^9 is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, halo(C_1-C_6 alkoxy), halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, $C(O)R^{10}$, C_1-C_6 haloalkyl, NO_2, CN, CF_3, $SO_2(C_1$-C_6 alkyl), $S(O)(C_1$-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, and $C(O)N(R^{10})_2$, wherein each aryl is independently phenyl or naphthyl and each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and wherein the 2 adjacent substituents of said cycloalkyl, aryl, or heteroaryl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S; or R^8 and R^9 are optionally

taken together, with the nitrogen atom to which they are attached, to form a 4-6 membered monocyclic ring containing 0-2 additional heteroatoms selected from N, O and S; and all other variables are as defined in the second embodiment.

In a first feature of the second aspect of the second embodiment, R^8 is C_1-C_3 alkyl, wherein said alkyl is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, $C(O)R^{10}$, C_1-C_6 haloalkyl, NO_2, CN, CF_3, $SO_2(C_1$-C_6 alkyl), $S(O)(C_1$-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, and $C(O)N(R^{10})_2$; and R^9 is C_1-C_3 alkyl, C_1-C_3 alkoxy, phenyl, or -$(CH_2)_{1-2}$-phenyl, wherein said alkyl or alkoxy is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, $C(O)R^{10}$, C_1-C_6 haloalkyl, NO_2, CN, CF_3, $SO_2(C_1$-C_6 alkyl), $S(O)(C_1$-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, and $C(O)N(R^{10})_2$; or R^8 and R^9 are optionally taken together, with the nitrogen atom to which they are attached, to form a 4-6 membered monocyclic saturated ring containing 0-1 additional heteroatoms selected from N and O; and all other variables are as defined in the second embodiment. In a second feature of the second aspect of the second embodiment, R^8 is methyl; and all other variables are as defined in the second embodiment. In a third feature of the second aspect of the second embodiment, R^9 is methyl, methoxy, ethyl, i-propyl, phenyl, or benzyl; and all other variables are as defined in the second embodiment. In a fourth feature of the second aspect of the second embodiment, R^8 and R^9 are taken together to form a heteocyclic ring selected from the following:



; and all other variables are as defined in the second embodiment. In a fifth feature of the second aspect of the second embodiment, R^8 is methyl and R^9 is methoxy; and all other variables are as defined in the second embodiment.

A third embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^2 is C_1-C_6 alkyl or C_2-C_6 alkenyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a first aspect of the third embodiment, R^2 is C_1-C_4 alkyl or C_2-C_4 alkenyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a second aspect of the third embodiment, R^2 is C_2-C_4 alkenyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a feature of the second aspect of the third embodiment, R^2 is vinyl; and all other variables are as defined in the second embodiment or as defined in any one of the preceding embodiments. In a third aspect of the third embodiment, R^2 is C_1-C_4 alkyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a

feature of the third aspect of the third embodiment, R^2 is ethyl; and all other variables are as defined in the third embodiment or as defined in any one of the preceding embodiments.

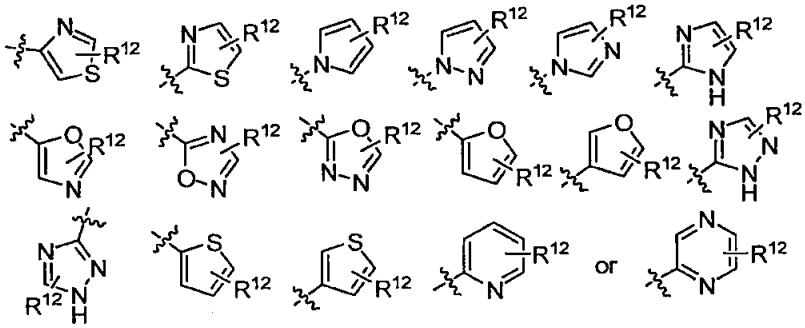
A fourth embodiment of the present invention is a compound of formula **I, II, II-A, II-B, III, III-A,** or **III-B,** or a pharmaceutically acceptable salt or hydrate thereof, wherein R^3 is C_3-C_8 cycloalkyl, Het, or C_1-C_8 alkyl optionally substituted with 1 to 3 halo substituents; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a first aspect of the fourth embodiment, R^3 is C_5-C_7 cycloalkyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, or C_1-C_8 alkyl optionally substituted with 1 to 3 halo substituents; and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments. In a second aspect of the fourth embodiment, R^3 is C_5-C_6 cycloalkyl or C_1-C_8 alkyl optionally substituted with 1 to 3 halo substituents; and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments. In a third aspect of the fourth embodiment, R^3 is propyl or butyl; and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments. In a feature of the third aspect of the fourth embodiment, R^3 is i-propyl, n-butyl, i-butyl or t-butyl; and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments. In a fourth aspect of the fourth embodiment, R^3 is cyclopentyl or cyclohexyl; and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments. In a fifth aspect of the fourth embodiment, R^3 is CH_2CF_3 or CH_2CHF_2; and all other variables are as defined in the fourth embodiment or as defined in any one of the preceding embodiments.

A fifth embodiment of the present invention is a compound of formula **I, II, II-A, II-B, III, III-A,** or **III-B,** or a pharmaceutically acceptable salt or hydrate thereof, wherein R^5 is H or halo; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In one aspect of the fifth embodiment, R^5 is H, F, or Cl; and all other variables are defined in the fifth embodiment or as defined in any one of the preceding embodiments. In another aspect of the fifth embodiment, R^5 is H; and all other variables are defined in the fifth embodiment or as defined in any one of the preceding embodiments.

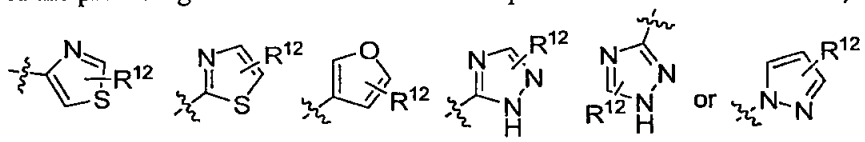
A sixth embodiment of the present invention is a compound of formula **I, II, II-A, II-B, III, III-A,** or **III-B,** or a pharmaceutically acceptable salt or hydrate thereof, wherein R^5 is aryl or heteroaryl; wherein aryl is phenyl or naphthyl and heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein said aryl or heteroaryl is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^7)_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), C_3-C_6 cycloalkyl, C_3-C_6 cycloalkoxy, NO_2, CN, CF_3, $SO_2(C_1$-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$,

$S(O)(C_1\text{-}C_6$ alkyl), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

In a first aspect of the sixth embodiment, R^5 is aryl wherein aryl is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^7)_2$, $N(C_1\text{-}C_6$ alkyl)$O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, halo($C_1\text{-}C_6$ alkoxy), $C_3\text{-}C_6$ cycloalkyl, $C_3\text{-}C_6$ cycloalkoxy, NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $S(O)(C_1\text{-}C_6$ alkyl), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$; and all other variables are as defined in the sixth embodiment or as defined in any one of the preceding embodiments. In a second aspect of the sixth embodiment, R^5 is



; wherein R^{12} is H, $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxy, $N(R^7)_2$, $NHCOR^{13}$, $NHCONHR^{13}$ or $NHCOOR^{13}$ and each R^{13} is independently $C_1\text{-}C_6$ alkyl or $C_3\text{-}C_6$ cycloalkyl; and all other variables are as defined in the sixth embodiment or as defined in any one of the preceding embodiments. In a third aspect of the sixth embodiment, R^5 is



; wherein R^{12} is H, $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxy, $N(R^7)_2$, $NHCOR^{13}$, $NHCONHR^{13}$ or $NHCOOR^{13}$ and each R^{13} is independently $C_1\text{-}C_6$ alkyl or $C_3\text{-}C_6$ cycloalkyl; and all other variables are as defined in the sixth embodiment or as defined in any one of the preceding embodiments.

In a fourth aspect of the sixth embodiment, R^5 is unsubstituted phenyl; and all other variables are as defined in the sixth embodiment or as defined in any one of the preceding embodiments.

A seventh embodiment of the present invention is a compound of formula **I, II, II-A, II-B, III, III-A,** or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^5 is $C_1\text{-}C_6$ alkyl, $C_3\text{-}C_8$ cycloalkyl, $C_1\text{-}C_6$ haloalkyl, or heterocyclyl wherein heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein said heterocyclyl, cycloalkyl, or alkyl is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^7)_2$, $N(C_1\text{-}C_6$ alkyl)$O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, halo($C_1\text{-}C_6$ alkoxy), $C_3\text{-}C_6$ cycloalkyl, $C_3\text{-}C_6$ cycloalkoxy, NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $S(O)(C_1\text{-}C_6$ alkyl),

$NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$; wherein the 2 adjacent substituents of said cycloalkyl or heterocyclyl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a first aspect of the seventh embodiment, R^5 is C_1-C_6 alkyl; and all other variables are as defined in the seventh embodiment or as defined in any one of the preceding embodiments. In a feature of the first aspect of the seventh embodiment, R^5 is methyl; and all other variables are as defined in the seventh embodiment or as defined in any one of the preceding embodiments. In a second aspect of the seventh embodiment, R^5 is heterocyclyl wherein heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein said heterocyclyl, cycloalkyl, or alkyl is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^7)_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), C_3-C_6 cycloalkyl, C_3-C_6 cycloalkoxy, NO_2, CN, CF_3, $SO_2(C_1$-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $S(O)(C_1$-C_6 alkyl), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$; wherein the 2 adjacent substituents of said heterocyclyl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S; and all other variables are as defined in the seventh embodiment or as defined in any one of the preceding embodiments. In a feature of the second aspect of the seventh embodiment, R^5 is N-morpholinyl; and all other variables are as defined in the seventh embodiment or as defined in any one of the preceding embodiments. In a third aspect of the seventh embodiment, R^5 is C_1-C_6 haloalkyl; and all other variables are as defined in the seventh embodiment or as defined in any one of the preceding embodiments. In a feature of the third aspect of the seventh embodiment, R^5 is CF_3; and all other variables are as defined in the seventh embodiment or as defined in any one of the preceding embodiments.

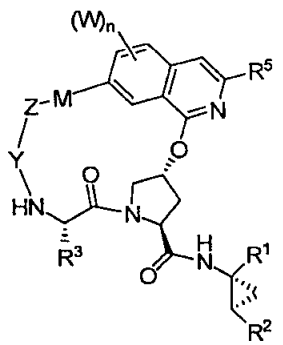
An eighth embodiment of the present invention is a compound of formula **I, II, II-A, II-B, III, III-A,** or **III-B,** or a pharmaceutically acceptable salt or hydrate thereof, wherein R^5 is $N(R^7)_2$; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In one aspect of the eighth embodiment, R^5 is $N(R^7)_2$ wherein R^7 is H or C_1-C_6 alkyl; and all other variables are as defined in the eighth embodiment or as defined in any one of the preceding embodiments.

A ninth embodiment of the present invention is a compound of formula **I, II, II-A, III,** or **III-A,** or a pharmaceutically acceptable salt or hydrate thereof, wherein R^{11} is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy or halo; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a first aspect of the ninth embodiment, R^{11} is C_1-C_6 alkoxy; and all other variables are as defined in the ninth embodiment or as defined in any one of the preceding embodiments. In a feature of the first aspect of the ninth embodiment, R^{11} is methoxy; and all other variables are as

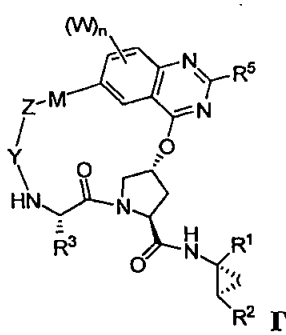
defined in the ninth embodiment or as defined in any one of the preceding embodiments. In a second aspect of the ninth embodiment, R^{11} is C_1-C_6 alkyl; and all other variables are as defined in the ninth embodiment or as defined in any one of the preceding embodiments. In a feature of the second aspect of the ninth embodiment, R^{11} is methyl; and all other variables are as defined in the ninth embodiment or as defined in any one of the preceding embodiments. In a third aspect of the ninth embodiment, R^{11} is halo or hydroxy; and all other variables are as defined in the ninth embodiment or as defined in any one of the preceding embodiments. In a feature of the third aspect of the ninth embodiment, R^{11} is OH, Cl, or Br; and all other variables are as defined in the ninth embodiment or as defined in any one of the preceding embodiments. In a fourth aspect of the ninth embodiment, R^{11} is H; and all other variables are as defined in the ninth embodiment or as defined in any one of the preceding embodiments.

A tenth embodiment of the present invention is a compound of formula **I, II, II-A, III,** or **III-A**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^5 and R^{11} are taken together to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 1-2 oxygen atoms; and all other variables are as originally defined or as defined in any one of the preceding embodiments.

An eleventh embodiment of the present invention is a compound of formula **IV-A** or **IV-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^5 is H, halo, aryl, heteroaryl, or $N(R^7)_2$; R^1 is CO_2R^{10} or $CONHSO_2R^6$ wherein R^6 is C_3-C_6 cycloalkyl, C_1-C_6 alkyl, phenyl or benzyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments.



IV-A



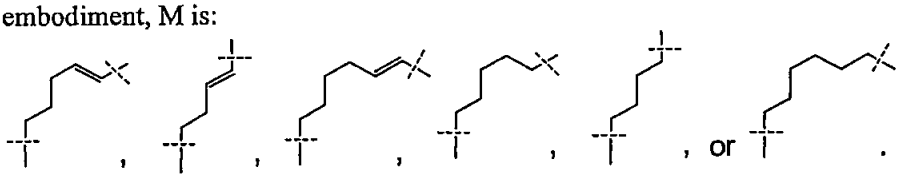
IV-B

A twelfth embodiment of the present invention is a compound of formula **I, II, II-A, II-B, III, III-A,** or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein Y is C=O or SO_2; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In one aspect of the twelfth embodiment, Y is C=O; and all other variables are as defined in the twelfth embodiment or as defined in any one of the preceding embodiments.

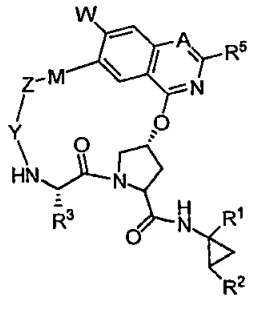
A thirteenth embodiment of the present invention is a compound of formula **I, II, II-A, II-B, III, III-A,** or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein Z is O, NH,

$N(C_1\text{-}C_8$ alkyl) or $C(R^{10})_2$; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In one aspect of the thirteenth embodiment, Z is O, NH, $N(CH_3)$, or CH_2; and all other variables are as defined in the thirteenth embodiment or as defined in any one of the preceding embodiments.

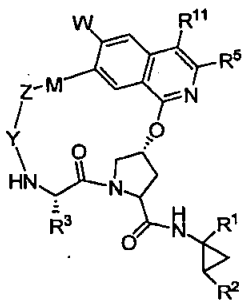
A fourteenth embodiment of the present invention is a compound of formula **I, II, II-A, II-B, III, III-A,** or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein M is $C_1\text{-}C_8$ alkylene or $C_2\text{-}C_8$ alkenylene, wherein said alkylene or alkenylene is optionally substituted with 1 or 2 substituents selected from $C_1\text{-}C_8$ alkyl, $C_3\text{-}C_8$ cycloalkyl($C_1\text{-}C_8$ alkyl), or aryl($C_1\text{-}C_8$ alkyl); and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a first aspect of the fourteenth embodiment, M is unsubstituted $C_1\text{-}C_8$ alkylene or unsubstituted $C_2\text{-}C_8$ alkenylene; and all other variables are as defined in the fourteenth embodiment or as defined in any one of the preceding embodiments. In a second aspect of the fourteenth embodiment, M is unsubstituted C_4 alkylene or unsubstituted C_4 alkenylene; and all other variables are as defined in the fourteenth embodiment or as defined in any one of the preceding embodiments. In a third aspect of the fourteenth embodiment, M is unsubstituted C_5 alkylene or unsubstituted C_5 alkenylene; and all other variables are as defined in the fourteenth embodiment or as defined in any one of the preceding embodiments. In a fourth aspect of the fourteenth embodiment, M is unsubstituted C_6 alkylene or unsubstituted C_6 alkenylene; and all other variables are as defined in the fourteenth embodiment or as defined in any one of the preceding embodiments. In a fifth aspect of the fourteenth embodiment, M is unsubstituted C_7 alkylene or unsubstituted C_7 alkenylene; and all other variables are as defined in the fourteenth embodiment or as defined in any one of the preceding embodiments. In a feature of the first aspect of the fourteenth embodiment, M is:



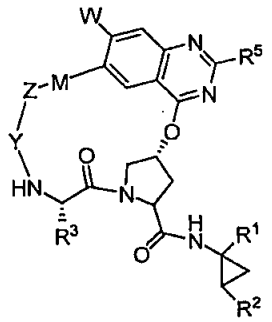
A fifteenth embodiment of the present invention is a compound of formula **I, II, II-A, II-B, III, III-A,** or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein n is 1; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In one aspect of the fifteenth embodiment, W is ortho to the variable M as depicted in formulae **Ia, IIa, II-Aa, II-Ba, IIIa, III-Aa, III-Ba, IV-Aa** and **IV-Ba.**



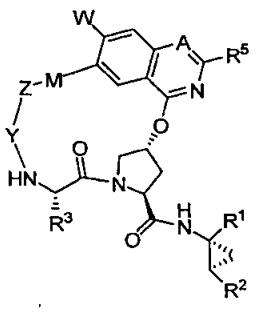
IIa



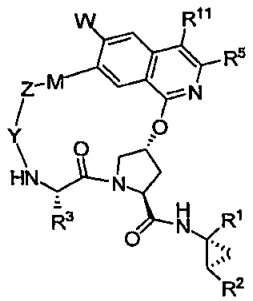
II-Aa



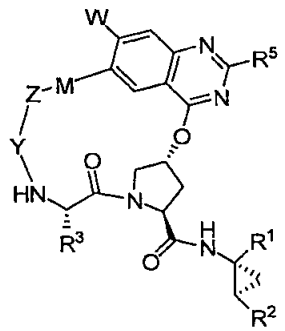
II-Ba



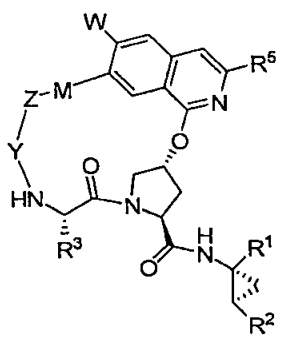
IIIa



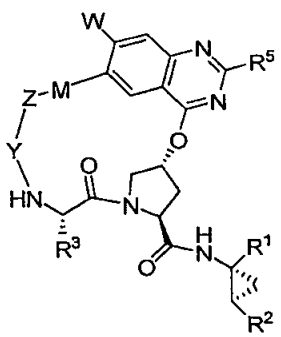
III-Aa



III-Ba



IV-Aa

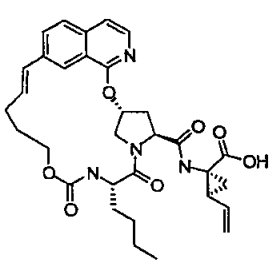


IV-Ba

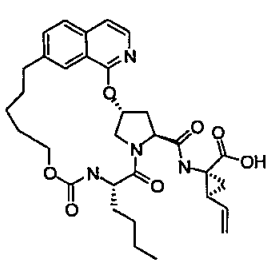
A sixteenth embodiment of the present invention is a compound of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**, or a pharmaceutically acceptable salt or hydrate thereof, wherein n is 2; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In one aspect of the sixteenth embodiment, the 2 adjacent W moieties are taken together to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0-2 heteroatoms selected from N, O and S. In another aspect of the sixteenth embodiment, the 2 adjacent W moieties are taken together to form a 5-membered saturated cyclic ring having 0-2 heteroatoms selected from N, O and S.

A seventeenth embodiment of the present invention is a compound of formula **I, II, II-A, II-B, III, III-A,** or **III-B,** or a pharmaceutically acceptable salt or hydrate thereof, wherein W is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, OH, halo, halo(C_1-C_6 alkoxy), $C(O)N(R^7)_2$, $C(O)R^7$, $N(R^7)_2$,or heterocyclyl; and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a first aspect of the seventeenth embodiment, W is H; and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments. In a second aspect of the seventeenth embodiment, W is C_1-C_6 alkoxy; and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments. In a feature of the second aspect of the seventeenth embodiment, W is methoxy; and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments. In a third aspect of the seventeenth embodiment, W is C_1-C_6 alkyl, halo, OH, or $N(R^7)_2$ wherein R^7 is H or C_1-C_6 alkyl; and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments. In a feature of the third aspect of the seventeenth embodiment, W is methyl; and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments. In a fourth aspect of the seventeenth embodiment, W is halo(C_1-C_6 alkoxy); and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments. In a feature of the fifth aspect of the seventeenth embodiment, W is OCF_3, $OCHF_2$, $OC(CH_3)_3$, or $OCH(CH_3)_2$; and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments. In a sixth aspect of the seventeenth embodiment, W is $C(O)N(R^7)_2$, $C(O)R^7$, or heterocyclyl; and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments. In a feature of the sixth aspect of the seventeenth embodiment, W is $C(O)N(R^7)_2$ wherein R^7 is H or C_1-C_6 alkyl; $C(O)R^7$ wherein R^7 is a 5-membered heteroaryl having 1 heteroatom O or S; or heterocyclyl wherein heterocyclyl is a 6-membered saturated ring having 1 or 2 heteroatoms selected from N, O and S; and all other variables are as defined in the seventeenth embodiment or as defined in any one of the preceding embodiments.

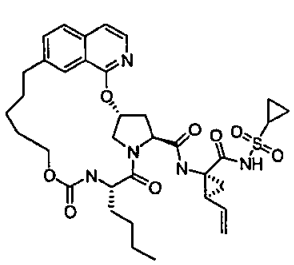
An eighteenth embodiment of the present invention is a compound, or a pharmaceutically acceptable salt or hydrate thereof, selected from the group consisting of the compounds **III-1** to **III-38**.



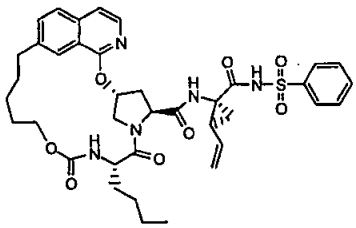
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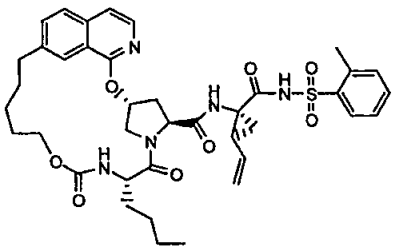
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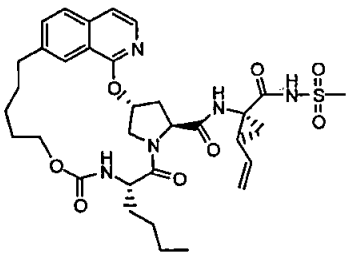
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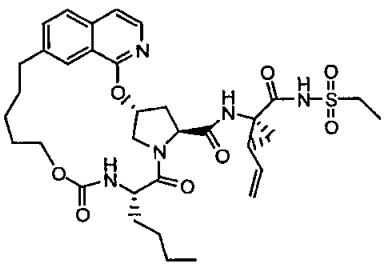
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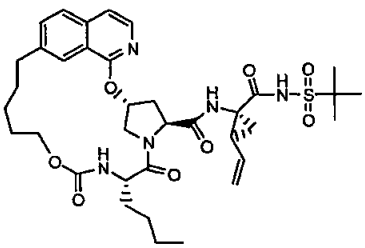
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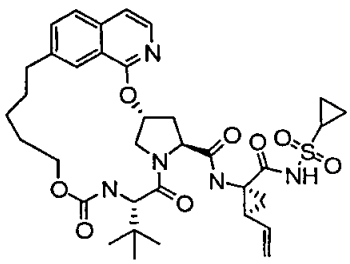
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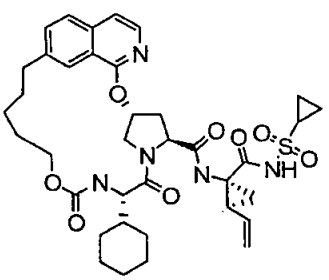
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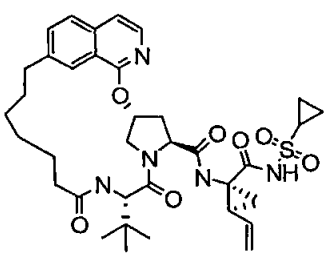
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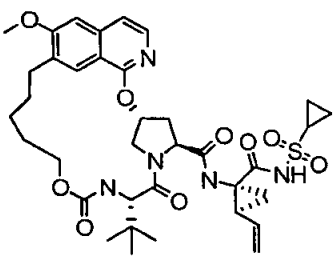
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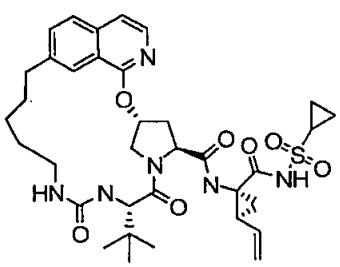
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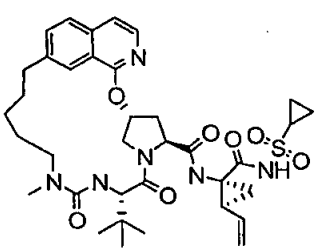
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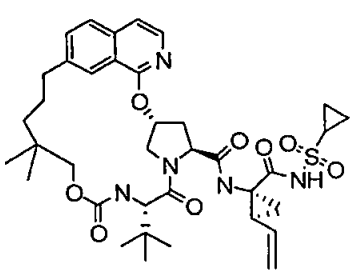
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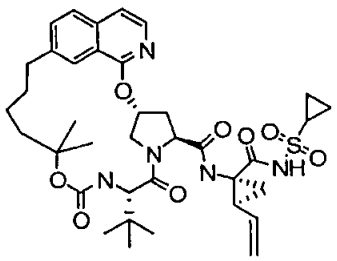
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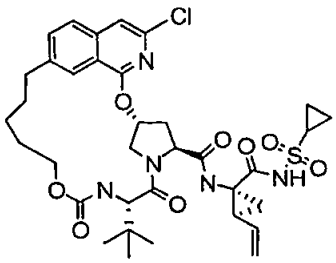
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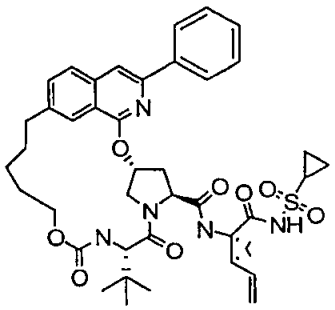
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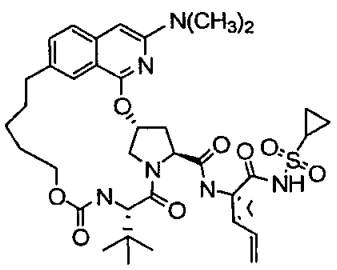
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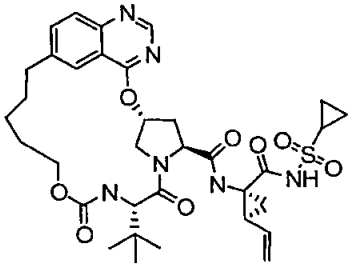
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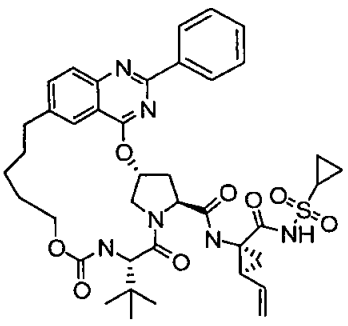
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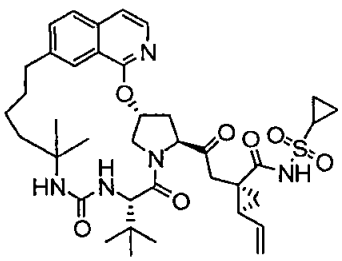
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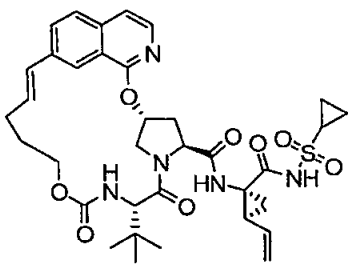
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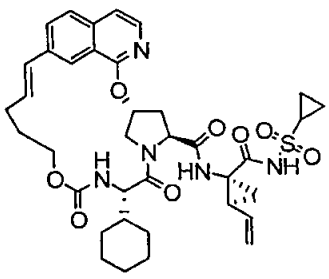
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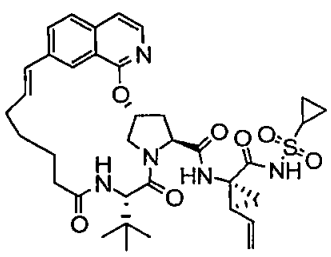
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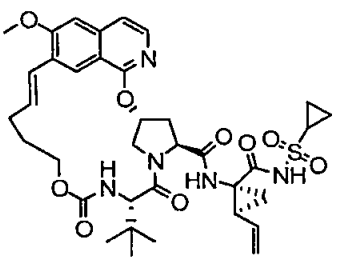
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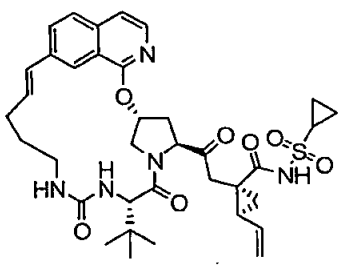
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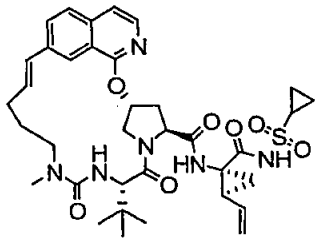
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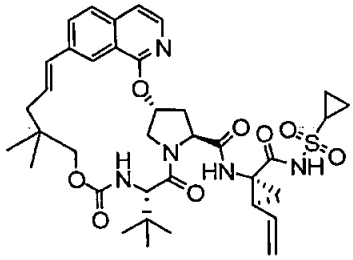
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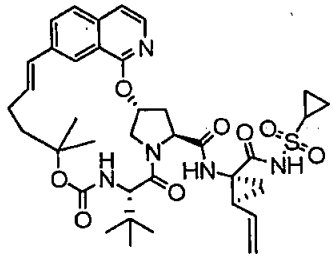
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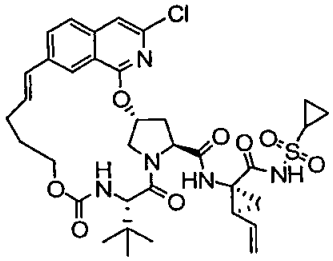
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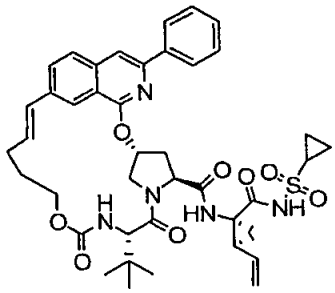
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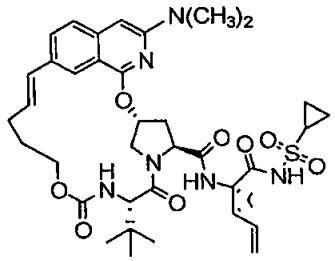
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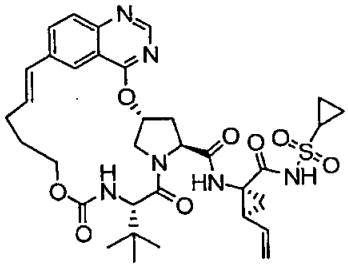
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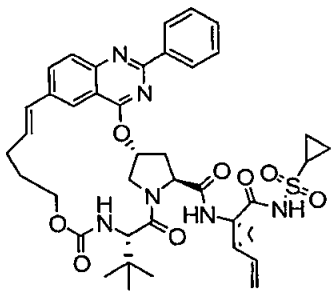
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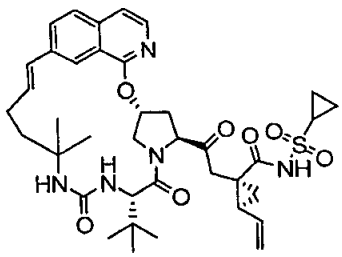
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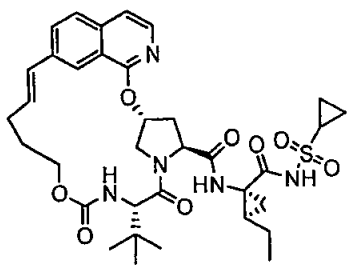
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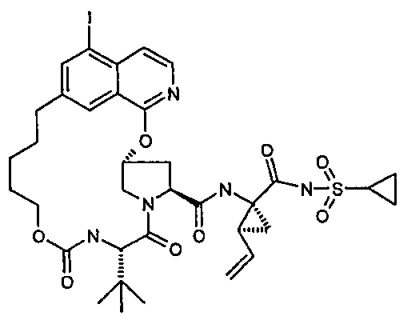
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III-36

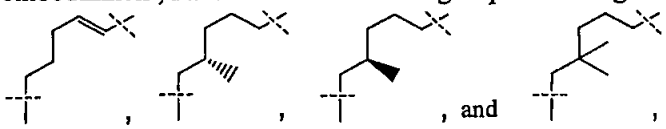


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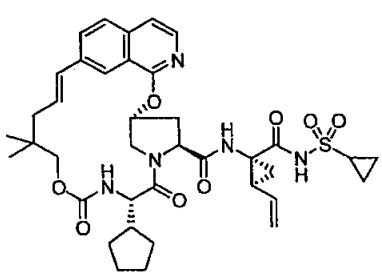
III-38

A nineteenth embodiment of the present invention is a compound of formula **III**, or a pharmaceutically acceptable salt or hydrate thereof, wherein R^1 is $CONHSO_2R^6$, R^6 is C_3-C_8 cycloalkyl, C_1-C_8 alkyl, aryl, or aryl(C_1-C_4)alkyl, R^2 is C_1-C_4 alkyl or C_2-C_4 alkenyl, R^3 is C_5-C_6 cycloalkyl or C_1-C_8 alkyl optionally substituted with 1 to 3 halo substituents, R^5 is H, halo, aryl, heteroaryl or $N(R^7)_2$, and all other variables are as originally defined or as defined in any one of the preceding embodiments. In a first aspect of the nineteenth embodiment, R^5 is H, and all other variables are as defined in the nineteenth embodiment or as defined in any one of the preceding embodiments. In a feature of the first aspect of the nineteenth embodiment, R3 is C5-C6 cycloalkyl or C3-C5-alkyl, and all other variables are as defined in the nineteenth embodiment or as defined in any one of the preceding embodiments. In another feature of the first aspect of the nineteenth embodiment, R6 is C3-C5 cycloalkyl, and all other variables are as defined in the nineteenth embodiment or as defined in any one of the preceding embodiments. In a second aspect of the nineteenth embodiment, R^2 is C_2-C_4 alkenyl, R^5 is H, R^6 is C_3-C_8 cycloalkyl, W is R^7 or H, Y is C(=O), Z is O, and n is 1, and all other variables are as defined in the nineteenth embodiment or as defined in any one of the preceding embodiments. In a third aspect of the nineteenth embodinment, M is selected from the group consisting of:

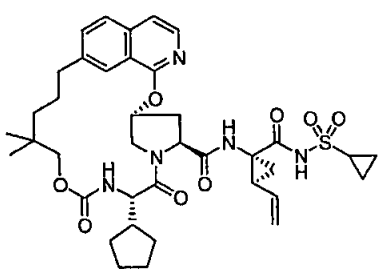


and all other variables are as defined in the nineteenth embodiment or as defined in any one of the preceding embodiments.

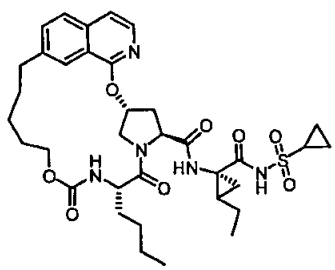
A twentieth embodiment of the present invention is a compound, or a pharmaceutically acceptable salt or hydrate thereof, selected from the group consisting of the compounds **III-39** to **III-187**.



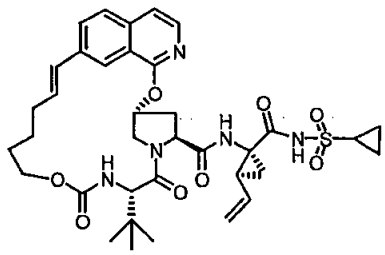
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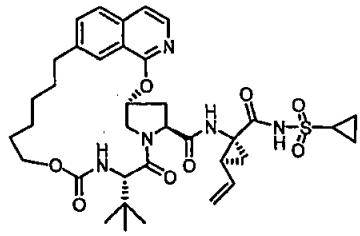
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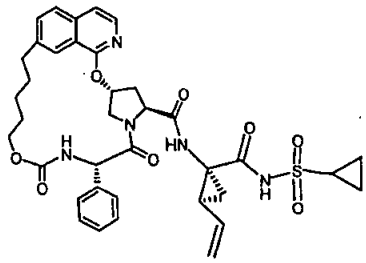
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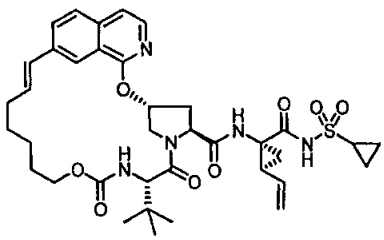
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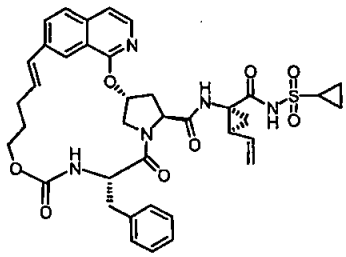
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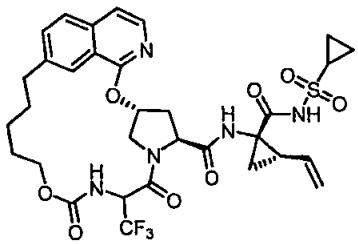
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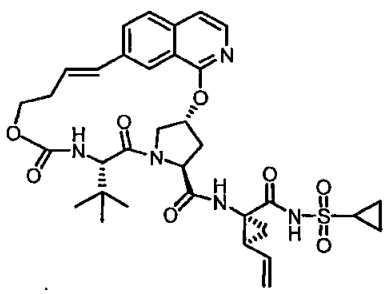
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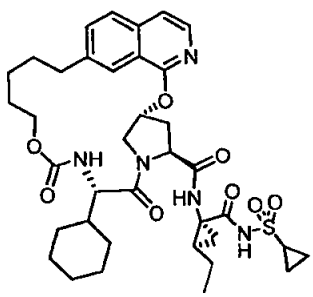
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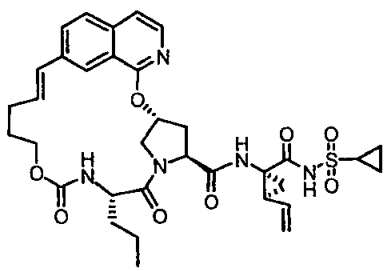
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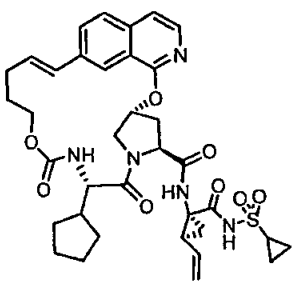
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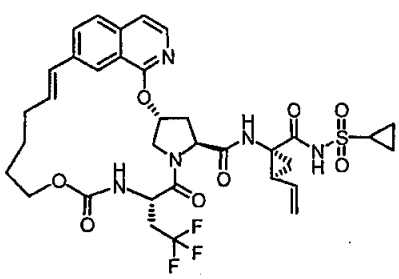
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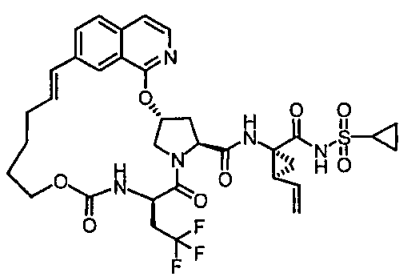
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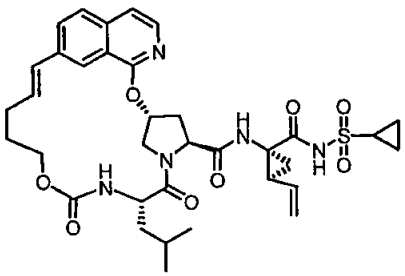
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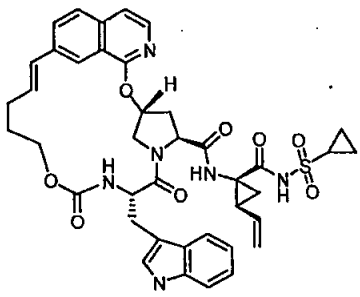
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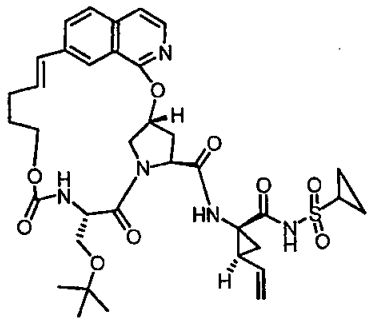
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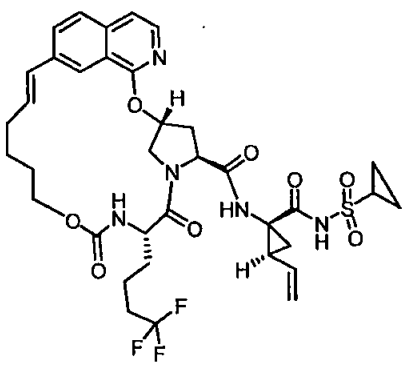
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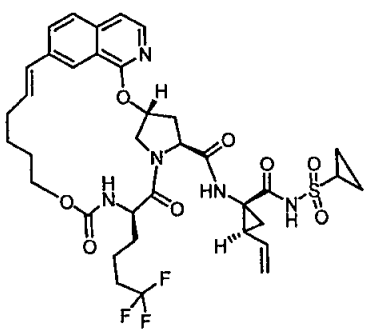
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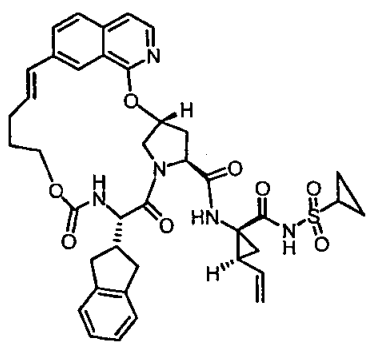
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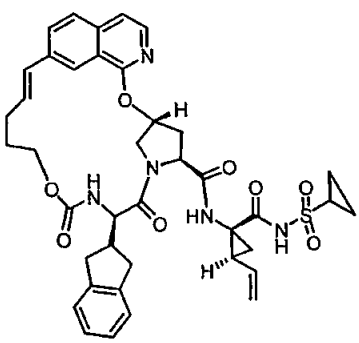
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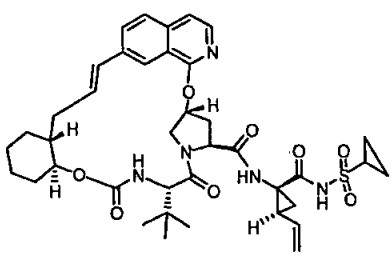
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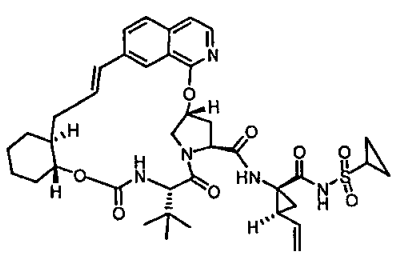
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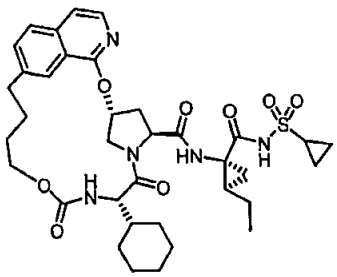
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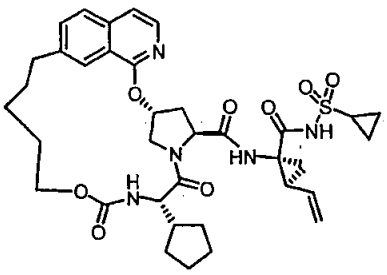
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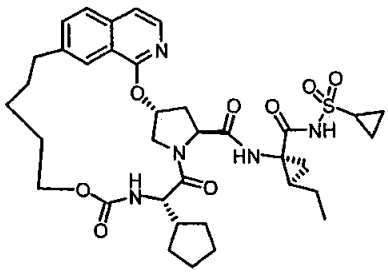
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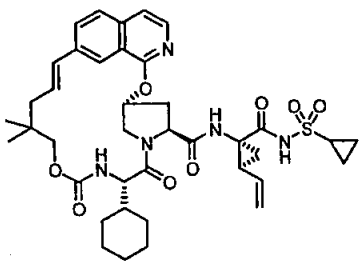
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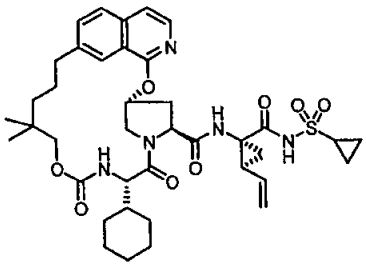
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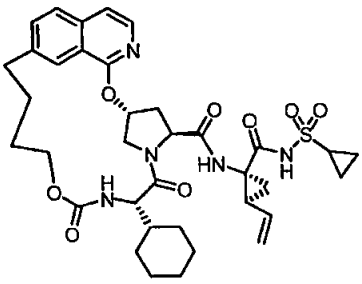
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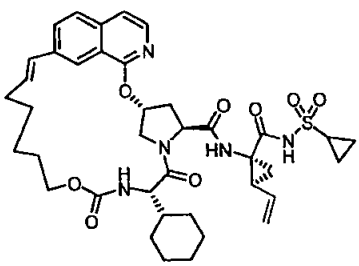
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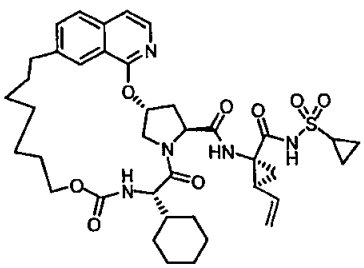
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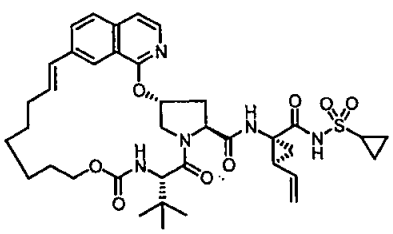
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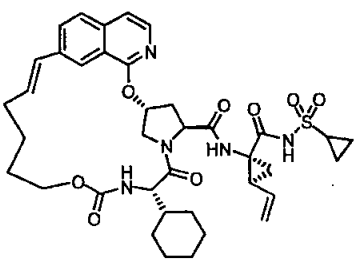
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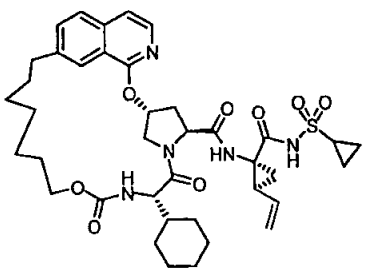
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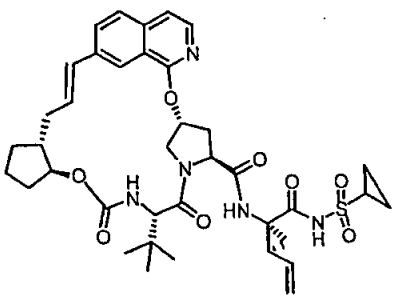
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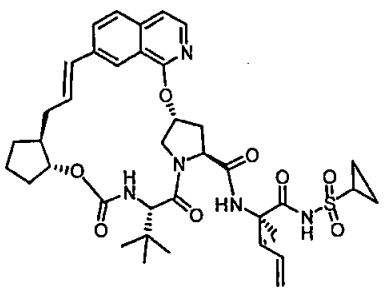
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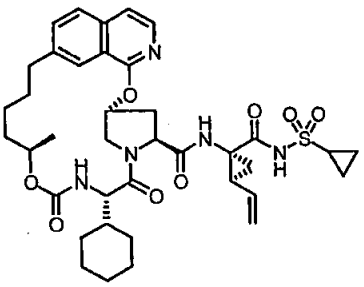
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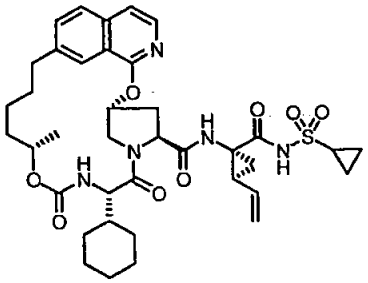
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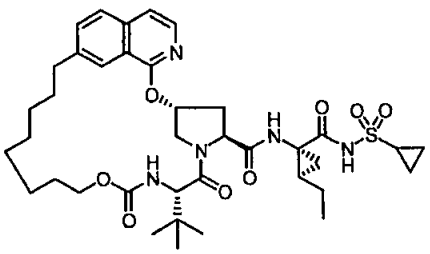
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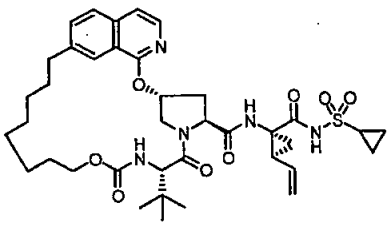
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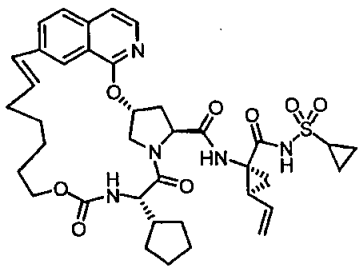
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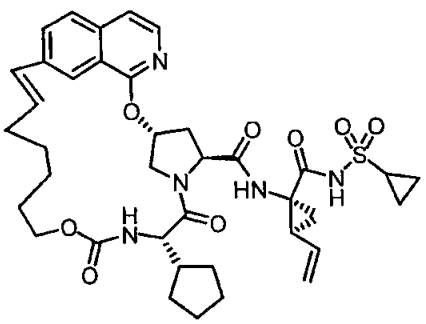
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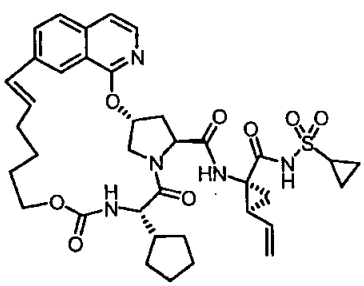
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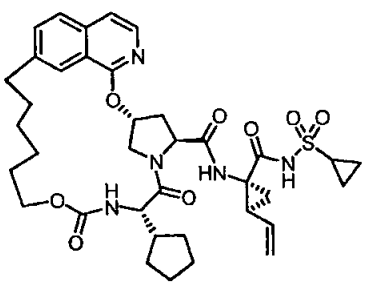
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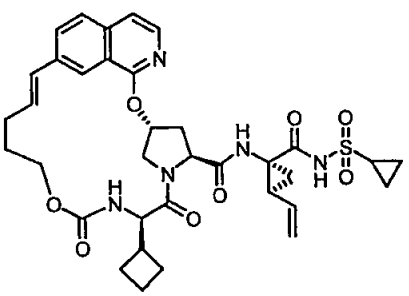
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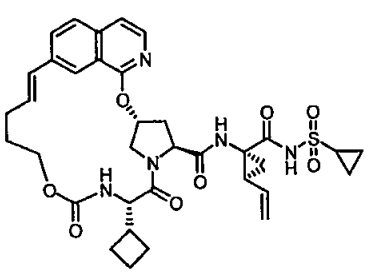
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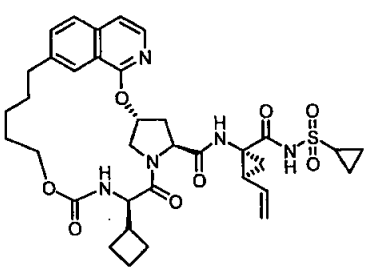
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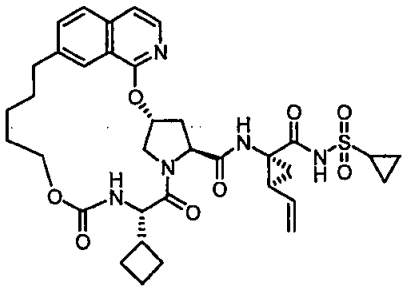
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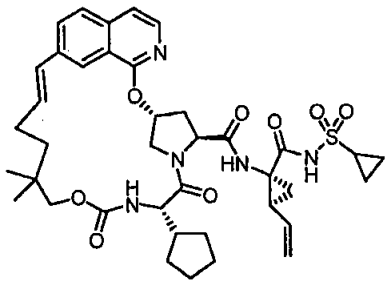
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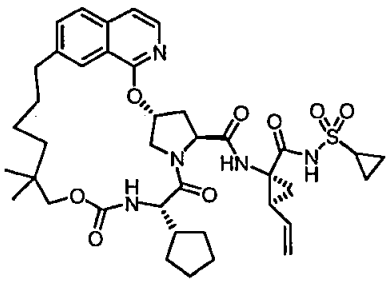
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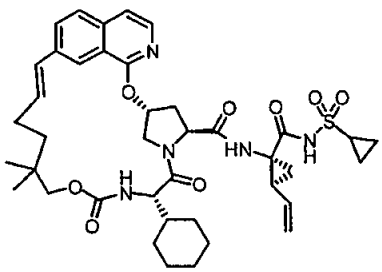
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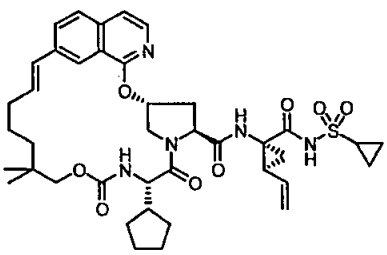
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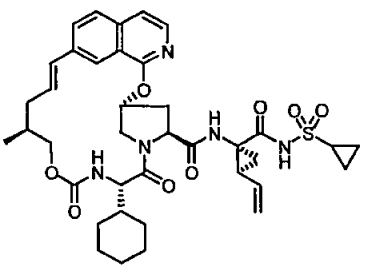
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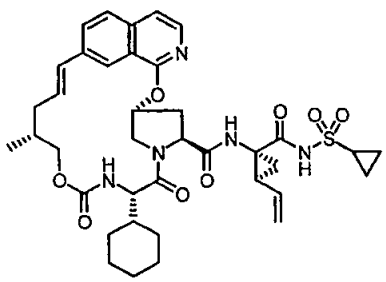
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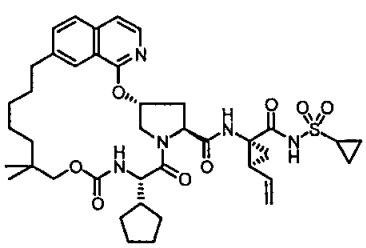
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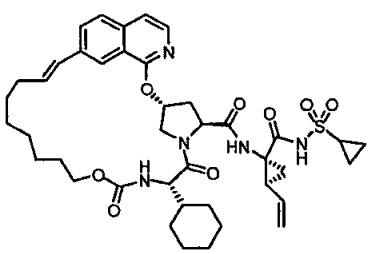
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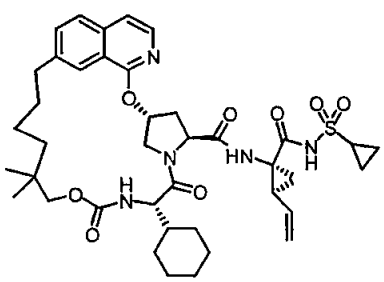
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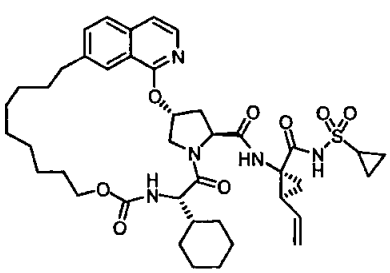
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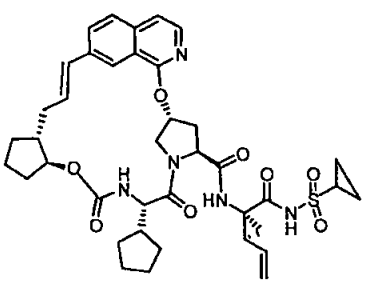
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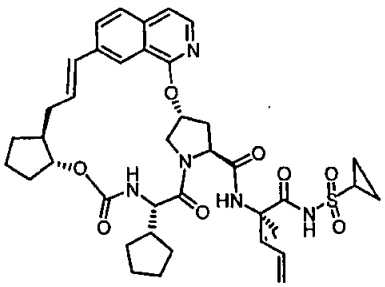
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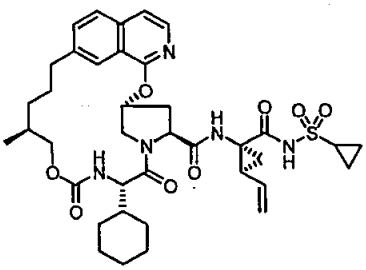
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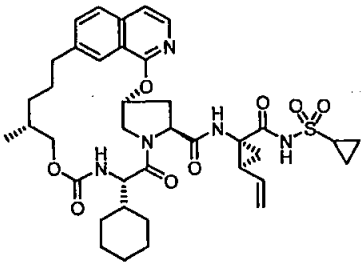
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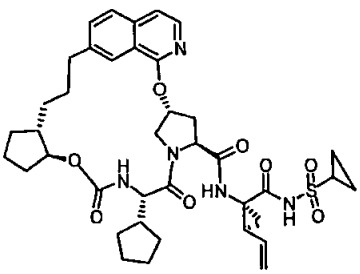
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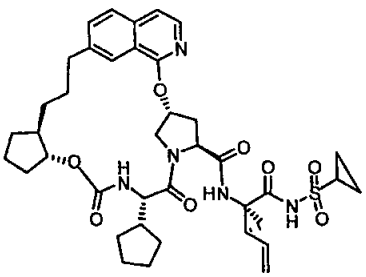
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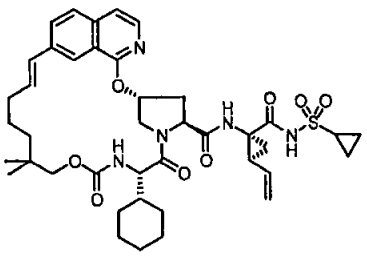
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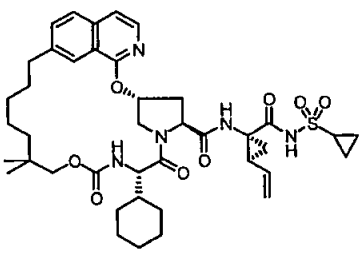
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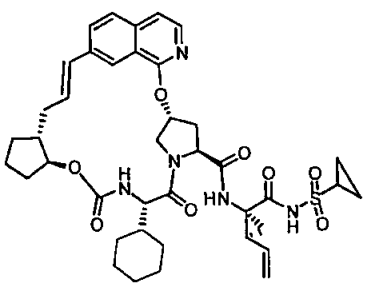
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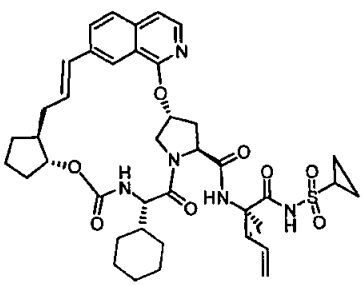
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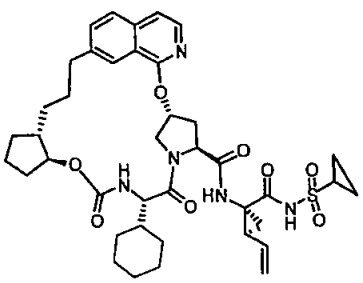
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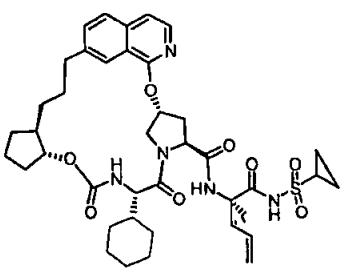
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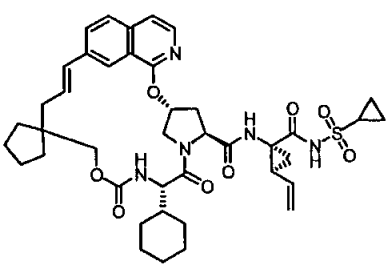
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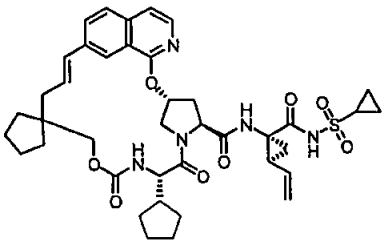
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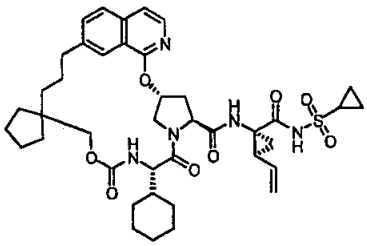
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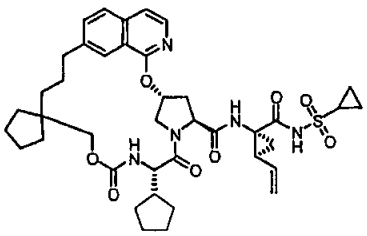
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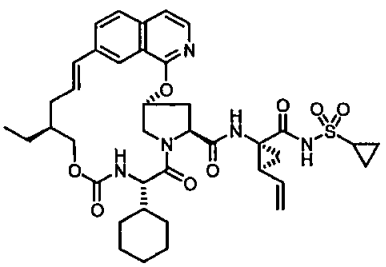
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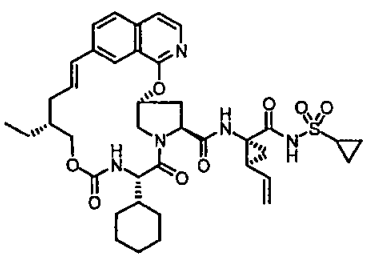
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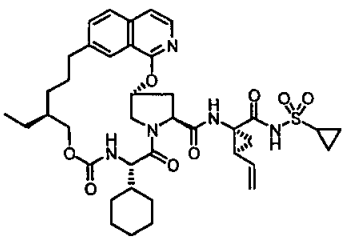
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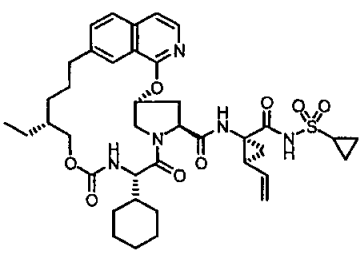
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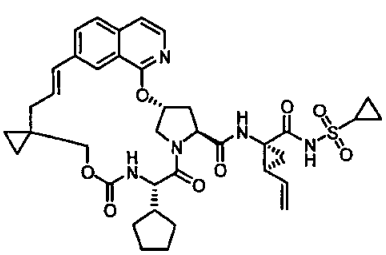
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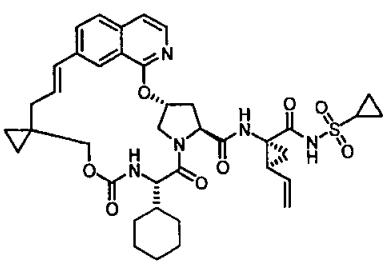
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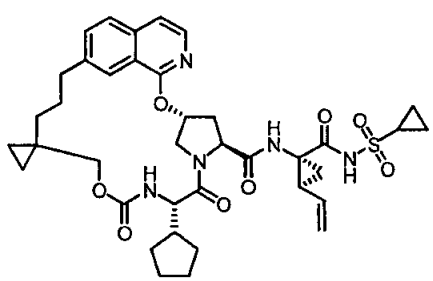
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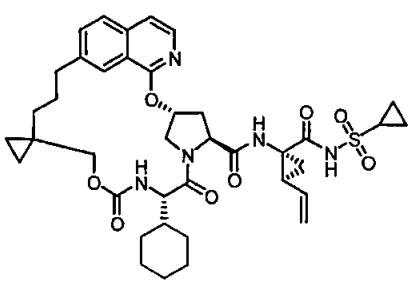
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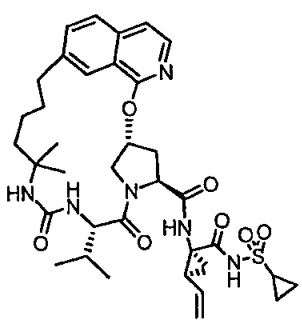
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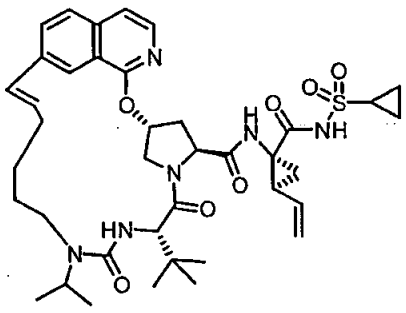
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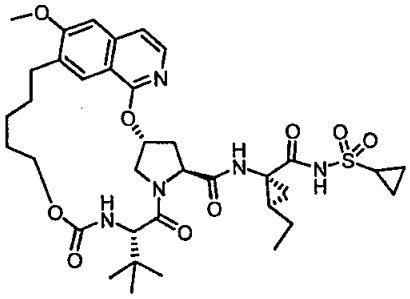
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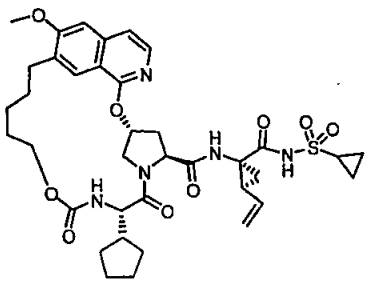
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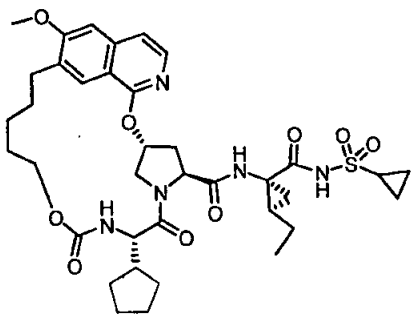
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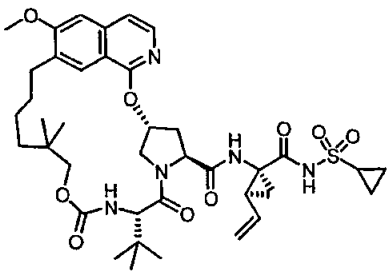
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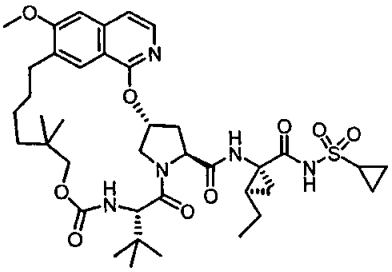
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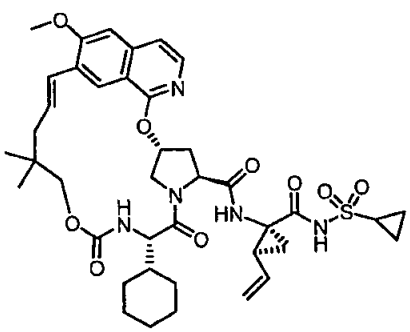
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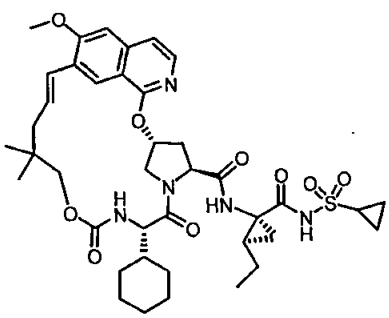
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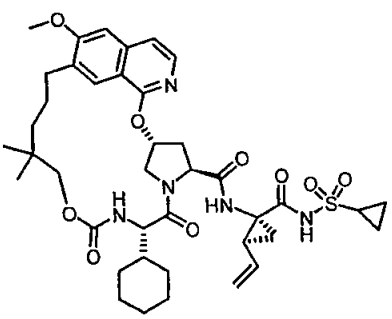
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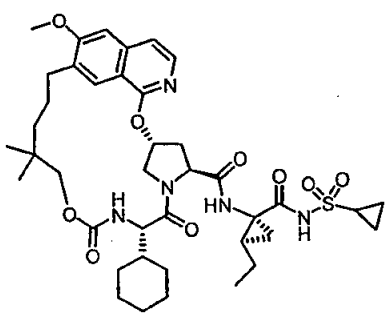
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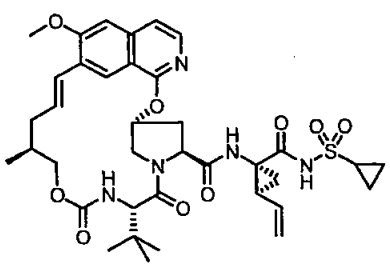
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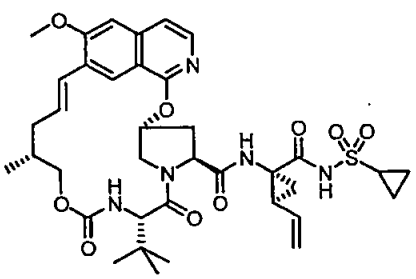
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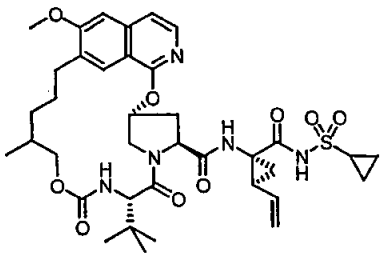
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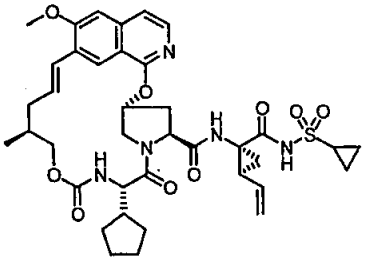
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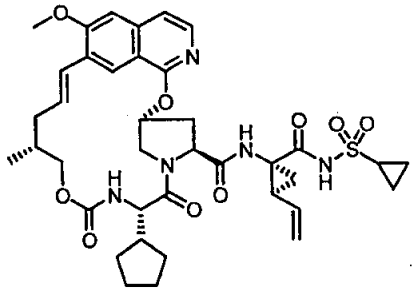
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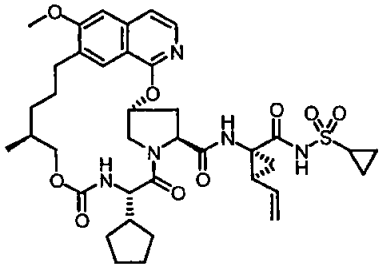
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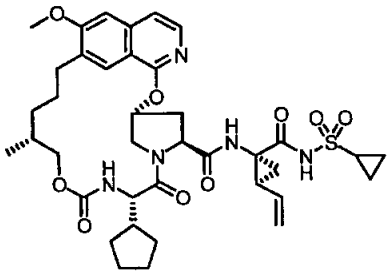
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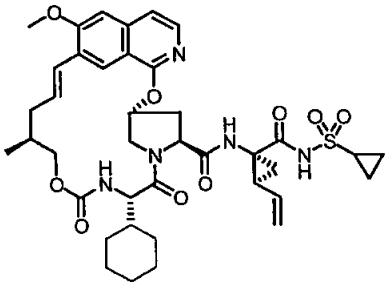
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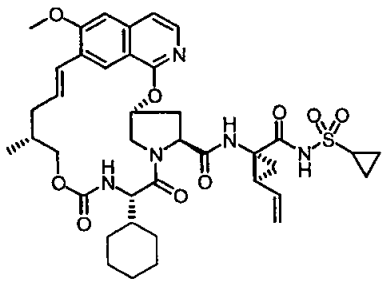
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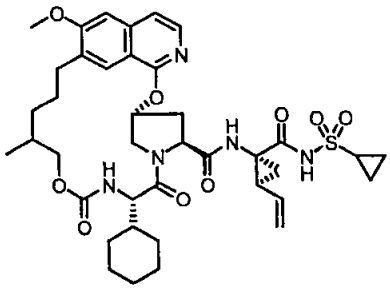
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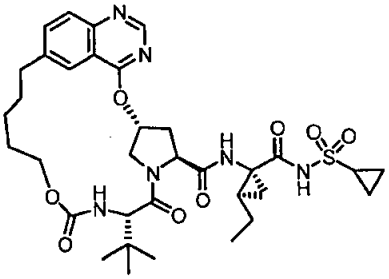
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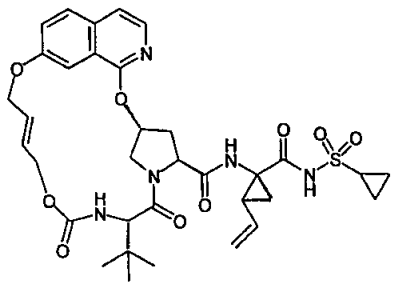
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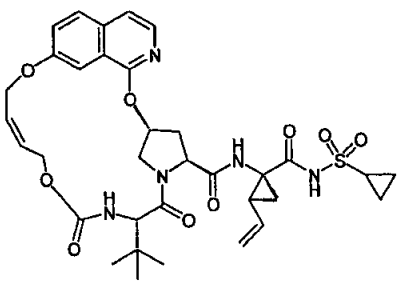
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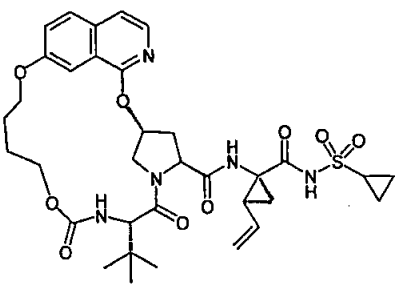
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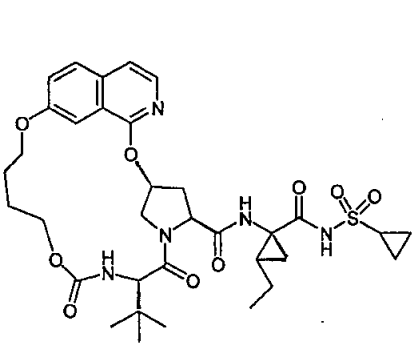
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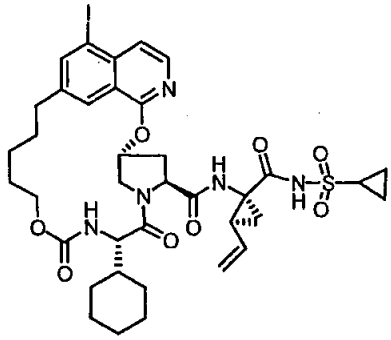
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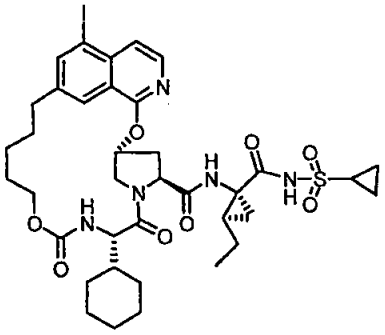
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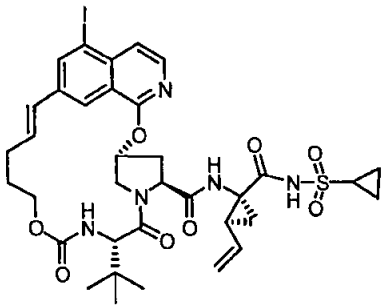
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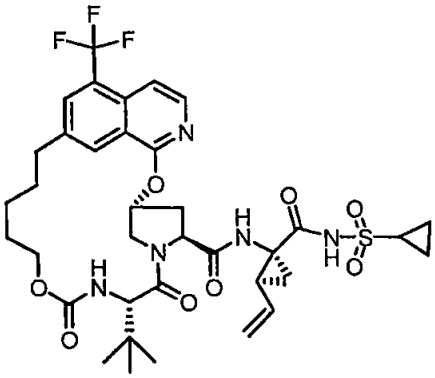
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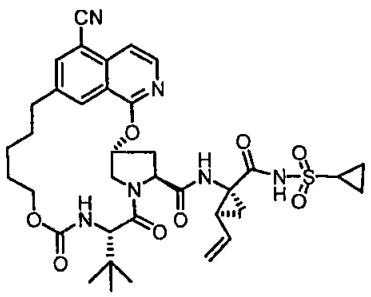
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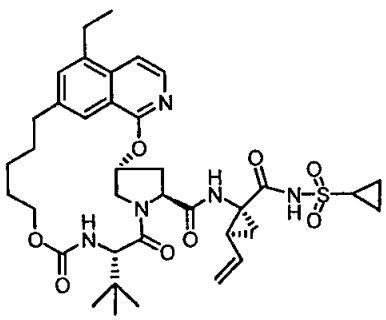
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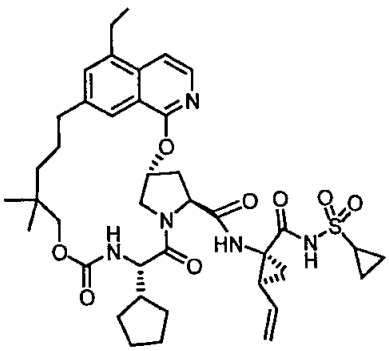
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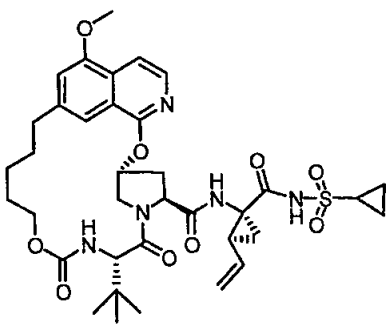
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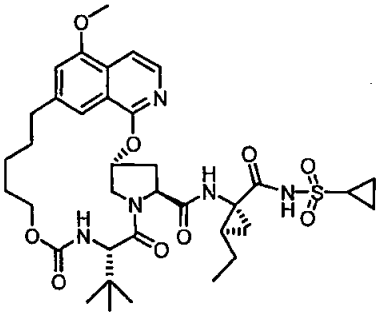
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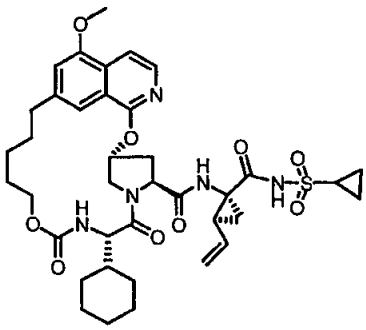
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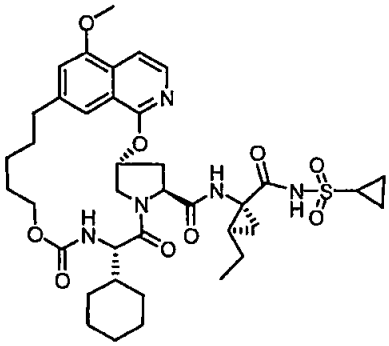
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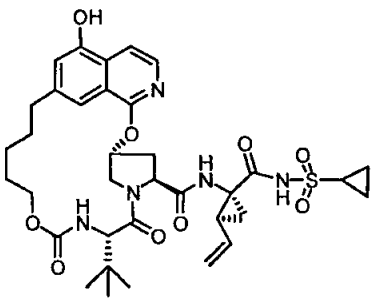
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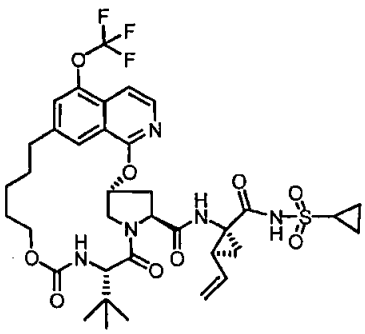
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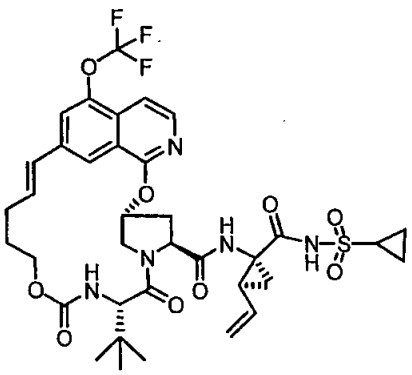
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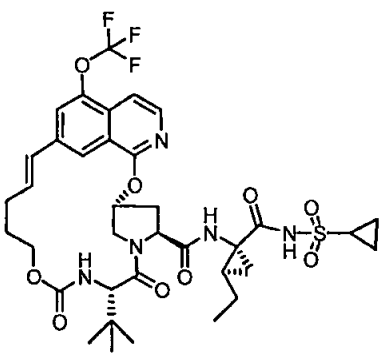
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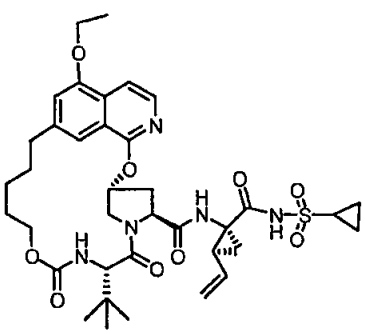
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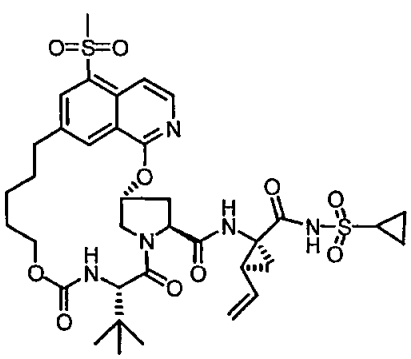
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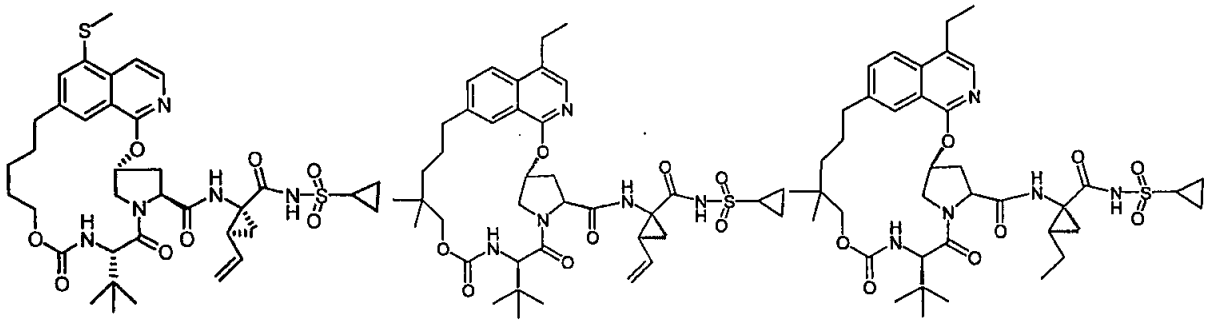
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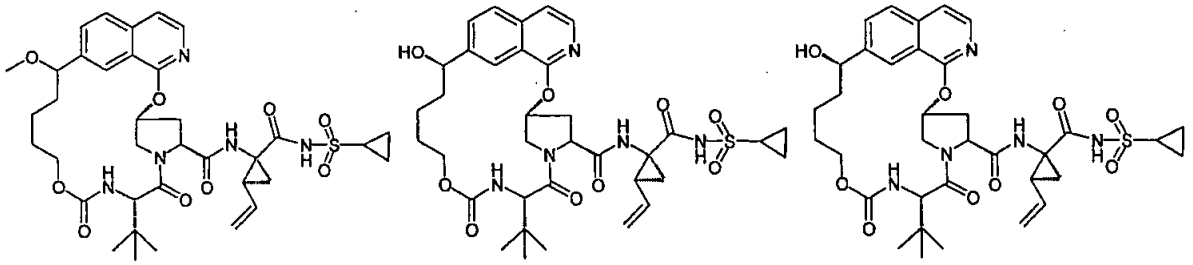
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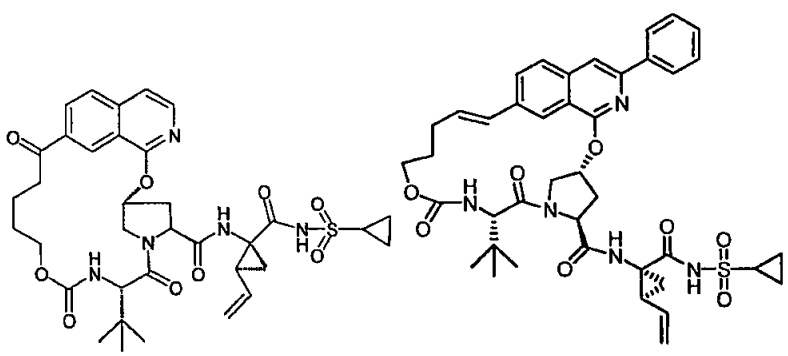
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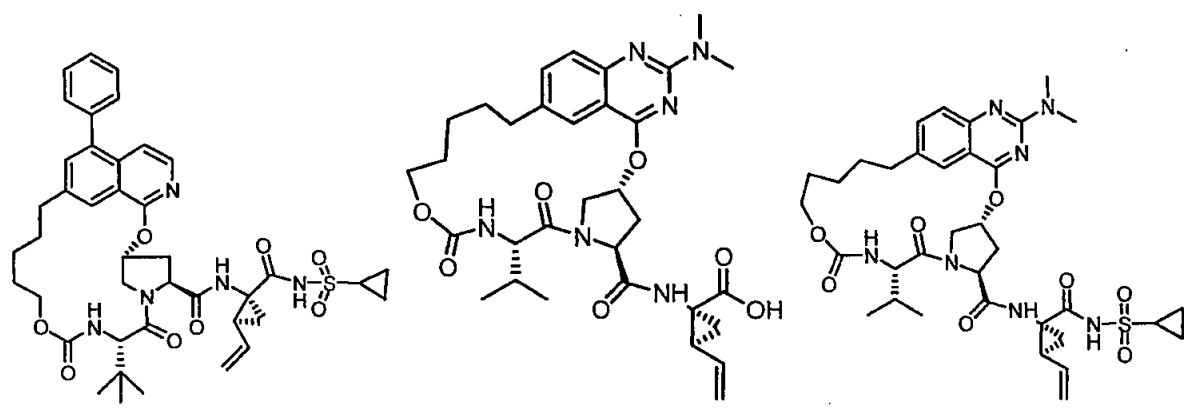
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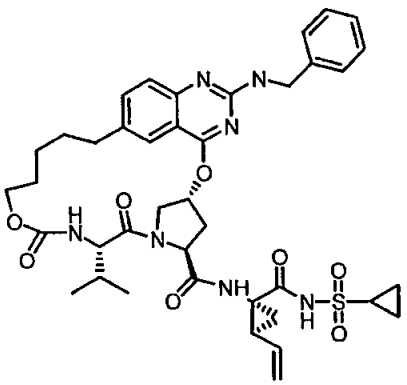
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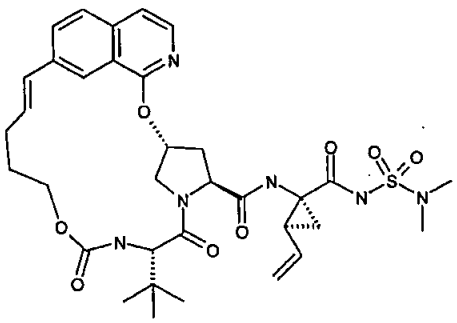


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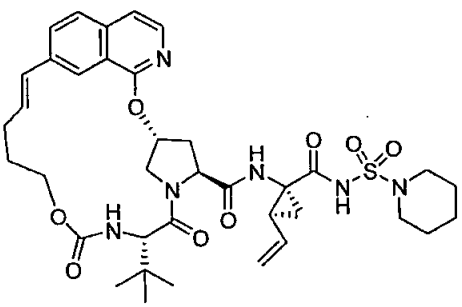


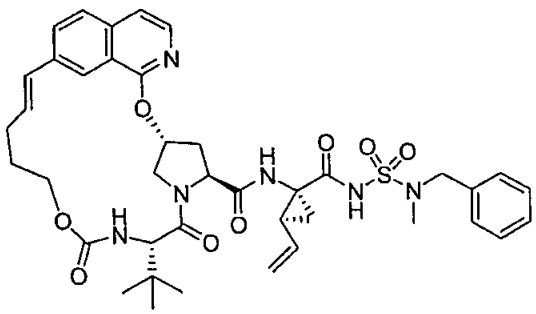
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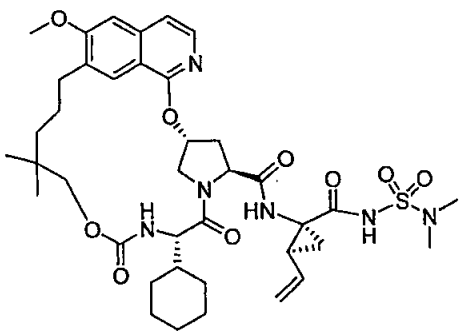


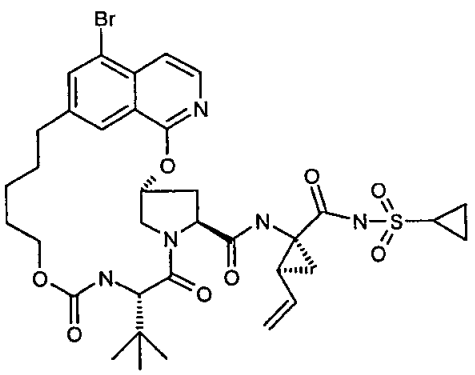
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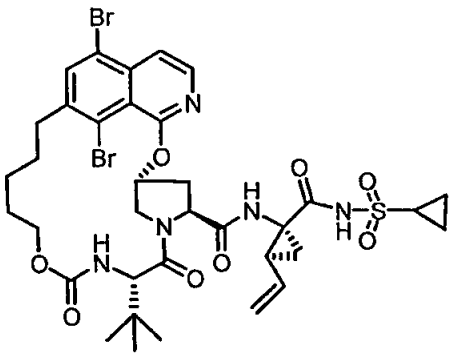


III-179 III-180

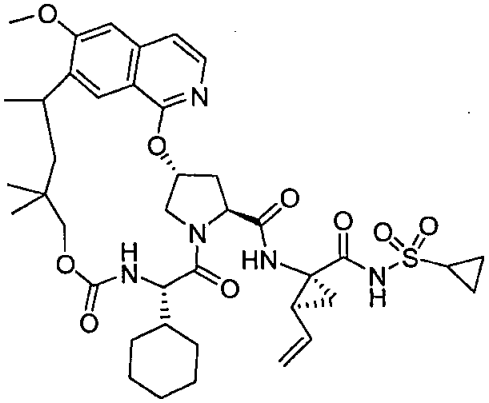




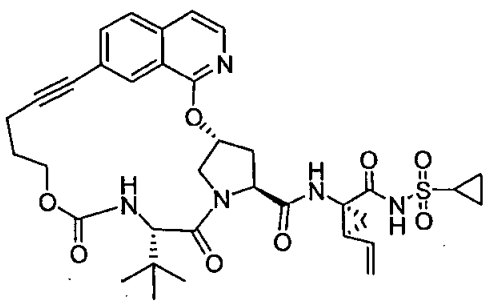
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III-183

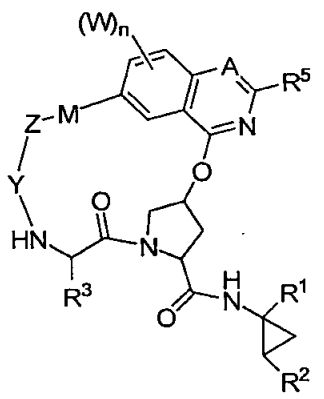


III-184



III-185

A twenty-first embodiment of the present invention is a compound of formula (I) and/or a pharmaceutically acceptable salt and/or hydrate thereof:



I

wherein:

n is 1 or 2;

R^1 is CO_2R^{10}, $CONR^{10}SO_2R^6$, $CONR^{10}SO_2NR^8R^9$, or tetrazolyl;

R^2 is C_1-C_6 alkyl, C_2-C_6 alkenyl or C_3-C_8 cycloalkyl, wherein said alkyl, alkenyl or cycloalkyl is optionally substituted with 1 to 3 halo;

R^3 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8)alkyl, aryl(C_1-C_8)alkyl, or Het, wherein aryl is phenyl or naphthyl and said alkyl, cycloalkyl, or aryl is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), NO_2, CN, CF_3, $SO_2(C_1$-C_6 alkyl), $S(O)(C_1$-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$;

Het is a 5-6 membered saturated cyclic ring having 1, 2 or 3 heteroatoms selected from N, O and S, wherein said ring is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), NO_2, CN, CF_3, $SO_2(C_1$-C_6 alkyl), $S(O)(C_1$-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$;

R^4 is H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl(C_1-C_8)alkyl, or aryl(C_1-C_8)alkyl; wherein aryl is phenyl or naphthyl and said alkyl, cycloalkyl, or aryl is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), NO_2, CN, CF_3, $SO_2(C_1$-C_6 alkyl), $S(O)(C_1$-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$;

R^5 is H, halo, OH, C_1-C_6 alkoxy, C_1-C_6 alkyl, CN, CF_3, SR^{10}, $SO_2(C_1$-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, $N(R^7)_2$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein said aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkoxy, alkyl or alkoxy is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^7)_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), C_3-C_6 cycloalkyl, C_3-C_6 cycloalkoxy, NO_2, CN, CF_3, $SO_2(C_1$-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $S(O)(C_1$-C_6 alkyl), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$; wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

R^6 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_5)alkyl, aryl, aryl(C_1-C_4)alkyl, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl, or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 W' substituents; and wherein each aryl is independently phenyl or naphthyl, each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen;

Y is C(=O), SO_2, or C(=N-CN);

Z is $C(R^{10})_2$, O, or $N(R^4)$;

M is C_1-C_{12} alkylene or C_2-C_{12} alkenylene, wherein said alkylene or alkenylene is optionally substituted with 1 or 2 substituents selected from the group consisting of C_1-C_8 alkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), and aryl(C_1-C_8 alkyl); and the 2 substituents on adjacent carbon atoms of M are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

A is $C(R^{11})$ or N;

when R^5 is other than H, R^{11} is H, C_1-C_6 alkyl, halo, OR^{10}, SR^{10}, or $N(R^{10})_2$;

when R^5 is H, R^{11} is H, C_1-C_6 alkyl, halo, OH, C_1-C_6 alkoxy, CN, CF_3, SR^{10}, SO_2(C_1-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, $N(R^7)_2$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein said aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkoxy, alkyl or alkoxy is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^7)_2$, N(C_1-C_6 alkyl)O(C_1-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), C_3-C_6 cycloalkyl, C_3-C_6 cycloalkoxy, NO_2, CN, CF_3, SO_2(C_1-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, S(O)(C_1-C_6 alkyl), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$; wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

or R^5 and R^{11} are optionally taken together to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0-2 heteroatoms selected from N, O and S;

each R^7 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl(C_1-C_5)alkyl, aryl, aryl(C_1-C_4)alkyl, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl, or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 W' substituents; and wherein each aryl is independently phenyl or naphthyl, each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen;

each W is independently halo, OR^7, C_1-C_6 alkyl, CN, CF_3, NO_2, SR^7, CO_2R^7, $CON(R^7)_2$, $C(O)R^7$, $N(R^{10})C(O)R^7$, $SO_2(C_1$-C_6 alkyl), $S(O)(C_1$-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, $N(R^7)_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), halo(C_1-C_6 alkoxy), $NR^{10}SO_2R^7$, $SO_2N(R^7)_2$, $NHCOOR^7$, $NHCONHR^7$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein 2 adjacent W moieties are optionally taken together with the atoms to which they are attached to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0-2 heteroatoms selected from N, O and S;

each W' is independently halo, OR^{10}, C_1-C_6 alkyl, CN, CF_3, NO_2, SR^{10}, CO_2R^{10}, $CON(R^{10})_2$, $C(O)R^{10}$, $N(R^{10})C(O)R^{10}$, $SO_2(C_1$-C_6 alkyl), $S(O)(C_1$-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, $N(R^{10})_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), halo(C_1-C_6 alkoxy), $NR^{10}SO_2R^{10}$, $SO_2N(R^{10})_2$, $NHCOOR^{10}$, $NHCONHR^{10}$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein 2 adjacent W' moieties are optionally taken together with the atoms to which they are attached to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0-2 heteroatoms selected from N, O and S;

R^8 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), aryl, aryl(C_1-C_4 alkyl), heteroaryl, heterocyclyl, heteroaryl(C_1-C_4 alkyl), or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, aryl,

heteroaryl or heterocyclyl is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, halo(C_1-C_6 alkoxy), halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, $C(O)R^{10}$, C_1-C_6 haloalkyl, NO_2, CN, CF_3, $SO_2(C_1$-C_6 alkyl), $S(O)(C_1$-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, and $C(O)N(R^{10})_2$; wherein each aryl is independently phenyl or naphthyl; each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

R^9 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, aryl, aryl(C_1-C_4 alkyl), heteroaryl, heterocyclyl, heteroaryl(C_1-C_4 alkyl), or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, halo(C_1-C_6 alkoxy), halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, $C(O)R^{10}$, C_1-C_6 haloalkyl, NO_2, CN, CF_3, $SO_2(C_1$-C_6 alkyl), $S(O)(C_1$-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, and $C(O)N(R^{10})_2$; wherein each aryl is independently phenyl or naphthyl; each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

or R^8 and R^9 are optionally taken together, with the nitrogen atom to which they are attached, to form a 4-8 membered monocyclic ring containing 0-2 additional heteroatoms selected from N, O and S; and

each R^{10} is independently H or C_1-C_6 alkyl.

A twenty-second embodiment of the present invention is a compound, or a pharmaceutically acceptable salt or hydrate thereof, which is compound **III-23** ((1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-tert-Butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-ethanediylidene-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid).

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising an effective amount of a compound of formula **I, II, II-A, II-B, III, III-A,** or **III-B** and a pharmaceutically acceptable carrier.

(b) The pharmaceutical composition of (a), further comprising a second therapeutic agent selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent.

(c) The pharmaceutical composition of (b), wherein the HCV antiviral agent is an antiviral selected from the group consisting of a HCV protease inhibitor and a HCV NS5B polymerase inhibitor.

(d) A pharmaceutical combination which is (i) a compound of formula **I, II, II-A, II-B, III, III-A,** or **III-B** and (ii) a second therapeutic agent selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent; wherein the compound of formula **I, II, II-A, II-B, III, III-A,** or **III-B** and the second therapeutic agent are each employed in an amount that renders the combination effective for inhibiting HCV NS3 protease, or for treating or preventing infection by HCV.

(e) The combination of (d), wherein the HCV antiviral agent is an antiviral selected from the group consisting of a HCV protease inhibitor and a HCV NS5B polymerase inhibitor.

(f) A method of inhibiting HCV NS3 protease in a subject in need thereof which comprises administering to the subject an effective amount of a compound of formula **I, II, II-A, II-B, III, III-A,** or **III-B**.

(g) A method of preventing or treating infection by HCV in a subject in need thereof which comprises administering to the subject an effective amount of a compound of formula **I I, II, II-A, II-B, III, III-A,** or **III-B**.

(h) The method of (g), wherein the compound of formula **I, II, II-A, II-B, III, III-A,** or **III-B** is administered in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent.

(i) The method of (h), wherein the HCV antiviral agent is an antiviral selected from the group consisting of a HCV protease inhibitor and a HCV NS5B polymerase inhibitor.

(j) A method of inhibiting HCV NS3 protease in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), or (c) or the combination of (d) or (e).

(k) A method of preventing or treating infection by HCV in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), or (c) or the combination of (d) or (e).

The present invention also includes a compound of the present invention (i) for use in, (ii) for use as a medicament for, or (iii) for use in the preparation of a medicament for: (a) inhibiting HCV NS3 protease, or (b) preventing or treating infection by HCV. In these uses, the compounds of the present invention can optionally be employed in combination with one or more second therapeutic agents selected from HCV antiviral agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(k) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, aspects, classes, sub-classes, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt or hydrate as appropriate.

As used herein, the term "alkyl" refers to any linear or branched chain alkyl group having a number of carbon atoms in the specified range. Thus, for example, "C_{1-6} alkyl" (or "C_1-C_6 alkyl") refers to all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. As another example, "C_{1-4} alkyl" refers to n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl.

The term "haloalkyl" refers to an alkyl group wherein a hydrogen has been replaced by a halogen. The term "alkoxy" refers to an "alkyl-O-" group.

The term "alkylene" refers to any linear or branched chain alkylene group (or alternatively "alkanediyl") having a number of carbon atoms in the specified range. Thus, for example, "-C_{1-6} alkylene-" refers to any of the C_1 to C_6 linear or branched alkylenes. A class of alkylenes of particular interest with respect to the invention is -$(CH_2)_{1-6}$-, and sub-classes of particular interest include -$(CH_2)_{1-4}$-, -$(CH_2)_{1-3}$-, -$(CH_2)_{1-2}$-, and -CH_2-. Also of interest is the alkylene -$CH(CH_3)$-.

The terms "cycloalkyl" refers to any cyclic ring of an alkane or alkene having a number of carbon atoms in the specified range. Thus, for example, "C_{3-8} cycloalkyl" (or "C_3-C_8 cycloalkyl") refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The term "cycloalkoxy" refers to a "cycloalkyl-O-" group.

The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro, chloro, bromo, and iodo).

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heteroaryl ring described as containing from "1 to 3 heteroatoms" means the ring can contain 1, 2, or 3 heteroatoms. It is also to be understood that any range cited herein includes within its scope all of the sub-ranges within that range. The oxidized forms of the heteroatoms N and S are also included within the scope of the present invention.

When any variable (e.g., R^7 and R^{10}) occurs more than one time in any constituent or in formula **I, II, II-A, II-B, III, III-A,** or **III-B** or in any other formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Unless expressly stated to the contrary, substitution by a named substituent is permitted on any atom in a ring (e.g., aryl, a heteroaromatic ring, or a saturated heterocyclic ring) provided such ring substitution is chemically allowed and results in a stable compound. A "stable" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic or prophylactic administration to a subject).

Terms referring to 2 substituents "on adjacent carbon atoms" which "optionally taken together" form specified cyclic rings, and 2 substituents "on the same carbon atom" which "optionally taken together" form specified cyclic rings, mean that the 2 substituents can form a ring that includes both of the adjacent carbon atoms, or can form a ring that includes the same carbon atom. For example, ring 1 shown below is formed by two single carbon substituents each attached to adjacent carbon atoms, and ring 2 shown below is formed by two single carbon substituents each attached to the same carbon atom:



ring 1 ring 2

As a result of the selection of substituents and substituent patterns, certain of the compounds of the present invention can have asymmetric centers and can occur as mixtures of stereoisomers, or as individual diastereomers, or enantiomers. All isomeric forms of these compounds, whether isolated or in mixtures, are within the scope of the present invention.

As would be recognized by one of ordinary skill in the art, certain of the compounds of the present invention can exist as tautomers. For the purposes of the present invention a reference to a compound of formula **I, II, II-A, II-B, III, III-A,** or **III-B** is a reference to the compound per se, or to any one of its tautomers per se, or to mixtures of two or more tautomers.

The compounds of the present inventions are useful in the inhibition of HCV protease (e.g., HCV NS3 protease) and the prevention or treatment of infection by HCV. For example, the compounds of this invention are useful in treating infection by HCV after suspected past exposure to HCV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

The compounds of this invention are useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating

enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to HCV protease, e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes.

The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt which possesses the effectiveness of the parent compound and which is not biologically or otherwise undesirable (e.g., is neither toxic nor otherwise deleterious to the recipient thereof). Suitable salts include acid addition salts which may, for example, be formed by mixing a solution of the compound of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, or benzoic acid. Many of the compounds of the invention carry an acidic moiety, in which case suitable pharmaceutically acceptable salts thereof can include alkali metal salts (e.g., sodium or potassium salts), alkaline earth metal salts (e.g., calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention mean providing the compound or a prodrug of the compound to the individual in need of treatment. When a compound of the invention or a prodrug thereof is provided in combination with one or more other active agents (e.g., antiviral agents useful for treating HCV infection), "administration" and its variants are each understood to include concurrent and sequential provision of the compound or salt (or hydrate) and other agents.

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

By "pharmaceutically acceptable" is meant that the ingredients of the pharmaceutical composition must be compatible with each other and not deleterious to the recipient thereof.

The term "subject" (alternatively referred to herein as "patient") as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. In one embodiment, the effective amount is a "therapeutically effective amount" for the alleviation of the symptoms of the disease or condition being treated. In another embodiment, the effective amount is a

"prophylactically effective amount" for prophylaxis of the symptoms of the disease or condition being prevented. The term also includes herein the amount of active compound sufficient to inhibit HCV NS3 protease and thereby elicit the response being sought (i.e., an "inhibition effective amount"). When the active compound (i.e., active ingredient) is administered as the salt, references to the amount of active ingredient are to the free acid or free base form of the compound.

For the purpose of inhibiting HCV NS3 protease and preventing or treating HCV infection, the compounds of the present invention, optionally in the form of a salt or a hydrate, can be administered by any means that produces contact of the active agent with the agent's site of action. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but typically are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. The compounds of the invention can, for example, be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in the form of a unit dosage of a pharmaceutical composition containing an effective amount of the compound and conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. Liquid preparations suitable for oral administration (e.g., suspensions, syrups, elixirs and the like) can be prepared according to techniques known in the art and can employ any of the usual media such as water, glycols, oils, alcohols and the like. Solid preparations suitable for oral administration (e.g., powders, pills, capsules and tablets) can be prepared according to techniques known in the art and can employ such solid excipients as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like. Parenteral compositions can be prepared according to techniques known in the art and typically employ sterile water as a carrier and optionally other ingredients, such as a solubility aid. Injectable solutions can be prepared according to methods known in the art wherein the carrier comprises a saline solution, a glucose solution or a solution containing a mixture of saline and glucose. Further description of methods suitable for use in preparing pharmaceutical compositions of the present invention and of ingredients suitable for use in said compositions is provided in Remington's Pharmaceutical Sciences, 18th edition, edited by A. R. Gennaro, Mack Publishing Co., 1990.

The compounds of this invention can be administered orally in a dosage range of 0.001 to 1000 mg/kg of mammal (e.g., human) body weight per day in a single dose or in divided doses. One preferred dosage range is 0.01 to 500 mg/kg body weight per day orally in a single dose or in divided doses. Another preferred dosage range is 0.1 to 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions can be provided in the form of tablets or capsules containing 1.0 to 500 milligrams of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, and 500 milligrams of the active ingredient for the symptomatic

adjustment of the dosage to the patient to be treated. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

As noted above, the present invention also relates to a method of inhibiting HCV NS3 protease, inhibiting HCV replication, or preventing or treating HCV infection with a compound of the present invention in combination with one or more therapeutic agents and a pharmaceutical composition comprising a compound of the present invention and one or more therapeutic agents selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent. Such therapeutic agents active against HCV include, but are not limited to, ribavirin, levovirin, viramidine, thymosin alpha-1, interferon-β, interferon-α, pegylated interferon-α (peginterferon-α), a combination of interferon-α and ribavirin, a combination of peginterferon-α and ribavirin, a combination of interferon-α and levovirin, and a combination of peginterferon-α and levovirin. Interferon-α includes, but is not limited to, recombinant interferon-α2a (such as Roferon interferon available from Hoffmann-LaRoche, Nutley, NJ), pegylated interferon-α2a (Pegasys™), interferon-α2b (such as Intron-A interferon available from Schering Corp., Kenilworth, NJ), pegylated interferon-α2b (PegIntron™), a recombinant consensus interferon (such as interferon alphacon-1), and a purified interferon-α product. Amgen's recombinant consensus interferon has the brand name Infergen®. Levovirin is the L-enantiomer of ribavirin which has shown immunomodulatory activity similar to ribavirin. Viramidine represents an analog of ribavirin disclosed in WO 01/60379 (assigned to ICN Pharmaceuticals). In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms.

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS3 serine protease. HCV NS3 serine protease is an essential viral enzyme and has been described to be an excellent target for inhibition of HCV replication. Both substrate and non-substrate based inhibitors of HCV NS3 protease inhibitors are disclosed in WO 98/22496, WO 98/46630, WO 99/07733, WO 99/07734, WO 99/38888, WO 99/50230, WO 99/64442, WO 00/09543, WO 00/59929, GB-2337262, WO 02/48116, WO 02/48172, and U.S. Patent No. 6,323,180.

Ribavirin, levovirin, and viramidine may exert their anti-HCV effects by modulating intracellular pools of guanine nucleotides via inhibition of the intracellular enzyme inosine monophosphate dehydrogenase (IMPDH). IMPDH is the rate-limiting enzyme on the biosynthetic route in *de novo* guanine nucleotide biosynthesis. Ribavirin is readily phosphorylated intracellularly and the monophosphate derivative is an inhibitor of IMPDH. Thus, inhibition of IMPDH represents another

useful target for the discovery of inhibitors of HCV replication. Therefore, the compounds of the present invention may also be administered in combination with an inhibitor of IMPDH, such as VX-497, which is disclosed in WO 97/41211 and WO 01/00622 (assigned to Vertex); another IMPDH inhibitor, such as that disclosed in WO 00/25780 (assigned to Bristol-Myers Squibb); or mycophenolate mofetil [see A.C. Allison and E.M. Eugui, Agents Action, 44 (Suppl.): 165 (1993)].

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with the antiviral agent amantadine (1-aminoadamantane) [for a comprehensive description of this agent, see J. Kirschbaum, Anal. Profiles Drug Subs. 12: 1-36 (1983)].

The compounds of the present invention may also be combined for the treatment of HCV infection with antiviral 2'-*C*-branched ribonucleosides disclosed in R. E. Harry-O'kuru, et al., J. Org. Chem., 62: 1754-1759 (1997); M. S. Wolfe, et al., Tetrahedron Lett., 36: 7611-7614 (1995); U.S. Patent No. 3,480,613 (Nov. 25, 1969); International Publication Number WO 01/90121 (29 November 2001); International Publication Number WO 01/92282 (6 December 2001); and International Publication Number WO 02/32920 (25 April 2002); and International Publication Number WO 04/002999 (8 January 2004); and International Publication Number WO 04/003000 (8 January 2004); and International Publication Number WO 04/002422 (8 January 2004); the contents of each of which are incorporated by reference in their entirety. Such 2'-*C*-branched ribonucleosides include, but are not limited to, 2'-*C*-methyl-cytidine, 2'-*C*-methyl-uridine, 2'-*C*-methyl-adenosine, 2'-*C*-methyl-guanosine, and 9-(2-*C*-methyl-β-D-ribofuranosyl)-2,6-diaminopurine, and the corresponding amino acid ester of the ribose C-2', C-3', and C-5' hydroxyls and the corresponding optionally substituted cyclic 1,3-propanediol esters of the 5'-phosphate derivatives.

The compounds of the present invention may also be combined for the treatment of HCV infection with other nucleosides having anti-HCV properties, such as those disclosed in WO 02/51425 (4 July 2002), assigned to Mitsubishi Pharma Corp.; WO 01/79246, WO 02/32920, and WO 02/48165 (20 June 2002), assigned to Pharmasset, Ltd.; WO 01/68663 (20 September 2001), assigned to ICN Pharmaceuticals; WO 99/43691 (2 Sept. 1999); WO 02/18404 (7 March 2002), assigned to Hoffmann-LaRoche; U.S. 2002/0019363 (14 Feb. 2002); WO 02/100415 (19 Dec. 2002); WO 03/026589 (3 Apr. 2003); WO 03/026675 (3 Apr. 2003); WO 03/093290 (13 Nov. 2003);: US 2003/0236216 (25 Dec. 2003); US 2004/0006007 (8 Jan. 2004); WO 04/011478 (5 Feb. 2004); WO 04/013300 (12 Feb. 2004); US 2004/0063658 (1 Apr. 2004); and WO 04/028481 (8 Apr. 2004); the content of each is incorporated herein by reference in its entirety.

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS5B polymerase. Such HCV NS5B polymerase inhibitors that may be used as combination therapy include, but are not limited to, those disclosed in WO 02/057287, US 6,777,395, WO 02/057425, US 2004/0067901, WO 03/068244,

WO 2004/000858, WO 04/003138 and WO 2004/007512; the content of each is incorporated herein by reference in its entirety. Other such HCV polymerase inhibitors include, but are not limited to, valopicitabine (NM-283; Idenix) and 2'-F-2'-beta-methylcytidine (see also WO 2005/003147, assigned to Pharmasset, Ltd.).

In one embodiment, nucleoside HCV NS5B polymerase inhibitors that are used in combination with the present HCV NS3 protease inhibitors are selected from the following compounds: 4-amino-7-(2-C-methyl-β-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-methylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-dimethylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-cyclopropylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-vinyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-hydroxymethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-fluoromethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-5-methyl-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxylic acid; 4-amino-5-bromo-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-5-chloro-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-5-fluoro-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 2,4-diamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 2-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 2-amino-4-cyclopropylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 2-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one; 4-amino-7-(2-C-ethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C,2-O-dimethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one; 2-amino-5-methyl-7-(2-C, 2-O-dimethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one; 4-amino-7-(3-deoxy-2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(3-deoxy-2-C-methyl-β-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-2-fluoro-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(3-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(3-C-methyl-β-D-xylofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2,4-di-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(3-deoxy-3-fluoro-2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2 ,3-d]pyrimidine; and the corresponding 5'-triphosphates; or a pharmaceutically acceptable salt thereof.

The compounds of the present invention may also be combined for the treatment of HCV infection with non-nucleoside inhibitors of HCV polymerase such as those disclosed in WO 01/77091 (18 Oct. 2001), assigned to Tularik, Inc.; WO 01/47883 (5 July 2001), assigned to Japan Tobacco, Inc.; WO 02/04425 (17 January 2002), assigned to Boehringer Ingelheim; WO 02/06246 (24 Jan. 2002), assigned to Istituto di Ricerche di Biologia Moleculare P. Angeletti S.P.A.; WO 02/20497 (3 March

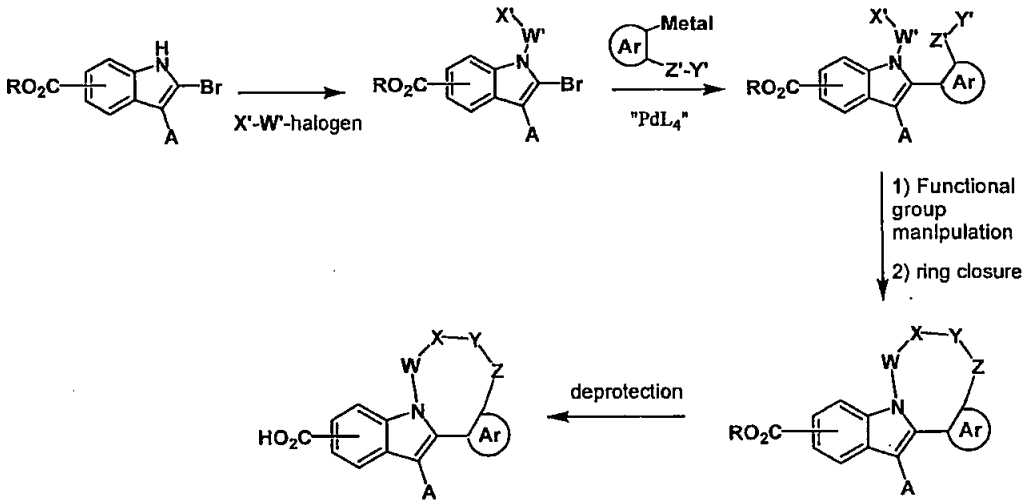
2002); WO 2005/016927 (in particular JTK003), assigned to Japan Tobacco, Inc.; the content of each is incorporated herein by reference in its entirety; and HCV-796 (Viropharma Inc.).

In one embodiment, non-nucleoside HCV NS5B polymerase inhibitors that are used in combination with the present HCV NS3 protease inhibitors are selected from the following compounds: 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(2-morpholin-4-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-3-methoxy-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; methyl ({[(14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocin-11-yl)carbonyl]amino}sulfonyl)acetate; ({[(14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocin-11-yl)carbonyl]amino}sulfonyl)acetic acid; 14-cyclohexyl-*N*-[(dimethylamino)sulfonyl]-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxamide; 3-chloro-14-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine 11-carboxylic acid; *N*'-(11-carboxy-14-cyclohexyl-7,8-dihydro-*6H*-indolo[1,2-e][1,5]benzoxazocin-7-yl)-*N,N*-dimethylethane-1,2-diaminium bis(trifluoroacetate); 14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid; 14-cyclohexyl-6-methyl-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-3-methoxy-6-methyl-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-3-methoxy-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[3-(dimethylamino)propyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-7-oxo-6-(2-piperidin-1-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(2-morpholin-4-ylethyl)-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(diethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(1-methylpiperidin-4-yl)-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-N-[(dimethylamino)sulfonyl]-7-oxo-6-(2-piperidin-1-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxamide; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-*N*-[(dimethylamino)sulfonyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxamide; 14-cyclopentyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 6-allyl-14-cyclohexyl-3-methoxy-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclopentyl-6-[2-(dimethylamino)ethyl]-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid;

14-cyclohexyl-6-[2-(dimethylamino)ethyl]-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 13-cyclohexyl-5-methyl-4,5,6,7-tetrahydrofuro[3',2':6,7][1,4]diazocino[1,8-*a*]indole-10-carboxylic acid; 15-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-6,7,8,9-tetrahydro-5*H*-indolo[2,1-*a*][2,6]benzodiazonine-12-carboxylic acid; 15-cyclohexyl-8-oxo-6,7,8,9-tetrahydro-5*H*-indolo[2,1-*a*][2,5]benzodiazonine-12-carboxylic acid; 13-cyclohexyl-6-oxo-6,7-dihydro-5*H*-indolo[1,2-*d*][1,4]benzodiazepine-10-carboxylic acid; and pharmaceutically acceptable salts thereof.

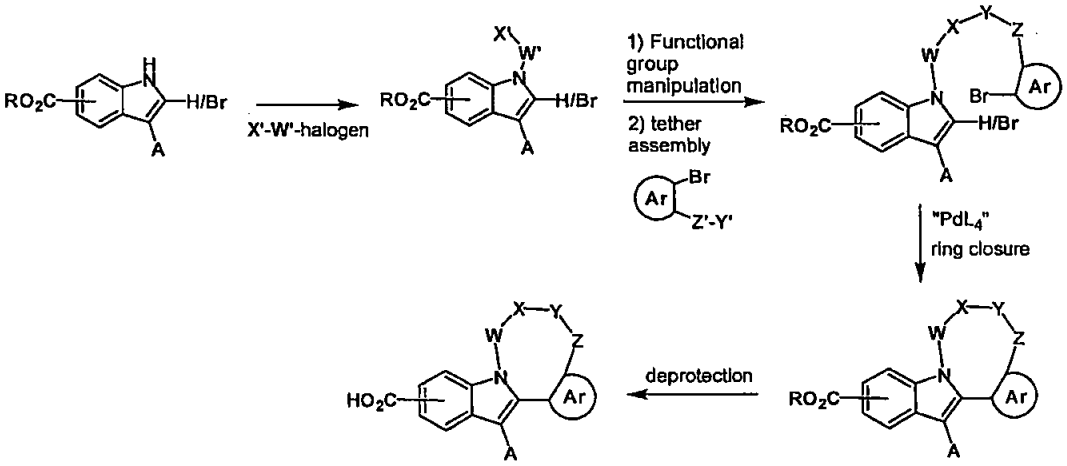
The above tetracyclic indole-based HCV NS5B polymerase inhibitors may be obtained following methods A-E as outlined below, wherein different variables may be selected in accordance with the specific tetracyclic indole compound to be prepared:

Method A



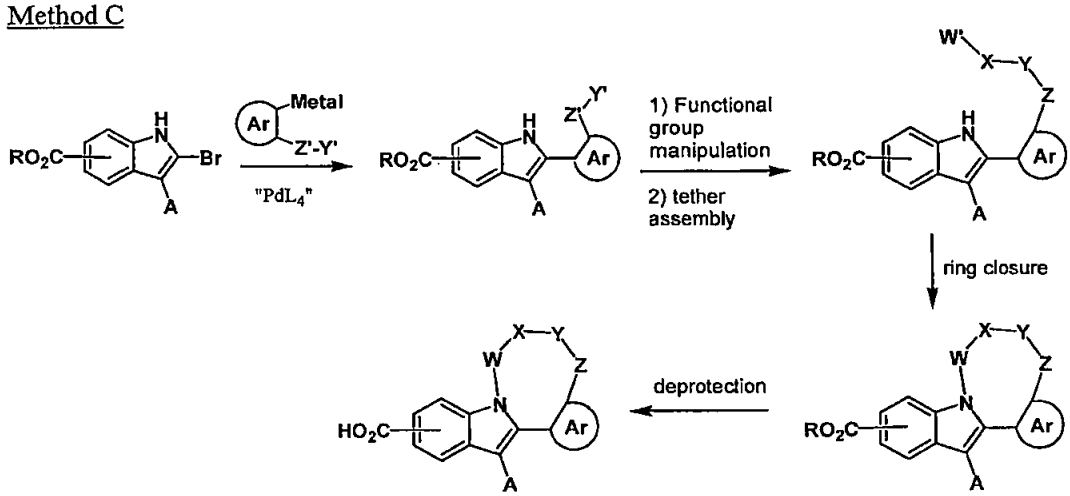
2-Bromoindole intermediate (prepared as described in published International patent application WO2004087714) was functionalized on the indole nitrogen to introduce pre-cursor functionality W'/X' to either or both of the elements W/X of the tether. Pd-mediated cross-coupling methodology (*eg*, Suzuki, Stille *etc*) then brought in the C2 aromatic bearing pre-cursor functionality Z'/Y' to either or both of the elements Z/Y of the tether. Functional group manipulation followed by ring closure afforded the tetracyclic system. Ester deprotection then yielded the target indole carboxylic acids, with the C2 aromatic tethered to the indole nitrogen.

Method B



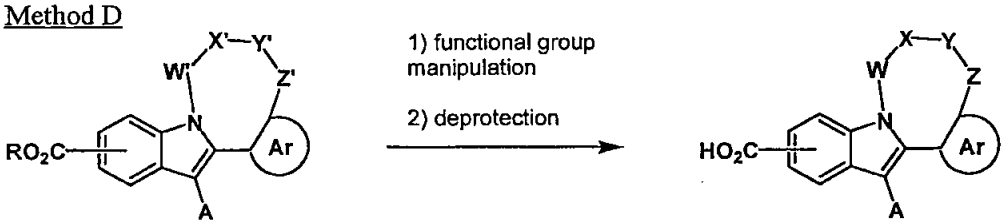
Following tether assembly out to the appropriate 2-haloaromatic, Pd-mediated ring closure afforded the fused tetracyclic system. Ester deprotection then yielded the target indole carboxylic acids, with the C2 aromatic tethered to the indole nitrogen.

Method C



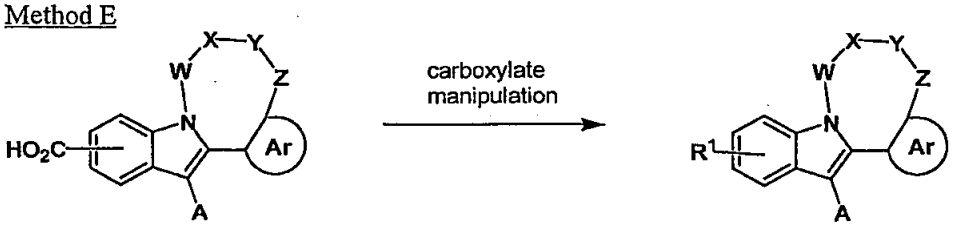
The C2 aromatic was introduced at the outset *via* Pd-mediated cross-coupling methodology (Suzuki, Stille *etc*). The tether was then built up, with cyclisation onto the indole nitrogen finally closing the ring. Ester deprotection then yielded the target indole carboxylic acids, with the C2 aromatic tethered to the indole nitrogen.

Method D



Fused tetracyclic intermediates arising from Methods A-C underwent manipulation of the functionality in the tether prior to ester deprotection to yield the target C2-tethered indole carboxylic acids.

Method E



C2-tethered indole carboxylic acids arising from Methods A-D were further derivatised through manipulation of the carboxylate functionality to give compounds bearing a carboxylate replacement or carboxamide. During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3rd edition, 1999. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

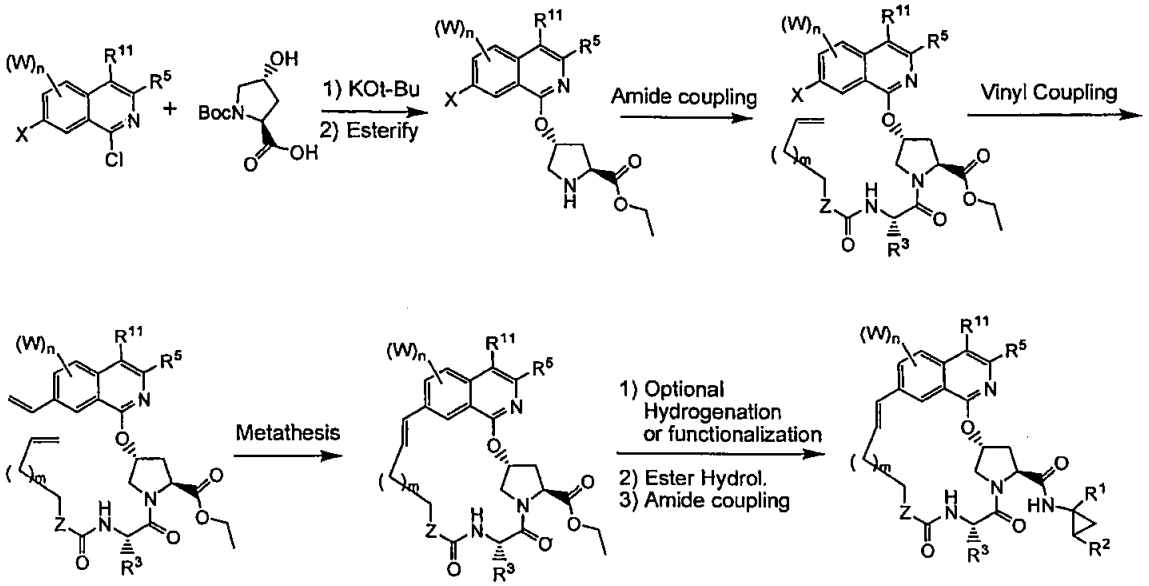
The HCV NS3 protease inhibitory activity of the present compounds may be tested using assays known in the art. One such assay is HCV NS3 protease time-resolved fluorescence (TRF) assay as described in Example 9. Other examples of such assays are described in e.g., International patent publication WO2005/046712. Compounds useful as HCV NS3 protease inhibitors would have a Ki less than 50 μM, more preferably less than 10 μM, and even more preferably less than 100 nM.

The present invention also includes processes for making compounds of formula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, or **III-B**. The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above. The following reaction schemes and examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope or spirit of the invention.

General Description of Synthesis:

The compounds of the present invention may be synthesized as outlined in the general Schemes 1, 2 and 3.

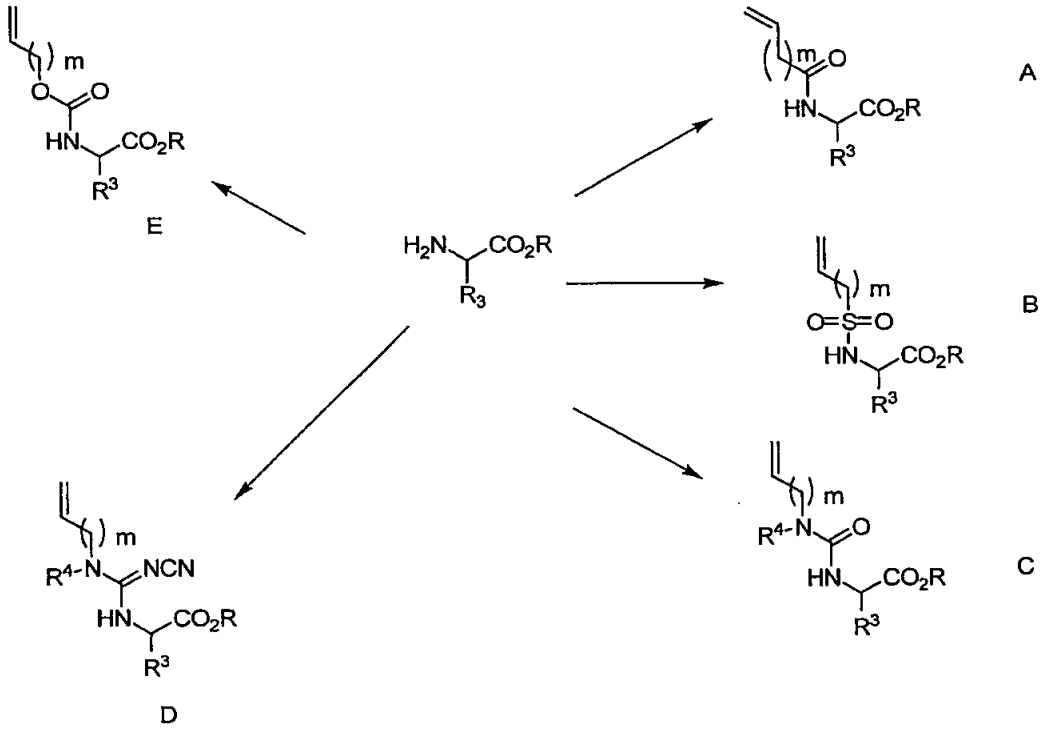
SCHEME 1



Scheme 1 (m=0-9) outlines the synthesis of a representative molecule. An appropriately protected 4-hydroxyproline derivative (for example, a carbamate protected nitrogen) can be reacted with potassium t-butoxide or equivalent reagent and then reacted with an appropriately substituted chloro-isoquinoline. The acid can then be esterified with acid in an appropriate alcohol solvent. These conditions also remove the BOC protecting group on the proline nitrogen.

Scheme 2 describes the synthesis of the olefin containing amino acid portion. An amino acid (either commercially available or may be prepared readily using known methods in the art) in which the acid functionality is protected as an ester (for example, R=methyl) can be converted to amides A by coupling an olefinic carboxylic acid utilizing a wide range of peptide coupling agents known to those skilled in the art such as DCC, EDC, BOP, TBTU, etc. Preparation of the sulfonamides B can be accomplished by reaction with the appropriate sulfonyl chloride in an organic solvent (e.g., THF) with an amine base as scavenger. Urea derivatives C may be prepared by reacting the aminoester with a reagent such as carbonyldiimidazole, to form an intermediate isocyanate (Catalano et al., WO 03/062192) followed by addition of a second olefin containing amine. Alternatively, phosgene, diphosgene or triphosgene may be used in place of carbonyldiimidazole. Cyanoguanidine derivatives D can be prepared by reaction of the amino acid ester with diphenyl C-cyanocarbonimidate in an organic solvent, followed by addition of a second olefin containing amine. Carbamate derivatives E may be prepared by reacting an olefin containing alcohol with carbonyldiimidazole (or phosgene, triphosgene or diphosgene) in an organic solvent, followed by addition of the amino ester.

SCHEME 2



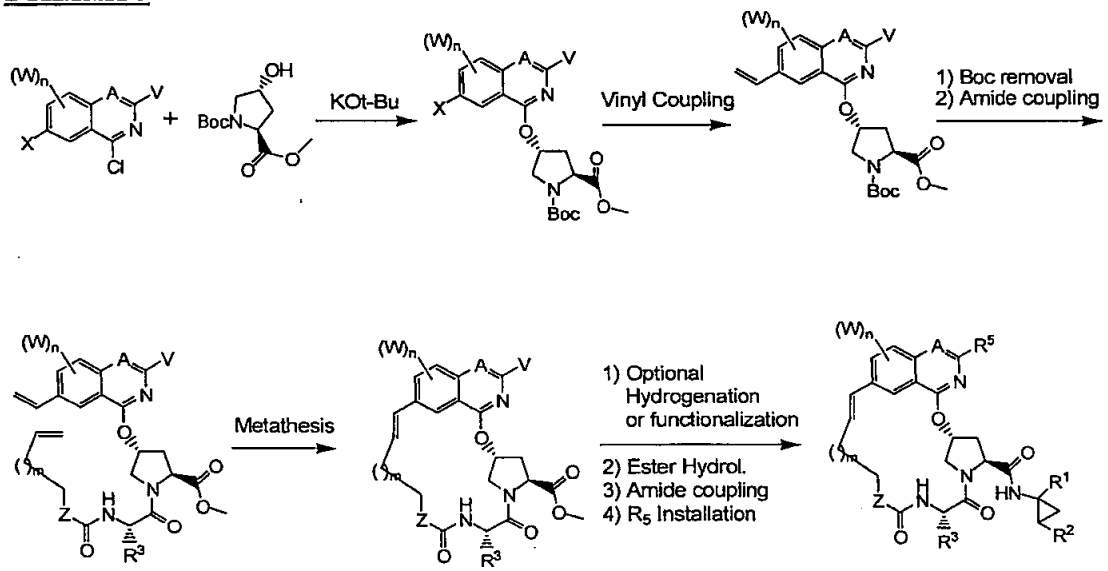
Following functionalization of the amine, the ester can be hydrolyzed under a range of basic conditions known to those skilled in the art (Theodora W. Greene, Protective Groups in Organic Synthesis, Third Edition, John Wiley and Sons, 1999).

Deprotection of the carbamate protecting group on the proline portion may be carried out by a variety of methods known to persons skilled in the art (Theodora W. Greene, Protective Groups in Organic Synthesis, Third Edition, John Wiley and Sons, 1999). To complete the synthesis of the compounds of this invention, the amino acid derivative can be coupled to the proline derivative via a wide range of peptide coupling reagents such as DCC, EDC, BOP, TBTU etc (see Scheme 1). The alkenyl functionality may be introduced at this stage by palladium catalyzed reaction of a halide substituent such as bromide or iodide, or other functionality such as a triflate with an organometallic reagent such as a vinyl or allyltrialkyltin. Macrocyclization is then achieved by an olefin metathesis using a range of catalysts that have been described in the literature for this purpose. At this stage the olefinic bond produced in the ring closing metathesis may be optionally hydrogenated to give a saturated linkage or functionalized in alternative ways such as cyclopropanation. The proline ester is then hydrolyzed under basic conditions and coupled with the cyclopropylamino acid ester (the appropriate alkenyl or alkylcyclopropane portion of the molecule can be prepared as described previously (Llinas-Brunet et al., US 6,323,180) and subjected to an additional basic hydrolysis step to provide the final compounds. The proline ester can also be hydrolyzed and directly coupled to an appropriately

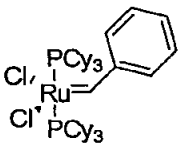
functionalized cyclopropylamino acid acyl sulfonamide (which can be prepared according to Wang X.A. et al. WO2003/099274) to provide the final compounds.

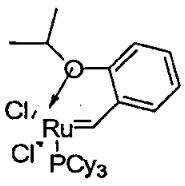
Molecules with 3-substituted isoquinolines or 2-substituted quinazolines may be prepared according to Scheme 3 (wherein V is, for example, halo such as chloro). An appropriately substituted 3-halo isoquinoline or 2-halo quinazoline can be employed in a sequence similar to the route shown in Scheme 1. In a final additional step, an R^5 group can be installed via displacement reactions or metal-mediated coupling reactions.

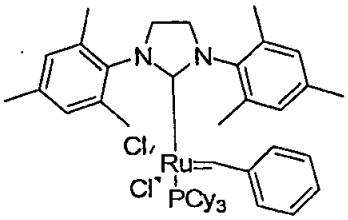
SCHEME 3

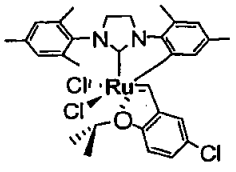


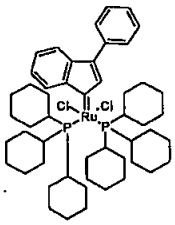
Olefin metathesis catalysts include the following Ruthenium based species: F: Miller et al *J. Am. Chem. Soc* 1996, 118, 9606; G: Kingsbury et al *J. Am. Chem. Soc* 1999, 121, 791; H: Scholl et al Org. Lett. 1999, 1, 953; Hoveyda et al US2002/0107138; K: Furstner et al. J. Org. Chem 1999, 64, 8275. The utility of these catalysts in ring closing metathesis is well known in the literature (e.g. Trnka and Grubbs, *Acc. Chem. Res.* 2001, 34, 18).

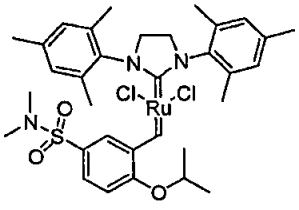

F


G


H


J


K


L

Structure L is the Zhan ruthenium metathesis catalyst RC-303 (Zhan catalyst 1B, RC-303, Zannan Pharma Ltd.)

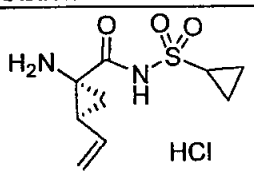
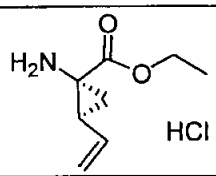
List of Abbreviations

BOP	Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate
Brosyl chloride	4-Bromophenyl sulfonylchloride
CH_3CN	Acetonitrile
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DMAP	4-Dimethylamino pyridine
DIPEA	Diisoproylethylamine
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
EDC	*N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl Acetate
EtOH	Ethanol
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HBr	Hydrobromic acid

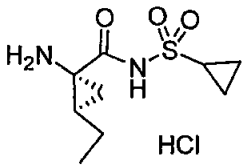
HCl	Hydrochloric acid
HOAc	Acetic acid
HOAt	1-Hydroxy-7-azabenzotriazole
LiOH	Lithium hydroxide
MeOH	Methanol
$MgSO_4$	Magnesium Sulfate
Na_2SO_4	Sodium sulfate
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
Nle	Norleucine
Pd/C	Palladium on carbon
PhMe	Toluene
PPh_3	Triphenylphosphine
RT	Room temperature
TBAF	Tetrabutylammonium fluoride
TBTU	O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
THF	Tetrahydofuran

Synthesis of Intermediates:

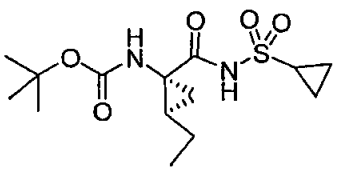
Synthesis of Intermediates A

Intermediate #	Structure	Name	Lit. Reference
A1		(1*R*,2*S*)-1-Amino-*N*-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide hydrochloride	Wang et al, US 6,995,174
A2		Ethyl (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylate hydrochloride	Llinas-Brunet et al, US 6,323,180

Intermediate A3: (1*R*,2*R*)-1-Amino-*N*-(cyclopropylsulfonyl)-2-ethylcyclopropanecarboxamide hydrochloride

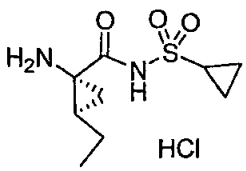


Step 1: tert-Butyl ((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)carbamate



A hydrogenaton vessel was charged with a methanol (1000 mL) slurry of tert-butyl ((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)carbamate (164 g, 0.50 mol) (Wang et al, US 6,995,174) and 5% Ru/C (dry, 7.5 wt%, 12.4 g) and set stirring. The vessel was placed under nitrogen (20 psig) and vented to atmospheric pressure three times to remove residual oxygen. The vessel was then placed under hydrogen (50 psig). After 20 hours, the vessel was vented to atmospheric pressure. The reaction slurry was then transferred out of the reaction and filtered through solka flok (34 grams, wetted w/ 100 mL methanol) to yield a clear, light brown solution. The solka flok was rinsed with methanol (200 mL x 2). The combined methanol solutions were concentrated under reduced pressure to yield crude product as a white solid (153 g).The crude product was slurried in ethyl acetate (800 mL), warmed to 40 °C and aged 30 minutes. The solution was then seeded, aged 30 minutes, and heptane (500 mL) was added via addition funnel over 30 minutes. The partially crystallized solid was cooled to room temperature and aged overnight after which additional heptane (500 mL) was added. After one hour, additional heptane (250 mL) was added via addition funnel, and the white slurry aged for one hour. The solution was filtered and the solid was rinsed with heptane/EtOAc (500 mL, 4:1) and dried under reduced pressure to give tert-butyl ((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)carbamate (125.9 g).

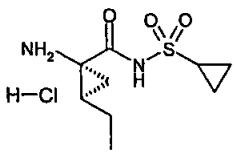
Step 2: (1*R*,2*R*)-1-Amino-*N*-(cyclopropylsulfonyl)-2-ethylcyclopropanecarboxamide hydrochloride (Intermediate A3)



A solution of the product from Step 1 above (92 g, 0.28 mol) in DCM (1200 mL) was cooled to 0 °C and HCl bubbled through the solution for 10 min, the cooling bath removed and the

reaction mixture stirred for 2 h. Nitrogen was bubbled through the reaction mixture for 5 min and the volatiles evaporated. The residue was azeotroped with DCM (x3) to give an off white powder (75 g). LRMS $(M+H)^+$ Calcd. = 233; found 233

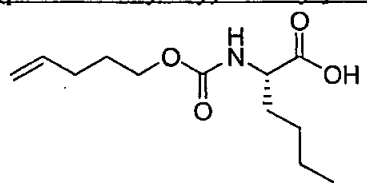
Alternative preparation of and name for Intermediate A3 (1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropanaminium chloride:



A mixture of (1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropanaminium chloride (0.05 g, 0.187 mmol) and palladium on carbon (10% wt., 0.01g) in EtOAc (5 mL) was vigorously stirred under hydrogen atmosphere provided by a hydrogen balloon for 1 hour. The reaction mixture was filtered and concentrated to give (1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropanaminium chloride (0.045 g, 89% yield).

Preparation of Intermediates B

Preparation of Intermediate B1: *N*-[(pent-4-en-1-yloxy)carbonyl]-L-norleucine:

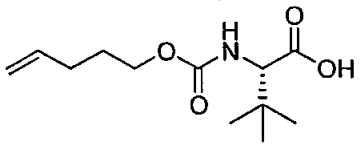


To a solution of 1-penten-4-ol (0.95 g, 11.0 mmol) in DMF (15 mL) at 0 °C was added carbonyldiimidazole (1.79 g, 11.0 mmol). The reaction mixture was warmed to room temperature and stirred for 30 min. L-norleucine methyl ester hydrochloride (2.0 g, 11.0 mmol) was then added, the reaction mixture was heated to 50 °C and stirred for 15 min. Upon cooling, the reaction mixture was diluted with ethyl ether and washed twice with water. The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by silica gel chromatography (gradient elution 10 to 90% ethyl acetate in hexanes) to afford 2.1 g (74%) methyl *N*-[(pent-4-en-1-yloxy)carbonyl]-L-norleucinate as a clear oil.

To a stirred solution of methyl *N*-[(pent-4-enyloxy)carbonyl]-L-norleucinate (8.50g, 33.03 mmol) in THF (20 mL) was added 1N NaOH (20 mL). This reaction solution was stirred at r.t. for 3 h, then acidified to pH 3 with 1N HCl and extracted with (3 x 250 mL) EtOAc. The combined EtOAc layer was washed with 50 mL water, 50 mL brine, dried over sodium sulfate, filtered and concentrated to

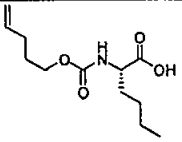
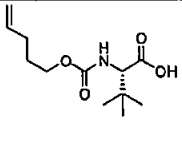
give 7.09 g (88%) of the title product as clear oil. LRMS (ESI) *m/z* 244 $[(M+H)^+$; calcd for $C_{12}H_{22}NO_4$: 244].

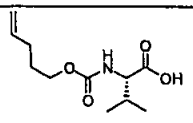
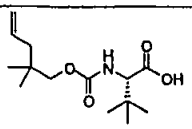
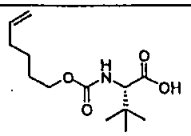
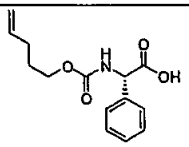
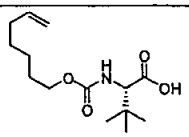
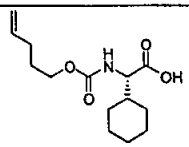
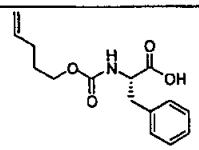
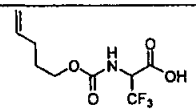
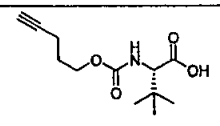
Preparation of Intermediate B2 (2S)-3,3-dimethyl-2-{[(pent-4-en-1-yloxy)carbonyl]amino}butanoic acid

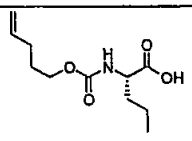
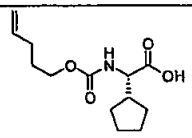
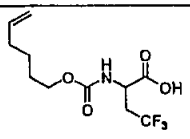
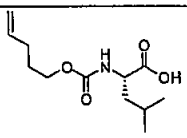
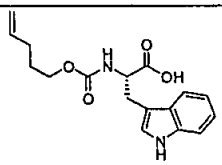
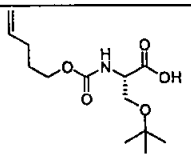
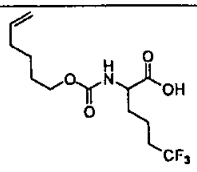
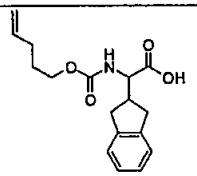


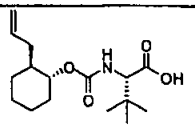
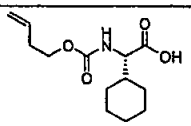
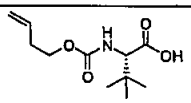
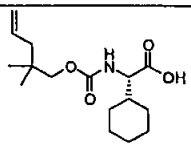
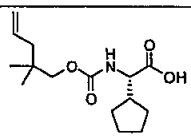
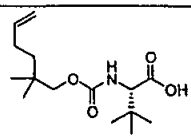
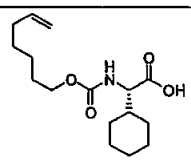
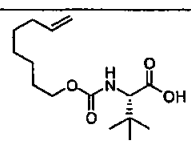
Diisopropylethyl amine (9.85 g, 76.2 mmol) was added dropwise to a 0 °C solution of 4-penten-1-ol (7.22 g, 83.9 mmol) and triphosgene (11.3 g, 38.1 mmol) in 160 mL dioxane. The resulting white suspension was stirred for 5 min at 0 °C, then allowed to warm to 25 °C over 1 h. The suspension was cooled to 0 °C with an ice bath and 1 N NaOH (76.2 mL) and *L-tert*-butylglycine (10.0 g, 76.2 mmol) were added. The reaction mixture was warmed to 25 °C and stirred for 18 h. The dioxane was removed *in vacuo* and the reaction mixture was basified to pH 12 with 1 N NaOH. The aqueous layer was extracted with dichloromethane (3x 150 mL), then acidified to pH~1 with 6 N HCl. The aqueous layer was extracted with dichloromethane (3 x 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give the compound as a tan oil (13.7 g, 73.9% yield). LRMS (ESI) *m/z* 244 $[(M+H)^+$; calcd for $C_{12}H_{22}NO_4$ 244].

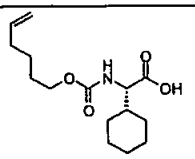
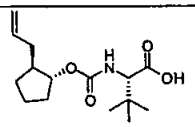
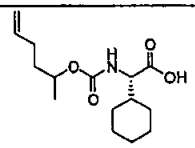
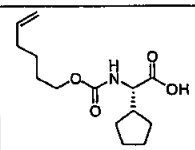
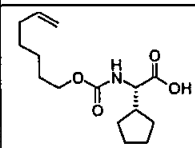
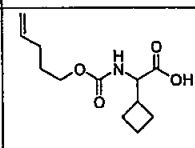
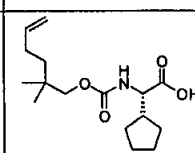
The following carbamate intermediates (B3-B49) were prepared using the chemistry described for the preparation of (2S)-3,3-dimethyl-2-{[(pent-4-en-1-yloxy)carbonyl]amino}butanoic acid (B2), by utilizing the appropriate amino acid and alcohol or the preparation of *N*-[(Pent-4-en-1-yloxy)carbonyl]-L-norleucine (B1) by utilizing the appropriate alcohol and amino ester.

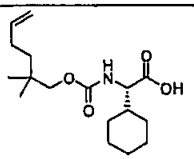
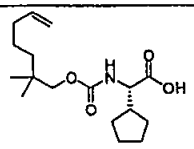
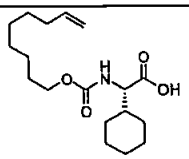
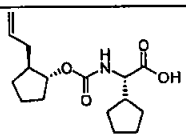
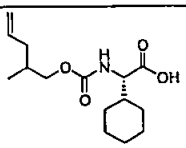
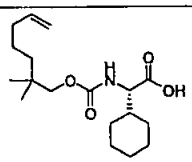
Int	Amino Acid	Alcohol	Structure	Name	LRMS $(M+H)^+$
B1	L-Norleucine	4-Penten-1-ol		*N*-[(Pent-4-en-1-yloxy)carbonyl]-L-norleucine (Intermediate 1)	244.3
B2	L-*t*-Butyl-glycine	4-Penten-1-ol		(2S)-3,3-Dimethyl-2-{[(pent-4-en-1-yloxy)carbonyl]amino}butanoic acid	244.2

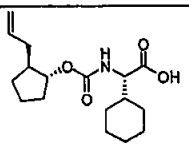
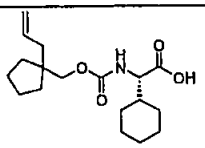
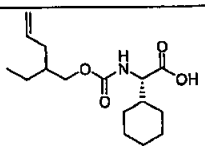
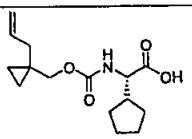
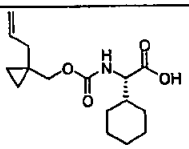
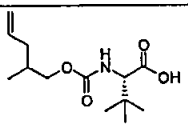
B3	L-Valine	4-Penten-1-ol		*N*-[(Pent-4-en-1-yloxy)carbonyl]-L-valine	230.3
B4	L-*t*-Butyl-glycine	3,3-Dimethyl-4-penten-1-ol Ref: *Tetrahedron Lett.* (**2004**), *45*, 2939.		*N*-{[(2,2-Dimethylpent-4-en-1-yl)oxy]carbonyl}-3-methyl-L-valine	272.3
B5	L-*t*-Butyl-glycine	5-Hexen-1-ol		*N*-[(Hex-5-en-1-yloxy)carbonyl]-3-methyl-L-valine	258.3
B6	L-Phenyl-glycine	4-Penten-1-ol		(2*S*)-{[(Pent-4-en-1-yloxy)carbonyl]amino}(phenyl)acetic acid	264.3
B7	L-*t*-Butyl-glycine	6-Hepten-1-ol		*N*-[(Hept-6-en-1-yloxy)carbonyl]-3-methyl-L-valine	272.3
B8	L-Cyclohexyl-glycine	4-Penten-1-ol		(2*S*)-Cyclohexyl{[(pent-4-en-1-yloxy)carbonyl]amino}acetic acid	270.3
B9	L-Phenyl alanine	4-Penten-1-ol		*N*-[(Pent-4-en-1-yloxy)carbonyl]-L-phenylalanine	278.2
B10	3,3,3-Trifluoroalanine	4-Penten-1-ol		3,3,3-trifluoro-*N*-[(pent-4-en-1-yloxy)carbonyl]alanine	256.2
B11	L-*t*-Butyl-glycine	4-Pentyn-1-ol		3-Methyl-*N*-[(pent-4-yn-1-yloxy)carbonyl]-L-valine	242.2

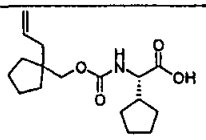
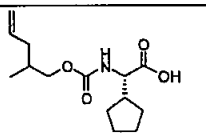
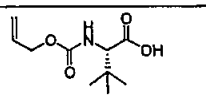
B12	L-Norvaline	4-Penten-1-ol		*N*-[(Pent-4-en-1-yloxy)carbonyl]-L-norvaline	230.3
B13	L-Cyclopentyl-glycine	4-Penten-1-ol		(2*S*)-Cyclopentyl{[(pent-4-en-1-yloxy)carbonyl]amino}acetic acid	256.3
B14	2-Amino-4,4,4-trifluorobutanoic acid	5-Hexen-1-ol		4,4,4-Trifluoro-2-{[(hex-5-en-1-yloxy)carbonyl]amino}butanoic acid	305.2 $(M+Na)^+$
B15	L-Leucine	4-Penten-1-ol		*N*-[(Pent-4-en-1-yloxy)carbonyl]-L-leucine	244.3
B16	L-Tryptophan	4-Penten-1-ol		*N*-[(Pent-4-en-1-yloxy)carbonyl]-L-tryptophan	317.4
B17	*O*-(*tert*-Butyl)- L-serine	4-Penten-1-ol		*O*-(*tert*-Butyl)-*N*-[(pent-4-en-1-yloxy)carbonyl]-L-serine	218.3 $(M-tBu)^+$
B18	6,6,6-trifluoronorleucine	5-Hexen-1-ol		6,6,6-Trifluoro-*N*-[(hex-5-en-1-yloxy)carbonyl]norleucine	353.2 $(M+MeCN)^+$
B19	Amino(2,3-dihydro-1*H*-inden-2-yl)acetic acid	4-Penten-1-ol		2,3-Dihydro-1*H*-inden-2-yl{[(pent-4-en-1-yloxy)carbonyl]amino}acetic acid	304.3

B20	L-*t*-Butyl-glycine	(trans)-2-allylcyclohexanol Ref: *Tetrahedron* (**2004**), *60*, 4837.		*N*-({[(trans)-2-Allylcyclohexyl]oxy}carbonyl)-3-methyl-L-valine	298.4
B21	L-Cyclohexyl-glycine	3-Buten-1-ol		(2*S*)-{[(But-3-en-1-yloxy)carbonyl]amino}(cyclohexyl)acetic acid	256.2
B22	L-*t*-Butyl-glycine	3-Buten-1-ol		*N*-[(But-3-en-1-yloxy)carbonyl]-3-methyl-L-valine	230.3
B23	L-Cyclohexyl-glycine	2,2-Dimethyl-4-penten-1-ol Ref: *Tetrahedron Lett.* (**2004**), *45*, 2939.		(2*S*)-Cyclohexyl({[(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl}amino)acetic acid	298.3
B24	L-Cyclopentyl-glycine	2,2-Dimethyl-4-penten-1-ol Ref: *Tetrahedron Lett.* (**2004**), *45*, 2939.		(2*S*)-Cyclopentyl({[(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl}amino)acetic acid	284.3
B25	L-*t*-Butyl-glycine	2,2-Dimethylhex-5-en-1-ol Ref: *J. Org. Chem.* (**1991**), *56*, 1623.		*N*-{[(2,2-Dimethylhex-5-en-1-yl)oxy]carbonyl}-3-methyl-L-valine	286.3
B26	L-Cyclohexyl-glycine	6-Hepten-1-ol		(2*S*)-Cyclohexyl{[(hept-6-en-1-yloxy)carbonyl]amino}acetic acid	298.3
B27	L-*t*-Butyl-glycine	7-Octen-1-ol		3-Methyl-*N*-[(oct-7-en-1-yloxy)carbonyl]-L-valine	286.3

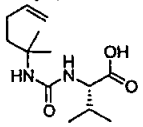
B28	L-Cyclohexyl-glycine	5-Hexen-1-ol		(2*S*)-Cyclohexyl{[(hex-5-en-1-yloxy)carbonyl]amino}acetic acid	284.4
B29	L-*t*-Butyl-glycine	(trans)-2-Allyl cyclopentanol Ref: *J. Chem. Soc., Perkin Trans 1* (**1994**), *11*, 1377.		*N*-({[(trans)-2-Allylcyclopentyl]oxy}carbonyl)-3-methyl-L-valine	284.2
B30	L-Cyclohexyl-glycine	1-Methylpent-4-en-1-ol Ref: *Tetrahedron Assym.* (**1998**), *9*, 657.		(2*S*)-Cyclohexyl({[(1-methylpent-4-en-1-yl)oxy]carbonyl}amino)acetic acid	284.2
B31	L-Cyclopentyl-glycine	5-Hexen-1-ol		(2*S*)-Cyclopentyl{[(hex-5-en-1-yloxy)carbonyl]amino}acetic acid	270.3
B32	L-Cyclopentyl-glycine	6-Hepten-1-ol		(2*S*)-Cyclopentyl{[(hept-6-en-1-yloxy)carbonyl]amino}acetic acid	284.4
B33	L-Cyclobutyl-glycine	4-Penten-1-ol		Cyclobutyl{[(pent-4-en-1-yloxy)carbonyl]amino}acetic acid	242.3
B34	L-Cyclopentyl-glycine	2,2-Dimethylhex-5-en-1-ol Ref: *J. Org. Chem.* (**1991**), *56*, 1623.		(2*S*)-Cyclopentyl({[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl}amino)acetic acid	298.3

B35	L-Cyclohexyl-glycine	2,2-Dimethylhex-5-en-1-ol Ref: *J. Org. Chem.* (**1991**), *56*, 1623.		(2*S*)-Cyclohexyl({[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl}amino)acetic acid	312.3
B36	L-Cyclopentyl-glycine	2,2-Dimethylhept-6-en-1-ol Ref: *J. Org. Chem.* (**1980**), *45*, 2685.		(2*S*)-Cyclopentyl({[(2,2-dimethylhept-6-en-1-yl)oxy]carbonyl}amino)acetic acid	312.2
B37	L-Cyclohexyl-glycine	8-Nonen-1-ol		(2*S*)-Cyclohexyl{[(non-8-en-1-yloxy)carbonyl]amino}acetic acid	326.3
B38	L-Cyclopentyl-glycine	(trans)-2-Allyl cyclopentanol Ref: *J. Chem. Soc., Perkin Trans 1* (**1994**), *11*, 1377.		(2*S*)-[({[(trans)-2-Allylcyclopentyl]oxy}carbonyl)amino](cyclopentyl)acetic acid	296.4
B39	L-Cyclohexyl-glycine	2-Methylpent-4-en-1-ol Ref: *Tetrahedron* (**1993**), *49*, 947.		(2*S*)-Cyclohexyl({[(2-methylpent-4-en-1-yl)oxy]carbonyl}amino)acetic acid	284.4
B40	L-Cyclohexyl-glycine	2,2-Dimethylhept-6-en-1-ol Ref: *J. Org. Chem.* (**1980**), *45*, 2685.		(2*S*)-Cyclohexyl({[(2,2-dimethylhept-6-en-1-yl)oxy]carbonyl}amino)acetic acid	326.4

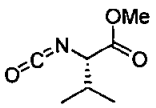
B41	L-Cyclohexyl-glycine	(trans)-2-Allyl cyclopentanol Ref: *J. Chem. Soc., Perkin Trans 1* (**1994**), *11*, 1377.		(2*S*)-[({[(trans)-2-Allylcyclopentyl]oxy} carbonyl)amino](cyclohexyl) acetic acid	310.5
B42	L-Cyclohexyl-glycine	(1-Allyl cyclopentyl) methanol Ref: *J. Org. Chem.* (**1992**), *57*, 1727.		(2*S*)-({[(1-Allylcyclopentyl)methoxy] carbonyl}amino) (cyclohexyl)acetic acid	324.3
B43	L-Cyclohexyl-glycine	2-Ethylpent-4-en-1-ol Ref: *Tetrahedron Lett.* (**1985**), *26*, 6085.		(2*S*)-Cyclohexyl({[(2-ethylpent-4-en-1-yl)oxy]carbonyl}amino) acetic acid	298.2
B44	L-Cyclopentyl-glycine	(1-Allyl cyclopropyl) methanol Ref: *Helv. Chim. Acta* (**1986**), *69*, 1655.		(2*S*)-({[(1-Allylcyclopropyl)methoxy]carbonyl}amino)(cyclopentyl)acetic acid	282.3
B45	L-Cyclohexyl-glycine	(1-Allyl cyclopropyl) methanol Ref: *Helv. Chim. Acta* (**1986**), *69*, 1655.		(2*S*)-({[(1-Allylcyclopropyl)methoxy]carbonyl}amino)(cyclohexyl)acetic acid	296.3
B46	L-*t*-Butyl-glycine	2-Methylpent-4-en-1-ol Ref: *Tetrahedron* (**1993**), *49*, 947.		3-Methyl-*N*-{[(2-methylpent-4-en-1-yl)oxy]carbonyl}-L-valine	258.3

B47	L-Cyclopentyl-glycine	(1-Allyl cyclopentyl) methanol Ref: *J. Org. Chem.* **(1992)**, *57*, 1727.		(2*S*)-({[(1-Allylcyclopentyl)methoxy] carbonyl}amino) (cyclopentyl)acetic acid	310.3
B48	L-Cyclopentyl-glycine	2-Methylpent-4-en-1-ol Ref: *Tetrahedron* **(1993)**, *49*, 947.		(2*S*)-Cyclopentyl({[(2-methylpent-4-en-1-yl)oxy]carbonyl}amino)acetic acid	270.2
B49	L-*t*-Butyl-glycine	Allyl alcohol		*N*-[(allyloxy)carbonyl]-3-methyl-L-valine	215.2

Intermediate B50: *N*-{[(1,1-Dimethylpent-4-en-1-yl)amino]carbonyl}-L-valine

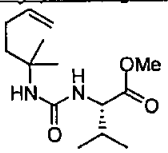


Step 1: Methyl *N*-(oxomethylene)-L-valinate



A mixture of L-valine methyl ester hydrochloride (10.0 g, 59.9 mmol), DCM (300 mL), and pyridine (19.3 mL, 240 mmol) was cooled in an ice / salt bath and a solution of 20% phosgene in toluene (35.6 mL, 719 mmol) added dropwise, maintaining the reaction temperature below 5°C during the addition. A white suspension resulted and after 1.5 h, the reaction mixture was poured into ice cold 1M hydrochloric acid and extracted with DCM (2 × 500mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and evaporated. Flash column chromatography on silica (95 hexane / 5 ethyl acetate) gave the title compound as a colorless oil (6.43g). ^{1}H NMR ($CDCl_3$ 500MHz) δ 3.94 (d, J = 4.0 Hz, 1 H), 3.82 (s, 3 H), 2.24 (m, 1 H), 1.03 (d, J = 7.0 Hz, 3 H), 0.90 (d, J = 6.5Hz, 3 H) ppm.

Step 2 : Methyl *N*-{[(1,1-dimethylpent-4-en-1-yl)amino]carbonyl}-L-valinate

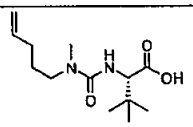
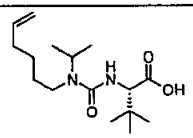


Methyl *N*-(oxomethylene)-L-valinate (2.80 g, 17.7 mmol) was added to 2-methylhex-5-en-2-amine [*J. Org. Chem.* (**1976**) *41*(5) 855-863.] (2.00 g, 17.7 mmol) in THF (15 mL). After 5 minutes, the reaction mixture was evaporated to give the title compound as a solid which was triturated with hexane and isolated by filtration (2.71g). LRMS $(M+H)^+ = 271.4$.

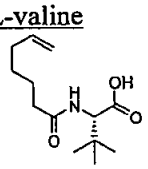
Step 3: *N*-{[(1,1-Dimethylpent-4-en-1-yl)amino]carbonyl}-L-valine (Intermediate B50)

1M lithium hydroxide (54 mL, 54 mmol) was added to *N*-{[(1,1-dimethylpent-4-en-1-yl)amino]carbonyl}-L-valine (2.94 g, 10.9 mmol) in THF (20 mL). The reaction mixture was stirred at RT under nitrogen for 18 hours then heated to reflux for 2 hours, cooled to room temperature and THF removed by evaporation. Water was then added and the mixture extracted with DCM (4×). The aqueous layer was made acidic with 1M hydrochloric acid and extracted with DCM (3 × 70 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent evaporated to give the title compound as a white foam (2.25 g). LRMS $(M+H)^+ = 257.3$.

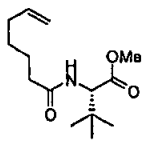
The following urea intermediates (B51-B52) were prepared using the chemistry described for the preparation of *N*-{[(1,1-dimethylpent-4-en-1-yl)amino]carbonyl}-L-valine (as described in Intermediate B50), by utilizing the appropriate amino acid and amine.

Int	Amino Acid	Amine	Structure	Name	LRMS $(M+H)^+$
B51	L-*t*-Butyl-glycine	*N*-Methylpent-4-en-1-amine		3-Methyl-*N*-{[methyl(pent-4-en-1-yl)amino]carbonyl}-L-valine	257.3
B52	L-*t*-Butyl-glycine	*N*-Isopropylhex-5-en-1-amine		*N*-{[Hex-5-en-1-yl(isopropyl)amino]carbonyl}-3-methyl-L-valine	299.3

Intermediate B53: N-Hept-6-enoyl-3-methyl-L-valine



Step 1: Methyl *N*-Hept-6-enoyl-3-methyl-L-valinate



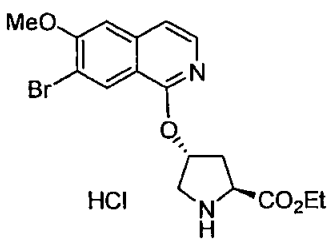
A solution of L-tert-leucine methyl ester (1.00 g, 6.89 mmol), 6-heptenoic acid (1.06 g, 8.26 mmol), EDC (1.58 g, 8.26 mmol) and HOAt (1.23 g, 8.26 mmol) in DMF (10 mL) was stirred at 22 °C for 2 h. The reaction mixture was diluted with aqueous saturated $NaHCO_3$ (30 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (3 x 30 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel, eluting with 5 - 50% EtOAc / hexane, to give the title product (1.42 g, 81%). LRMS (ESI) *m/z* 256.3 $[(M+H)^+$; calcd for $C_{14}H_{26}NO_3$: 256.2].

Step 2: N-Hept-6-enoyl-3-methyl-L-valine (Intermediate B53)

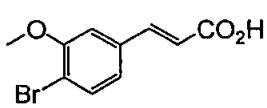
A solution of methyl *N*-hept-6-enoyl-3-methyl-L-valinate (1.40 g, 5.48 mmol) in THF (10 mL) and 1N NaOH (10 mL) was stirred at 22 °C for 2 h. The reaction mixture was acidified to pH 3 with 1 N HCl and extracted with EtOAc (3 x 150 mL). The combined EtOAc layers were washed with water (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated to give the title product (1.12 g, 84%). LRMS (ESI) *m/z* 242.3 $[(M+H)^+$; calcd for $C_{13}H_{24}NO_3$: 242.2].

Preparation of Intermediates C

Intermediate C1: Ethyl (4*R*)-4-[(7-bromo-6-methoxyisoquinolin-1-yl)oxy]-L-prolinate hydrochloride



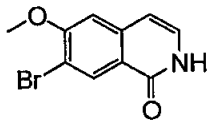
Step 1: (2E)-3-(4-Bromo-3-methoxyphenyl)acrylic acid



To a solution of 1-bromo-4-iodo-2-methoxybenzene (L. A. Hasvold et al, US 2004/0254159, EXAMPLE 57B) (33.45 g, 107 mmol) in MeCN (100 mL) was added acrylic acid (9.61 g,, 133 mmol), triethylamine (37.2 mL, 267 mmol) and palladium acetate (719 mg, 3.2 mmol). The reaction mixture was heated to 90 °C for 40 min, cooled to RT and poured into 2.4 L 1M HCl. After

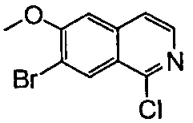
stirring for 30 min, the solid was filtered, heated to reflux in EtOH (230 mL), allowed to cool to RT and stirred overnight. The solid was filtered and washed with 1:1 EtOH hexane (50 mL) to give desired product. LRMS ESI$^+$ $(M+H)^+$ 257.0.

Step 2: 7-Bromo-6-methoxyisoquinolin-1(2H)-one



A portion of the product from Step 1 [(2E)-3-(4-bromo-3-methoxyphenyl)acrylic acid] (12.5 g, 48.6 mmol) was azeotroped with benzene and suspended in benzene (94 mL). Triethylamine (9.49 mL, 68.1 mmol) and diphenylphosphoryl azide (10.48 mL, 48.6 mmol) were added and the reaction mixture stirred at RT for 1 h. The mixture was filtered through a pad of silica and eluted with ~1 L of toluene, the volatiles evaporated, the residue resuspended in diphenylmethane (94 mL) and the mixture heated to reflux for three hours (internal temperature 250°C). The reaction mixture was allowed to cool to RT, stirred overnight, filtered and the solid washed with hexanes (100 mL) to give tan solid (7.4 g). LRMS ESI$^+$ $(M+H)^+$ 254.1.

Step 3: 7-Bromo-1-chloro-6-methoxyisoquinoline

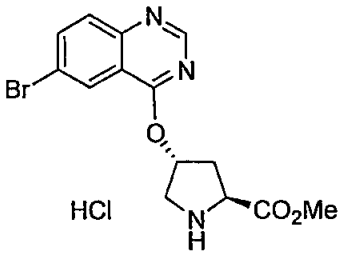


A mixture of the product from Step 2 (7-bromo-6-methoxyisoquinolin-1(2H)-one) (4.7 g, 18.5 mmol) in phosphorus oxychloride (30 mL) was heated to reflux for 2 h, cooled to RT, the volatiles evaporated and the residue partitioned between 3M NaOH and DCM. The organic phase was dried over Na_2SO_4, solvent evaporated and the solid triturated with Et_2O (20 mL) and filtered to give a solid (3.75 g). LRMS ESI$^+$ $(M+H)^+$ 274.0.

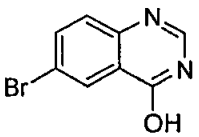
Step 4: Ethyl (4*R*)-4-[(7-bromo-6-methoxyisoquinolin-1-yl)oxy]-L-prolinate hydrochloride (Intermedate C1)

The title compound was prepared from the product of Step 3 (7-bromo-1-chloro-6-methoxyisoquinoline), utilizing the procedure described in EXAMPLE 10, Step 1. LRMS ESI$^+$ $(M+H)^+$ 395.0.

Intermediate C2: Methyl (4*R*)-4-[(6-bromoquinazolin-4-yl)oxy]-L-prolinate hydrochloride

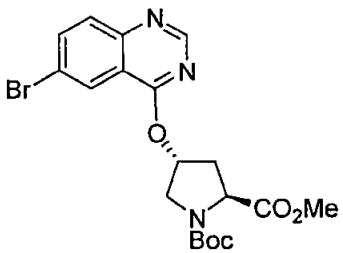


Step 1: 4-Hydroxy-6-bromoquinazoline



Bromoanthranilic acid (12.0 g, 55.5 mmol) and formamidine acetate (29.2 g, 281 mmol) were combined in acetic acid (96 mL) and heated to reflux for 2 h. The reaction mixture was cooled, concentrated to remove acetic acid and poured into water (500 mL). The reaction mixture was stirred for 0.5 h and resulting solids filtered. The solids were air dried to give a tan solid (12.0 g). LRMS $(M+H)^+ = 225.0$.

Step 2: 1-tert-Butyl 2-methyl (2S,4R)-4-[(6-bromoquinazolin-4-yl)oxy]pyrrolidine-1,2-dicarboxylate

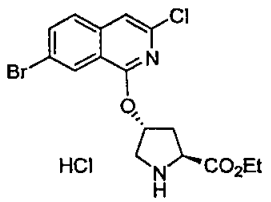


To a solution of N-boc-cis-hydroxyproline methyl ester (2.0 g, 8.15 mmol), 4-hydroxy-6-bromoquinazoline (1.84 g, 8.15 mmol) and triphenylphosphine (2.57 g, 9.79 mmol) at 0 °C in THF (80 mL) was added diisopropylazodicarboxylate (1.98 g, 9.79 mmol) dropwise. The mixture was stirred at 25 °C for 18 h. The reaction was diluted with EtOAc (100 mL), washed with 10% aqueous Na_2CO_3 (2 x 50 mL) and water (2 x 50 mL). The combined aqueous layers were backextracted with EtOAc (50 mL) and the combined EtOAc extracts dried over Na_2SO_4, filtered and concentrated to an oil. The oil was chromatographed on silica using 25 to 60% EtOAc/hexane to give the title compound (3.46 g). LRMS $(M+H)^+ = 452.2$.

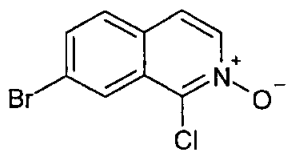
Step 3: Methyl (4*R*)-4-[(6-bromoquinazolin-4-yl)oxy]-L-prolinate hydrochloride (Intermedate C2)

To a solution of 1-tert-butyl 2-methyl (2S,4R)-4-[(6-bromoquinazolin-4-yl)oxy]pyrrolidine-1,2-dicarboxylate (3.46 g, 6.65 mmol) in dioxane (80 mL) at 0 °C was introduced anhydrous HCl (g) over 30 min. The reaction was complete by HPLC/MS. The reaction mixture was concentrated and the resulting solids were azeotroped with diethyl ether (50 mL) to give the title compound (3.0 g). LRMS $(M+H)^+ = 352.2$.

Intermediate C3: Ethyl (4*R*)-4-[(7-bromo-3-chloroisoquinolin-1-yl)oxy]-L-prolinate hydrochloride

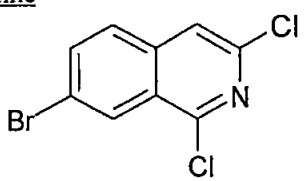


Step 1: 7-Bromo-1-chloroisoquinoline 2-oxide



To a solution of 7-bromo-1-chloroisoquinoline (4.0 g, 15.8 mmol) in DCM (100 mL) at 0 °C was added mCPBA (~77%, 7.46 g, 33.3 mmol). The reaction was allowed to stir at room temperature for 24 hours, diluted with DCM (100 mL) and washed with 1N NaOH and brine. The DCM extracts were dried over Na_2SO_4, filtered, concentrated and chromatographed on silica eluting with 5 to 15% acetone/DCM to give the title compound (1.43 g). LRMS $(M+H)^+ = 258.0$.

Step 2: 7-Bromo-1,3-dichloroisoquinoline

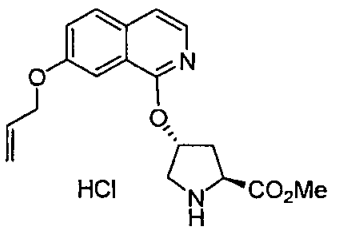


7-Bromo-1-chloroisoquinoline 2-oxide (1.43 g, 5.56 mmol) and $POCl_3$ (20 mL) were heated at reflux for 2 h. The reaction mixture was cooled and carefully poured onto a mixture of ice/water (500 g), stirred for 1 h and the pH adjusted to 10.0 with 10M NaOH. The mixture was extracted with chloroform (2x100 mL) and the chloroform extracts washed with brine, dried over $MgSO_4$, filtered and concentrated to give the title compound (1.40 g). LRMS $(M+H)^+ = 276.0$.

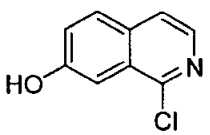
Step 3: Ethyl (4*R*)-4-[(7-bromo-3-chloroisoquinolin-1-yl)oxy]-L-prolinate hydrochloride (Intermediate C3)

Ethyl (4*R*)-4-[(7-bromo-3-chloroisoquinolin-1-yl)oxy]-L-prolinate hydrochloride was prepared from 7-bromo-1,3-dichloroisoquinoline according to the procedure for EXAMPLE 10, Step 1. LRMS $(M+H)^+ = 399.1$.

Intermediate C4: Methyl (4*R*)-4-{[7-(allyloxy)isoquinolin-1-yl]oxy}-L-prolinate

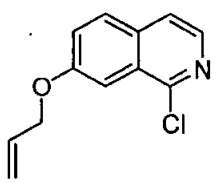


Step 1: 1-Chloroisoquinolin-7-ol



7-Bromo-1-chloroisoquinoline (2.0 g, 8.25 mmol), bis(pinacolato)diboron (2.20 g, 8.66 mmol), potassium acetate (2.43 g, 24.7 mmol) and $PdCl_2$(dppf)DCM adduct (0.337 g, 0.412 mmol) were combined under nitrogen in dioxane (40 mL) and heated in an oil bath at 100 °C for 24 h. The reaction mixture was cooled, diluted with EtOAc (100 mL) and washed with 10% aqueous $KHSO_4$. The organic phase was dried over Na_2SO_4, filtered and concentrated to an oil. The oil was dissolved in acetone (100 mL) and a solution of Oxone (5.07 g, 8.25 mmol) in water (20 mL) added over 2 min. The reaction mixture was stirred for 10 min, diluted with aqueous sodium bisulfate solution and stirred for an additional 20 min. and then concentrated to remove acetone. The resulting mixture was filtered to give the title compound (1.4 g) which was used without further purification. LRMS $(M+H)^+ = 180.1$.

Step 2: 7-(Allyloxy)-1-chloroisoquinoline



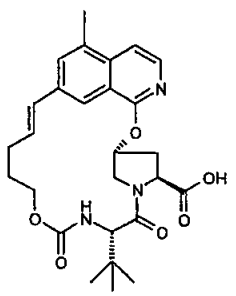
1-Chloroisoquinolin-7-ol (4.87 gm, 20,34 mmol) and cesium carbonate (6.63 g, 20.34 mmol) were combined in acetonitrile (100 mL) and stirred for 2 min. Allyl bromide (1.76 mL, 20.34 mmol) was added and the reaction mixture stirred for 30 min. The reaction mixture was diluted with aqueous $KHSO_4$ (40 mL) and EtOAc (100mL) and stirred. The organic extract was removed, dried over Na_2SO_4, concentrated and chromatographed on silica gel using 20-50% EtOAc/hexanes to give 0.85 g of an oil which solidified upon storing in the freezer. LRMS $(M+H)^+ = 220.1$.

Step 3: Methyl (4*R*)-4-{[7-(allyloxy)isoquinolin-1-yl]oxy}-L-prolinate (Intermedate C4)

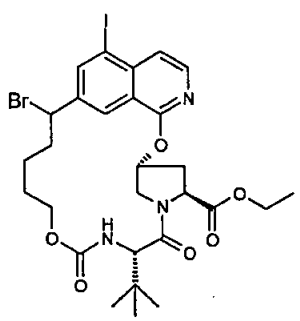
Intermediate C4 was prepared according to the procedure described in Example 10 Step 1, using 7-(allyloxy)-1-chloroisoquinoline. LRMS $(M+H)^+ = 329.3$.

Preparation of Intermediates D

Intermediate D1: (2R,4S,7S)-7-tert-Butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid



Step 1: Ethyl (2R,4S,7S)-15-bromo-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



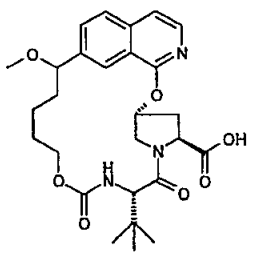
Ethyl (2R,4S,7S)-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 13, Step 1) (120 mg, 0.188 mmol) was dissolved in carbon tetrachloride (3 mL),

followed by the addition of N-bromosuccinimide (37 mg, 0.207 mmol) and catalytic benzoyl peroxide (4 mg). The reaction mixture was heated to reflux under N_2 for 3 h, cooled and concentrated and the resulting residue was purified on silica gel (10-60% EtOAc in hexanes) to yield the title compound as a white foam (113 mg). LRMS $(M+H)^+$ = 716.4.

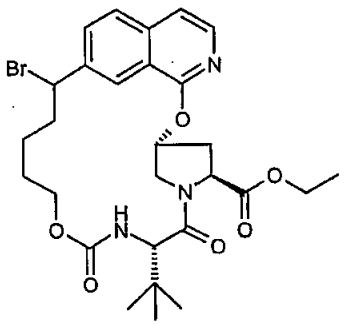
Step 2: (2R,4S,7S)-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid (Intermedate D1)

To a solution of the product from Step 1 (43 mg, 0.06 mmol) in THF (2 mL), under nitrogen, was added 1M potassium t-butoxide in THF (0.09 mL, 0.09 mmol), the reaction mixture stirred for 30 min and then a second portion of potassium t-butoxide (0.03 mL, 0.03 mmol) added. The reaction mixture was stirred for 45 min, diluted with water, acidified with 1N HCl and extracted with EtOAc (x2). The combined organics were washed with brine, dried over Na_2SO_4, filtered, concentrated, and azeotroped from Et_2O to yield the crude title compound as a dark yellow solid (36 mg). LRMS $(M+H)^+$ = 608.4.

Intermediate D2: (2R,4S,7S)-7-tert-Butyl-15-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid



Step 1: Ethyl (2R,4S,7S)-15-bromo-7-tert-butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate

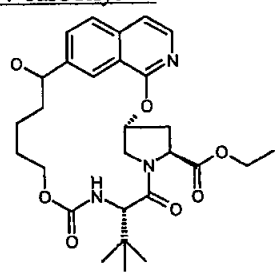


Ethyl (2R,4S,7S)-15-bromo-7-tert-butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate was prepared according to the procedure described for Intermediate D1, Step 1, starting with ethyl (2R,4S,7S)-7-tert-butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 11, Step 1). LRMS $(M+H)^+ = 590.5$.

Step 2: (2R,4S,7S)-7-tert-Butyl-15-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid (Intermedate D2)

A solution of the product from Step 1 (78 mg, 0.132 mmol) in MeOH (4 mL) was heated at 60 C for 6 h. Sodium hydroxide (1N, 0.528 mL, 0.528 mmol) was added and the reaction mixture was stirred for 4 h. The reaction mixture was concentrated and the resulting residue was partitioned between EtOAc and 1N HCl (x2). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield the title compound as a white foam (68 mg). LRMS $(M+H)^+ = 514.3$.

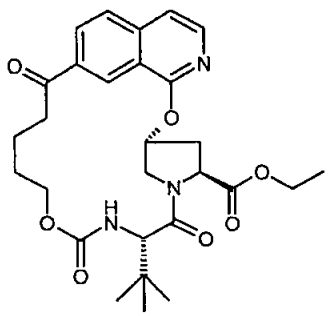
Intermediate D3: Ethyl (2R,4S,7S)-7-tert-butyl-15-hydroxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



To a solution of ethyl (2R,4S,7S)-15-bromo-7-tert-butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-

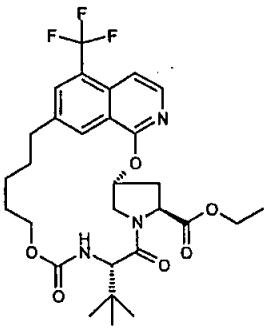
k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (Intermediate D2, Step 1) (89 mg, 0.151 mmol) in acetone (1 mL) was added a solution of silver nitrate (38 mg, 0.226 mmol) in H_2O (1mL). The reaction mixture was stirred in the dark for 16 h filtered, concentrated, and the resulting residue partitioned between DCM and H_2O (x3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified on silica gel (15% to 60% EtOAc in hexanes) to yield the title compound as a white foam (37 mg). LRMS $(M+H)^+ = 528.8$.

Intermediate D4: Ethyl (2R,4S,7S)-7-tert-butyl-6,9,15-trioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



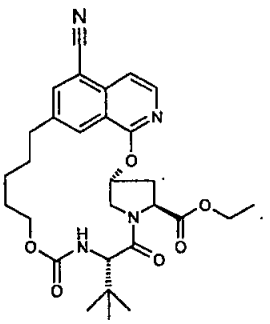
To a solution of ethyl (2R,4S,7S)-7-tert-butyl-15-hydroxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (Intermediate D3) (70 mg, 0.133 mmol) in DCM (3 mL) was added PCC (41 mg, 0.191 mmol) and the reaction mixture stirred for 4 h, filtered, concentrated, and the resulting residue purified on silica gel (0% to 5% acetone in DCM) to yield the title compound as a white solid (59 mg). LRMS $(M+H)^+ = 526.5$.

Intermediate D5: Ethyl (2R,4S,7S)-7-tert-butyl-6,9-dioxo-22-(trifluoromethyl)-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



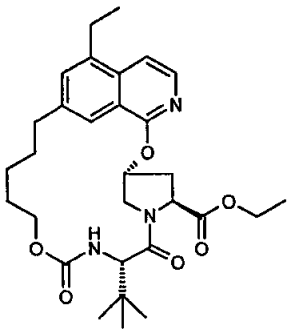
To a solution of ethyl (2R,4S,7S)-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 13, Step 1) (25 mg, 0.039 mmol) in DMF (1.5 mL) was added methyl fluorosulphonyldifluoroacetate (0.015 mL, 0.118 mmol) and copper (I) iodide (22 mg, 0.118 mmol). The mixture was heated to 150 °C in a microwave for 10 min, cooled, filtered, concentrated, and the resulting residue purified on silica gel (10% to 50% EtOAc in hexanes) to yield the title compound as a white solid (20 mg). LRMS $(M+H)^+ = 580.5$.

Intermediate D6: Ethyl (2R,4S,7S)-7-tert-butyl-22-cyano-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate

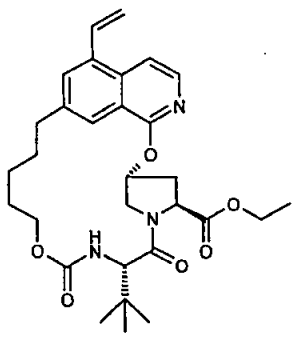


To a solution of ethyl (2R,4S,7S)-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 13, Step 1) (75 mg, 0.118 mmol) in DMF (1.5 mL) was added copper (I) cyanide (32 mg, 0.353 mmol) and the mixture heated to 150 °C in a sealed tube for 4 h. The reaction mixture was partitioned between EtOAc and saturated $NaHCO_3$ (x3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting crude material was purified on silica gel (10% to 50% EtOAc in hexanes) to yield the title compound as a white foam (40 mg). LRMS $(M+H)^+ = 537.4$.

Intermediate D7: Ethyl (2R,4S,7S)-7-tert-butyl-22-ethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



Step 1: Ethyl (2R,4S,7S)-7-tert-butyl-6,9-dioxo-22-vinyl-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



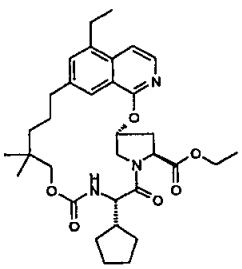
Nitrogen was bubbled through a solution of ethyl (2R,4S,7S)-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 13, Step 1) (90 mg, 0.141 mmol) in toluene (2 mL) for 30 min. Tributyl(vinyl)tin (0.049 mL, 0.169 mmol) and tetrakis(triphenylphosphine) palladium (0) (16 mg, 0.014 mmol) were added and the reaction mixture heated to reflux for 2 h. The cooled reaction mixture was concentrated and the residue purified by chromatography on silica gel (10% to 60% EtOAc in hexanes) to yield the title compound as a clear oil (58 mg). LRMS $(M+H)^+ = 538.5$.

Step 2: Ethyl (2R,4S,7S)-7-tert-butyl-22-ethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (Intermedate D7)

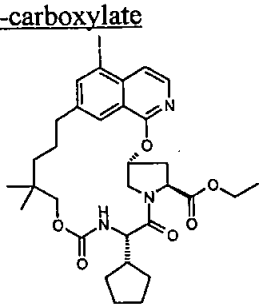
To a solution of ethyl (2R,4S,7S)-7-tert-butyl-6,9-dioxo-22-vinyl-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (58 mg, 0.108 mmol) in ethanol (5 mL) was added

10% palladium on carbon catalyst (20 mg). The reaction mixture was placed under a hydrogen balloon and stirred for 16 h. The reaction mixture was filtered, concentrated, and the title compound was obtained as white foam (46 mg). LRMS $(M+H)^+ = 540.5$.

Intermediate D8: Ethyl (2*R*,4*S*,7*S*)-7-cyclopentyl-22-ethyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



Step 1: Ethyl (2*R*,4*S*,7*S*)-7-cyclopentyl-22-iodo-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



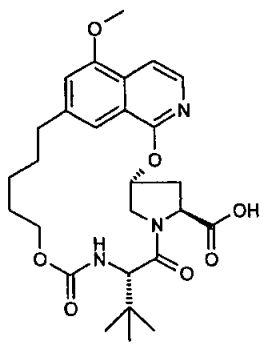
Ethyl (2*R*,4*S*,7*S*)-7-cyclopentyl-22-iodo-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate was prepared according to the procedure described for EXAMPLE 13, Step 1 using ethyl (2*R*,4*S*,7*S*)-7-cyclopentyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 15, Step 1). LRMS $(M+H)^+ = 678.3$.

Step 2: Ethyl (2*R*,4*S*,7*S*)-7-cyclopentyl-22-ethyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (Intermedate D8)

Ethyl (2*R*,4*S*,7*S*)-7-cyclopentyl-22-ethyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-

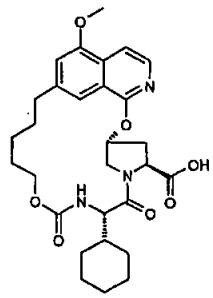
k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (Intermediate D8) was prepared according to the procedure described for Intermediate D7 using ethyl (2*R*,4*S*,7*S*)-7-cyclopentyl-22-iodo-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate. LRMS $(M+H)^+ = 580.3$.

Intermediate D9: (2R,4S,7S)-7-tert-butyl-22-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid

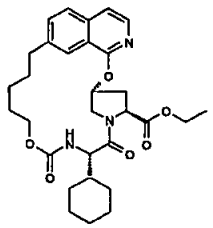


To a solution of ethyl (2R,4S,7S)-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 13, Step 1) (195 mg, 0.306 mmol) in MeOH (4 mL) was added sodium methoxide (30% in MeOH, 0.17 mL, 0.918 mmol) and copper (I) iodide (9 mg, 0.046 mmol). The reaction mixture was heated to 100 °C in the microwave for 20 min, cooled, sodium hydroxide (1N, 1.0 mL, 1.0 mmol) added and the reaction mixture was stirred for 4 h. The mixture was filtered, concentrated, and the residue partitioned between EtOAc and 1N HCl (x3). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield the crude title compound as a yellow oil. LRMS $(M+H)^+ = 514.4$.

Intermediate D10: (2*R*,4*S*,7*S*)-7-Cyclohexyl-22-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid

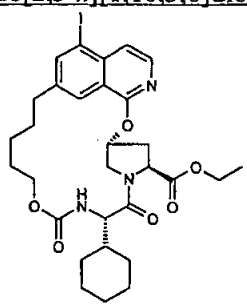


Step 1: Ethyl (2*R*,4*S*,7*S*)-7-cyclohexyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



Ethyl (2*R*,4*S*,7*S*)-7-cyclohexyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate was prepared using the procedures described in EXAMPLE 14, Steps 1-3 using Intermediate B8 in Step 1, followed by hydrogenation according to the procedure given in EXAMPLE 15, Step 1. LRMS $(M+H)^+ = 538.4$.

Step 2: Ethyl (2*R*,4*S*,7*S*)-7-cyclohexyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



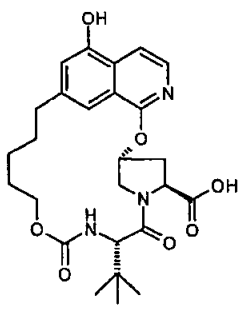
Ethyl (2*R*,4*S*,7*S*)-7-cyclohexyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate was prepared according to the procedure described for EXAMPLE 13, Step 1 using ethyl

(2*R*,4*S*,7*S*)-7-cyclohexyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate. LRMS $(M+H)^+$ = 664.4.

Step 3: (2*R*,4*S*,7*S*)-7-Cyclohexyl-22-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid (Intermediate D10)

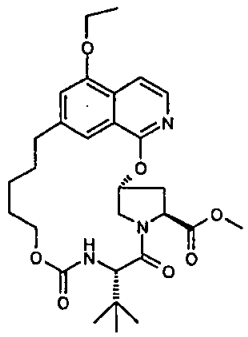
Intermediate D10 was prepared according to the procedure described for Intermediate D9 using ethyl (2*R*,4*S*,7*S*)-7-cyclohexyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate. LRMS $(M+H)^+$ = 540.4.

Intermediate D11: (2R,4S,7S)-7-tert-butyl-22-hydroxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid

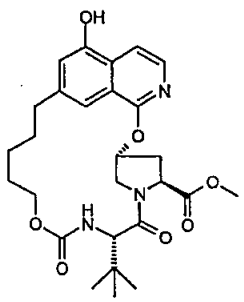


To a solution of (2R,4S,7S)-7-tert-butyl-22-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid (Intermediate D9) (53 mg, 0.103 mmol) in DCM (2 mL) was added boron tribromide (1M in DCM, 0.31 mL, 0.31 mmol) at -78 °C and the reaction mixture stirred for 1 h, then slowly warmed to RT and stirred for 1h. The reaction mixture was quenched with several drops of MeOH and H_2O and then concentrated. The residue was partitioned between EtOAc and 1N HCl (x3). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield the crude title compound as a gray solid (33 mg). LRMS $(M+H)^+$ = 500.3.

Intermediate D12: Methyl (2R,4S,7S)-7-tert-butyl-22-ethoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



Step 1: Methyl (2R,4S,7S)-7-tert-butyl-22-hydroxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



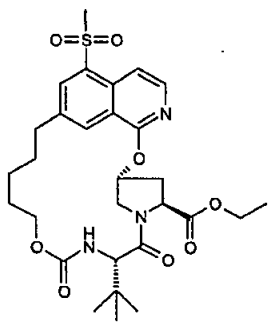
To a solution of (2R,4S,7S)-7-tert-butyl-22-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid (Intermediate D9) (53 mg, 0.103 mmol) in DCM (2 mL) was added boron tribromide (1M in DCM, 0.31 mL, 0.31 mmol) at -78 C and the reaction mixture was stirred for 1 h. Slowly warmed to RT and stirred for 1 h. The reaction was quenched with excess MeOH and then concentrated. The resulting residue was partitioned between EtOAc and 1N HCl. The layers were separated and the aqueous layer was extracted with EtOAc (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield the crude title compound as a gray solid (33 mg). LRMS $(M+H)^+ = 514.3$.

Step 2: Methyl (2R,4S,7S)-7-tert-butyl-22-ethoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (Intermedate D12)

To a solution of methyl (2R,4S,7S)-7-tert-butyl-22-hydroxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (254 mg, 0.495 mmol) in DMF (5 mL) was added

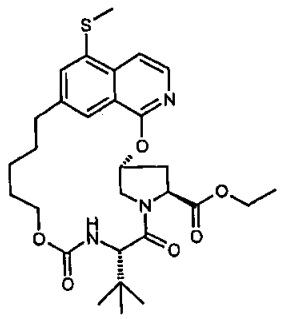
iodoethane (0.079 mL, 0.989 mmol) and DBU (0.185 mL, 1.24 mmol) and the reaction mixture stirred for 16 h. The reaction mixture was partitioned between EtOAc and 1N HCl. The layers were separated and the organic layer was washed with 1N HCl (2x), brine, dried over Na_2SO_4, filtered, and concentrated. The resulting crude compound was purified on silica gel (gradient elution 15% to 35% EtOAc in hexanes) to yield the title compound as a white foam (82 mg). LRMS $(M+H)^+ = 542.3$.

Intermediate D13: Ethyl (2R,4S,7S)-7-tert-butyl-22-(methylsulfonyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



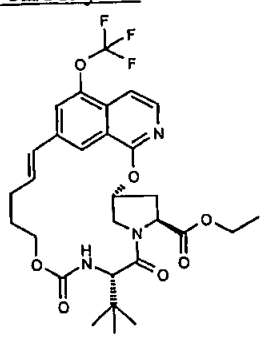
To a solution of ethyl (2R,4S,7S)-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 13, Step 1) (50 mg, 0.078 mmol) in DMSO (1 mL) was added sodium methanesulfinate (10 mg, 0.094 mmol), copper (I) trifluoromethanesulfonate toluene complex (1 mg, 0.004 mmol) and N,N'-dimethylethylendiamine (1 mg, 0.008 mmol). The reaction mixture was heated in a sealed tube at 110 °C for 16 h, cooled and partitioned between EtOAc and H_2O. The organic layer was washed with H_2O (2x), brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified on silica gel (25% to 60% EtOAc in hexanes) to yield the title compound as a white solid (23 mg). LRMS $(M+H)^+ = 590.3$.

Intermediate D14: Ethyl (2R,4S,7S)-7-tert-butyl-22-(methylthio)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



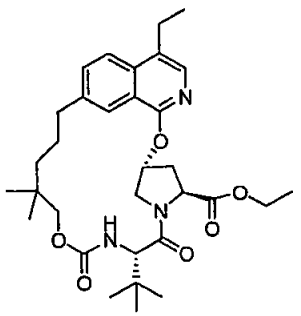
To a solution of ethyl (2R,4S,7S)-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 13, Step 1) (50 mg, 0.078 mmol) in pyridine (1 mL) was added dimethyldisulfide (0.004 mL, 0.039 mmol), and copper dust (1 mg, 0.016 mmol) and the mixture heated in a sealed tube at 100 °C for 16 h. The cooled reaction mixture was partitioned between EtOAc and 1N HCl and the layers were separated. The organic layer was washed with 1N HCl (2x), brine, dried over Na_2SO_4, filtered, and concentrated to yield the crude title compound as a yellow oil. LRMS $(M+H)^+$ = 558.4.

Intermediate D15: Ethyl (2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-6,9-dioxo-22-(trifluoromethoxy)-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate

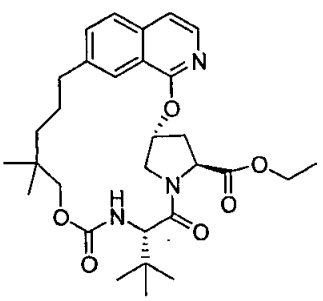


Ethyl (2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-6,9-dioxo-22-(trifluoromethoxy)-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate was prepared according to the procedures described for Intermediate C1 using 4-bromo-2-(trifluoromethoxy)iodobenzene in Step 1, followed by the procedures described in EXAMPLE 14, Steps 1-3 using Intermediate B2 in Step 1. LRMS $(M+H)^+$ = 596.3.

Intermediate D16: Ethyl (2R,4S,7S)-7-tert-butyl-19-ethyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate

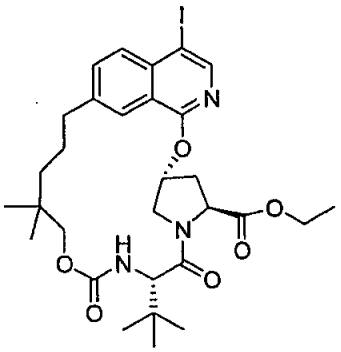


Step 1: Ethyl (2*R*,4*S*,7*S*)-7-*tert*-butyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



Ethyl (2*R*,4*S*,7*S*)-7-*tert*-butyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate was prepared using the procedure described for EXAMPLE 14, Steps 1-3 using Intermediate B4 in Step 1, followed by the hydrogenation procedure described in EXAMPLE 15, Step 1. LRMS $(M+H)^+ = 540.3$.

Step 2: Ethyl (2R,4S,7S)-7-tert-butyl-19-iodo-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



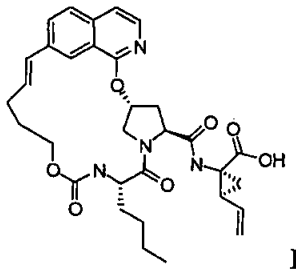
To a solution of ethyl (2*R*,4*S*,7*S*)-7-*tert*-butyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (0.5 g, 0.93 mmol) in DCM (5 mL) was added triflic acid (0.165 ml, 1.853 mmol) and N-iodosuccinimide (208 mg, 0.93 mmol) and the mixture stirred under N_2 for 16 h. An additional portion of NIS (208 mg, 0.93 mmol) was added and the reaction mixture was stirred for an additional 24 h. The reaction mixture was poured into saturated $NaHCO_3$ and extracted with DCM (2x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting crude compound was purified on silica gel (20% to 40% EtOAc in hexanes) to yield the title compound as a white foam (170 mg). LRMS $(M+H)^+ = 666.4$.

Step 3: Ethyl (2R,4S,7S)-7-tert-butyl-19-ethyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (Intermedate D16)

Ethyl (2R,4S,7S)-7-tert-butyl-19-ethyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate was prepared using the procedure described for Intermediate D7, Steps 1 and 2 using ethyl (2R,4S,7S)-7-tert-butyl-19-iodo-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate. LRMS $(M+H)^+ = 568.4$.

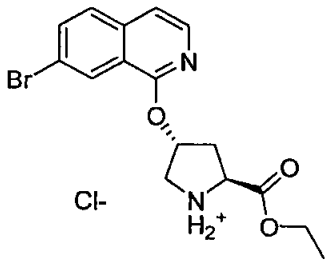
EXAMPLE 1

(1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-ethanediylidene-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid (III-1)



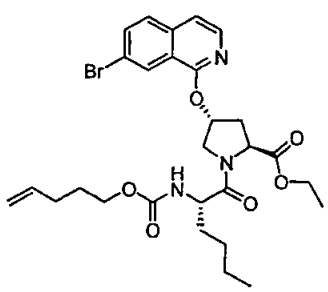
III-1

Step 1: Ethyl (4R)-4-[7-bromoisoquinolin-1-yl)oxy]-L-prolinate hydrochloride



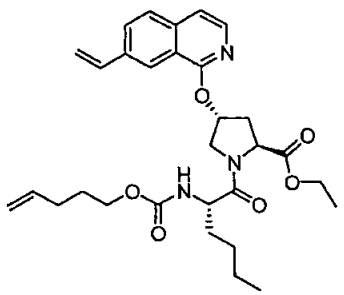
To a solution of trans 4-hydroxy L-BOC-proline (4.83 g, 20.9 mmol) in 100 mL DMSO at room temperature was added potassium t-butoxide (7.03 g, 62.66 mmol) in a single portion. The reaction mixture was stirred at r.t. for 30 min, cooled to 17 °C and 7-bromo-1-chloroisoquinoline (5.06 g, 20.9 mmol) added, the reaction allowed to warm to r.t. and stirred overnight. The reaction mixture was quenched with ice-cold 10% citric acid solution and partitioned with ethyl acetate. The organic layer was washed with aqueous citric acid solution, water and brine and the aqueous phases back extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate and the solvent evaporated to dark solid. The solid was dissolved in ethanol (120 mL), cooled to 0 °C and HCl bubbled through until the solution was saturated. The reaction mixture was then stirred at room temperature for 48 h and the volatiles evaporated under reduced pressure. The remaining solid was azeotroped with ethanol (4 x 100 mL) to give 11.95 g (>100% crude) of a gray solid used directly in the next step. LRMS (ESI) *m/z* 365 $[(M+H)^+$; calcd for $C_{16}H_{18}BrN_2O_3$: 365].

Step 2: Ethyl *N*-[(pent-4-en-1-yloxy)carbonyl]-l-norleucyl-(4R)-4-[(7-bromoisoquinolin-1-yl)oxy]-L-prolinate



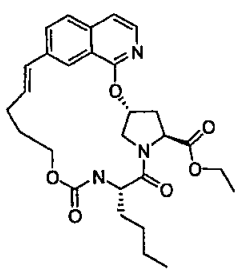
To a solution of crude ethyl (4R)-4-[7-bromoisoquinolin-1-yl)oxy]-L-prolinate hydrochloride (4 g, ~11 mmol) in DMF (30 mL) was added *N*-[(pent-4-en-1-yloxy)carbonyl]-L-norleucine (Intermediate B1) (4.0 g, 16.4 mmol), diisopropylethylamine (4.9 mL, 27 mmol) and TBTU (5.13 g, 16 mmol). The reaction mixture was stirred at room temperature overnight and partitioned between water and ethyl acetate. The organic layer was washed with water, saturated sodium bicarbonate solution, brine, dried over anhydrous sodium sulfate and the solvent was then evaporated. The crude product was purified by chromatography on silica (10-100% EtOAc hexane) to give desired product (3.3 g). LRMS (ESI) *m/z* 590 [$(M+H)^+$; calcd for $C_{28}H_{37}BrN_3O_6$: 590].

Step 3: Ethyl N-[(pent-4-en-1-yloxy)carbonyl]-L-norleucyl-(4R)-4-[(7-vinylisoquinolin-1-yl)oxy]-L-prolinate



The bromide from step 2 (62 mg, 0.105 mmol) was dissolved in 5 mL toluene and nitrogen bubbled through for 15 min. Tributylvinyltin (0.037 mL, 0.126 mmol) and tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.005 mmol) were added and the reaction mixture heated to 100 °C under nitrogen. After 5h, the reaction was complete, the volatiles were evaporated and the residue purified by silica gel chromatography (10-75% EtOAc / hexane) to give a clear oil. LRMS (ESI) *m/z* 538 [$(M+H)^+$; calcd for $C_{30}H_{40}N_3O_6$: 538].

Step 4: Ethyl (2R,4S,7S)-7-butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxodiazacyclononadecine-4-carboxylate



The olefin from Step 3 (40 mg, 0.074 mmol) was dissolved in dichloroethane (10 mL) and nitrogen bubbled through the solution for 15 min. Dichloro(5-chloro-2-isopropoxybenzylidene)(1,3-

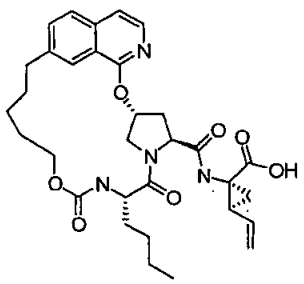
dimesitylimidazolidin-2-ylidene)ruthenium (Zhan ruthenium metathesis catalyst RC-301, Zhan Catalyst I (as depicted as J on page 35), RC-301, Zannan Pharma Ltd.) (5 mg, 0.007 mmol) was added and the reaction mixture heated in an 80 °C oil bath for 2 h, after which reaction was complete. Volatiles were evaporated and the residue purified by silica gel chromatography (10-75% EtOAc / hexane) to give the title compound (24 mg). LRMS (ESI) *m/z* 510 [$(M+H)^+$; calcd for $C_{28}H_{36}N_3O_6$: 510].

Step 5: (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-ethanediylidene-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid

The ester from Step 4 (24 mg, 0.047 mmol) was dissolved in THF (0.5 mL) and EtOH (0.5 mL) and a solution of LiOH in water (5 mg in 0.5 mL) was added. The reaction mixture was stirred at room temperature for 1.5 h after which HPLC analysis indicated complete reaction and 1M HCl (0.2 mL) was added and the mixture was evaporated to a solid. The solid was dissolved in DMF (2 mL) and (1R,2S)-1-amino-2-vinylcyclopropanecarboxylic acid ethyl ester hydrochloride (Intermediate A2)(Llinas-Brunet et al US6,323,180 and Wang et al WO 03/099274) ((4 mg, 0.019 mmol), diisopropylethylamine (0.017 mL, 0.095 mmol), and TBTU (6 mg, 0.019 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was purified directly by reverse phase HPLC to yield a white foam which was dissolved in THF (0.25 mL) and ethanol (0.25 mL) and a solution of LiOH in water (4.5 mg in 0.25 mL) was added. The reaction mixture was heated to 40 °C for 2 h, cooled to room temperature, 3M HCl (0.06 mL) and DMF (0.5 mL) were added and the reaction mixture was purified by reverse phase HPLC to give the desired product as solid. LRMS (ESI) *m/z* 591 [$(M+H)^+$; calcd for $C_{32}H_{39}N_4O_7$: 591].

EXAMPLE 2

(1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-Butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-ethanediylidene-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid (**III-2**)



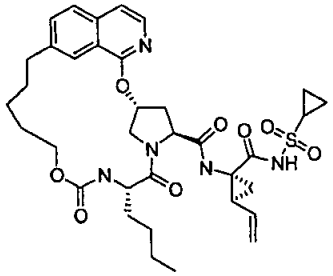
III-2

A solution of the olefin prepared as described in Example 1, Step 4 (180 mg, 0.353 mmol) in ethyl acetate (10 mL) was treated with 10% Pd/C and hydrogenated under a balloon of

hydrogen for 18 h. The catalyst was removed by filtration and the filtrate was evaporated to give an oil. The oil was treated as described in Example 1, Step 5 to afford the title compound. LRMS (ESI) *m/z* 593 [(M+H)$^+$; calcd for $C_{32}H_{40}N_4O_7$: 593].

EXAMPLE 3

(2R,4S,7S)-7-Butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,15,16-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (III-3)

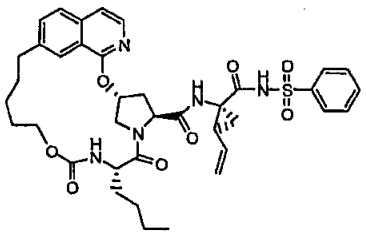


III-3

The title compound was prepared as described for Example 2, by using (1R,2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide hydrochloride (Intermediate A1)(Wang *et al* WO 03/099274) in place of (1R,2S)-1-amino-2-vinylcyclopropanecarboxylic acid ethyl ester hydrochloride in the coupling step. LRMS (ESI) *m/z* 696 [(M+H)$^+$; calcd for $C_{35}H_{45}N_5O_8S$: 696]. ^{1}H NMR (500 MHz, CD_3OD, ppm) δ 9.28 (s, 1 H), 7.97 (s, 1 H), 7.88 (d, *J* = 5.9 Hz, 1 H), 7.72 (d, *J* = 8.3 Hz, 1 H), 7.56 (dd, *J* = 8.3 and 1.7 Hz, 1 H), 7.28 (d, *J* = 5.9 Hz, 1 H), 6.13 (m, 1 H), 5.74 (m, 1 H), 5.27 (dd, *J* = 17.1 and 1.2 Hz, 1 H), 5.10 (dd, *J* = 10.3 and 1.5 Hz, 1 H), 4.65 (d, *J* = 11.2 Hz, 1 H), 4.53 (m, 1 H), 4.44 (t, *J* = 7.6 Hz, 1 H), 4.32 (m, 1 H), 3.99 (dd, *J* = 11.7 and 3.2 Hz, 1 H), 3.73 (m, 1 H), 2.96 (m, 1 H), 2.87 (m, 1 H), 2.71 (m, 1 H), 2.54 (m, 1 H), 2.28 (m, 1 H), 2.20 (m, 1 H), 1.60-1.90 (m, 6 H), 1.51 (m, 1 H), 1.12-1.40 (m, 10 H), 0.94 (t, *J* = 6.8 Hz, 3 H).

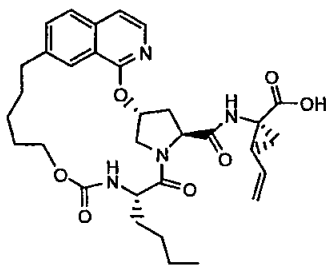
EXAMPLE 4

(2R,4S,7S)-7-Butyl-N-((1R,2S)-1-{[(phenylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (III-4)



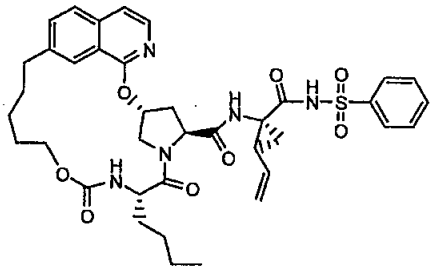
III-4

Step 1: (1R,2S)-1-({[(2R,4S,7S)-7-Butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyridine[2,3-k][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid



To a solution of the ethyl ester (initial hydrogenation product from Example 2) (400mg, 0.65 mmol) in tetrahydrofuran (10 mL), ethanol (5 mL) and water (5 mL) were added lithium hydroxide (155 mg, 6.45 mmol) and the mixture let stir at 40 °C for 24 h. The reaction was cooled, concentrated in vacuo to remove tetrahydrofuran and ethanol and diluted with 3N HCL (2.5 mL). The reaction was allowed to stir for 30 min and the resulting solids filtered and washed with water (1 mL). The solid was air dried to give the title compound as a white solid (0.44 g). LRMS (ESI) *m/z* 593 [$(M+H)^+$; calcd for $C_{32}H_{41}N_4O_7$: 593].

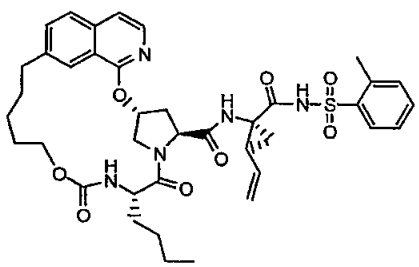
Step 2: (2R,4S,7S)-7-Butyl-6,9-dioxo-N-((1R,2S)-1-{[(phenylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyridine[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide



To a solution of the acid from Step 1 (30 mg, 0.05 mmol) in DMF (0.34 mL), under nitrogen, was added carbonyldiimidazole (13 mg, 0.078 mmol) and the mixture stirred at 40 °C for 2 hr. Benzenesulfonamide (12 mg, 0.078 mmol) was added and the reaction stirred overnight at 40 °C. The reaction was directly purified by reverse phase chromatography and the resulting product was concentrated in vacuo to give the title compound as a white solid (18 mg). LRMS (ESI) *m/z* 732 $[(M+H)^+$; calcd for $C_{38}H_{46}N_5O_8S$: 732].

EXAMPLE 5

(2R,4S,7S)- N-((1R,2S)-1-{[(2-methylphenylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-7-butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyridine[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (III-5)

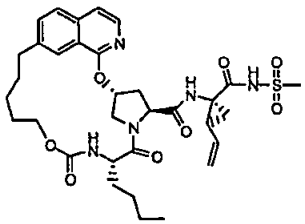


III-5

The title compound was prepared in a similar manner to that described in Example 4, replacing benzenesulfonamide with 2-methylphenylsulfonamide. LRMS (ESI) *m/z* 746 $[(M+H)^+$; calcd for $C_{39}H_{48}N_5O_8S$: 746].

EXAMPLE 6

(2R,4S,7S)-7-Butyl-N-((1R,2S)-1-{[(methylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (III-6)

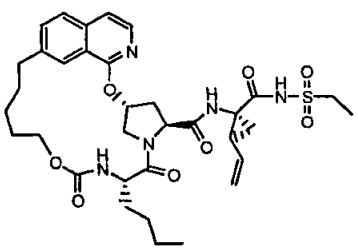


III-6

The title compound was prepared in a similar manner to that described in Example 4, replacing benzenesulfonamide with methanesulfonamide. LRMS (ESI) *m/z* 670 $[(M+H)^+$; calcd for $C_{33}H_{43}N_5O_8S$: 670].

EXAMPLE 7

(2R,4S,7S)-7-butyl-N-((1R,2S)-1-{[(ethylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (III-7)

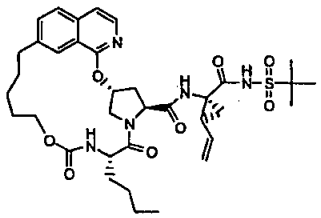


III-7

The title compound was prepared in a similar manner to that described in Example 4, replacing benzenesulfonamide with ethanesulfonamide. LRMS (ESI) *m/z* 684 $[(M+H)^+$; calcd for $C_{34}H_{46}N_5O_8S$: 684].

EXAMPLE 8

(2R,4S,7S)-7-Butyl-N-((1R,2S)-1-{[(t-butylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (III-8)



III-8

The title compound was prepared in a similar manner to that described in Example 4, replacing benzenesulfonamide with t-butylsulfonamide. LRMS (ESI) *m/z* 712 [$(M+H)^+$; calcd for $C_{36}H_{50}N_5O_8S$: 712].

EXAMPLE 9

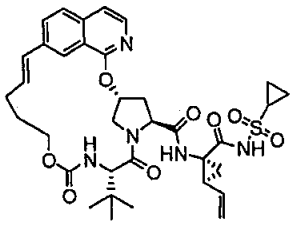
HCV NS3 protease time-resolved fluorescence (TRF) assay

The NS3 protease TRF assay was performed in a final volume of 100µl in assay buffer containing 50 mM HEPES, pH 7.5, 150 mM NaCl, 15 % glycerol, 0.15 % Triton X-100, 10 mM DTT, and 0.1 % PEG 8000. The NS3 protease was pre-incubated with various concentrations of inhibitors for 10-30 minutes. The peptide substrate for the assay is Ac-C(Eu)-DDMEE-Abu-[COO]-XSAK(QSY7)-NH2, where Eu is an europium-labeled group, Abu is 1-aminobutanoic acid which connects an ester linkage with 2-hydroxy propanoic acid (X). Hydrolysis of the peptide by NS3 protease activity causes in separation of the fluorophore from the quencher, resulting in an increase in fluorescence. Activity of the protease was initiated by adding the TRF peptide substrate (final concentration 50-100 nM). The reaction was quenched after 1 hour at room temperature with 100 µl of 500 mM MES, pH 5.5. Product fluorescence was detected using either a Victor V2 or Fusion fluorimeter (Perkin Elmer Life and Analytical Sciiences) with excitation at 340 nm and emission at 615 nm with 50-400 µs delay. Testing concentrations of different enzyme forms was selected with a signal to background ratio of 10-30. The inhibition constants were derived using a four-parameter fit.

Compounds **III-1** and **III-3** to **III-9, III-10, III-12, III-14, III-15, III-20, III-23, III-24, III-25, III-28, III-29, III-31, III-32, III-34, III-37, III-38, III-39 to III-46 and III-48 to III-185** were tested to have a Ki value of less than 100 nM in the NS3 protease TRF assay as described above.

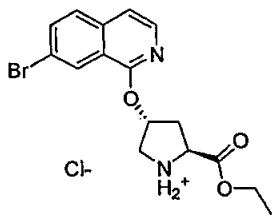
EXAMPLE 10

(1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-tert-Butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-ethanediylidene-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid (III-23)



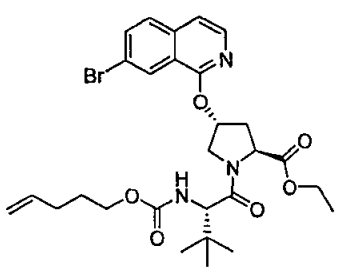
III-23

Step 1: Ethyl (4R)-4-[7-bromoisoquinolin-1-yl)oxy]-L-prolinate hydrochloride



To a solution of trans 4-hydroxy L-BOC-proline (4.83 g, 20.9 mmol) in 100 mL DMSO at room temperature was added potassium t-butoxide (7.03 g, 62.66 mmol) in a single portion. The reaction mixture was stirred at r.t. for 30 min, cooled to 17 °C and 7-bromo-1-chloroisoquinoline (5.06 g, 20.9 mmol) added, the reaction allowed to warm to r.t. and stirred overnight. The reaction mixture was quenched with ice-cold 10% citric acid solution and partitioned with ethyl acetate. The organic layer was washed with aqueous citric acid solution, water and brine and the aqueous phases back extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate and the solvent evaporated to dark solid. The solid was dissolved in ethanol (120 mL), cooled to 0°C and HCl bubbled through until the solution was saturated. The reaction mixture was then stirred at room temperature for 48 h and the volatiles evaporated under reduced pressure. The remaining solid was azeotroped with ethanol (4 x 100 mL) to give 11.95 g (>100% crude) of a gray solid used directly in the next step. LRMS (ESI) *m/z* 365 $[(M+H)^+$; calcd for $C_{16}H_{18}BrN_2O_3$: 365].

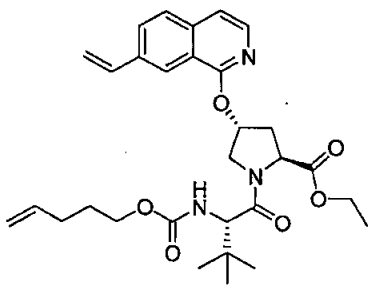
Step 2: Ethyl *N*-[(pent-4-en-1-yloxy)carbonyl]-l-tert-butyl-(4R)-4-[(7-bromoisoquinolin-1-yl)oxy]-L-prolinate



To a solution of crude ethyl (4R)-4-[7-bromoisoquinolin-1-yl)oxy]-L-prolinate hydrochloride (1.03 g, ~2.6 mmol) in DMF (10 mL) was added *N*-[(pent-4-en-1-yloxy)carbonyl]-L-tert-

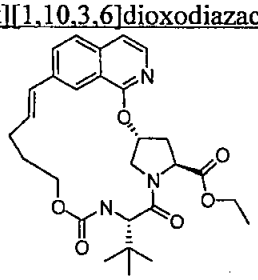
butylglycine (Intermediate B2) (0.44 g, 1.81 mmol), diisopropylethylamine (1.8 mL, 10.4 mmol) and TBTU (1.25 g, 3.9 mmol). The reaction mixture was stirred at room temperature overnight and partitioned between water and ethyl acetate. The organic layer was washed with water, saturated sodium bicarbonate solution, brine, dried over anhydrous sodium sulfate and the solvent was then evaporated. The crude product was purified by chromatography on silica (20-60% EtOAc hexane) to give desired product (0.9 g). LRMS (ESI) *m/z* 590 [$(M+H)^+$; calcd for $C_{28}H_{37}BrN_3O_6$: 590].

Step 3: Ethyl N-[(pent-4-en-1-yloxy)carbonyl]-L-tert-butylglycine-(4R)-4-[(7-vinylisoquinolin-1-yl)oxy]-L-prolinate



The bromide from step 2 (0.90 gm, 1.53 mmol) was dissolved in toluene (20 mL) and nitrogen bubbled through for 15 min. Tributylvinyltin (0.54 mL, 1.83 mmol) and tetrakis(triphenylphosphine)palladium(0) (178.0 mg, 0.153 mmol) were added and the reaction mixture heated to 100 °C under nitrogen. After 3h, the reaction was complete, the volatiles were evaporated and the residue purified by silica gel chromatography (20-50% EtOAc / hexane) to give a clear oil. LRMS (ESI) *m/z* 538 [$(M+H)^+$; calcd for $C_{30}H_{40}N_3O_6$: 538].

Step 4: Ethyl (2R,4S,7S)-7-tert-butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxodiazacyclononadecine-4-carboxylate



The olefin from Step 3 (1.0 gm, 1.86 mmol) was dissolved in dichloromethane (200 mL) and nitrogen bubbled through the solution for 30 min. Bis(tricyclohexylphosphine)-3-phenyl-1H-indene-1ylideneruthenium dichloride (Neolyst M1 catalyst, Strem Chemicals, CAS#250220-36-1) (300 mg, 0.30 mmol) dissolved in degassed dichloromethane was added over 30 minutes and the reaction let stir 24hrs or until complete. Volatiles were evaporated and the residue purified by silica gel chromatography (20-

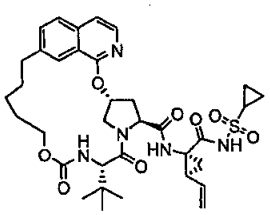
60% EtOAc / hexane) to give the title compound (0.73 gm). LRMS (ESI) *m/z* 510 [(M+H)$^+$; calcd for $C_{28}H_{36}N_3O_6$: 510].

Step 5: (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-tert-Butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-ethanediylidene-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid

The ester from Step 4 (0.73 gm, 0.1.43 mmol) was dissolved in THF (20 mL) and EtOH (10 mL) and a solution of LiOH in water (257 mg in 10 mL) was added. The reaction mixture was stirred at room temperature for 1.5 h after which HPLC analysis indicated complete reaction and 3M HCl (5.0 mL) was added and the mixture was evaporated to a solid. The solid was dissolved in ethyl acetate (20 mL) and water (20 mL) (pH~2.0) and ethyl acetate layer separated, dried over sodium sulfate, filtered and concentrated to a foam. The foam was dissolved in dichloromethane (40 mL) and cyclopropanesulfonic acid (1-(R)-amino-2-(S)-vinyl-cyclopropanecarbonyl)-amide hydrochloride salt (A1)(0.419 mg, 1.58 mmol) (Llinas-Brunet et al US03/15755 and Wang et al WO 03/099274), diisopropylethylamine (0.75 mL, 4.30 mmol), dimethylaminopyridine (0.087 gm, 0.72 mmol) and HATU (0.65 gm, 1.72 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was purified directly by reverse phase HPLC to yield the desired product as a solid. LRMS (ESI) *m/z* 694 [(M+H)$^+$; calcd for $C_{35}H_{44}N_5O_8S$: 694]. ^{1}H NMR (500 MHz, ppm) (d_6-DMSO) δ 10.40 (s, 1 H), 8.70 (s, 1 H), 8.45 (s, 1 H), 7.95 (d, *J* = 5.9 Hz, 1 H), 7.81 (d, *J* = 8.3 Hz, 1 H), 7.61 (dd, *J* = 8.6 and 1.7 Hz, 1 H), 7.35 (d, J = 5.9 Hz, 1 H), 7.25 (d, *J* = 7.32 Hz, 1 H), 6.62 (d, *J* = 15.9 Hz, 1 H), 6.39 (m, 1 H), 5.68 (s, 1 H), 5.56 (m, 1 H), 5.17 (d, *J* = 18.1 Hz, 1 H), 5.06 (d, *J* = 11.5 Hz, 1 H), 4.52 (d, *J* = 11.2 Hz, 1 H), 4.31 (m, 3 H), 3.95 (m, 1 H), 3.86 (dd, 1 H, J = 11.5 and 2.9 Hz), 2.92 (m, 1 H), 2.61 (m, 1 H), 2.95 (m, 2 H), 2.10 (m, 2 H), 1.85 (m, 1 H), 1.75 (m, 1 H), 1.66 (m, 1 H), 1.28 (m, 1 H), 1.00-1.15 (m, 4 H), 1.04 (s, 9 H).

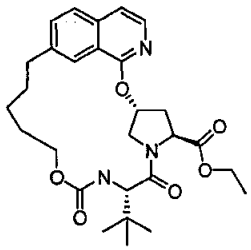
EXAMPLE 11

(2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (III-9)



III-9

Step 1: Ethyl (2R,4S,7S)-7-tert-butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



The ester from Example 10, Step 4 (512 mg, 1.00 mmol) was dissolved in ethyl acetate (40 mL) degassed with nitrogen and 10% palladium on carbon added (50 mg). The mixture was then purged with hydrogen 3 times and let stir under a hydrogen balloon for 24h. The reaction was filtered, concentrated in vacuo to give the compound (493 mg) as a foam. LRMS (ESI) *m/z* 512 [$(M+H)^+$; calcd for $C_{28}H_{38}N_3O_6$: 512].

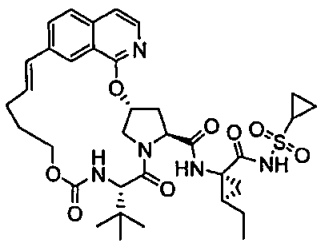
Step 2: (2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide

The title compound was prepared in a similar manner as described for the preparation of Example 10 Step 5 utilizing the ester from Step 1. LRMS (ESI) *m/z* 696 [$(M+H)^+$; calcd for $C_{35}H_{46}N_5O_8S$: 696].

^{1}H NMR (500 MHz, ppm, $CDCl_3$) δ 9.88 (s, 1 H), 7.92 (d, *J* = 7.1 Hz, 1 H), 7.78 (s, 1 H), 7.65 (d, *J* = 10.6 Hz, 1 H), 7.49 (dd, *J* = 10.7 and 1.6 Hz, 1 H), 7.30 (d, *J* = 7.1 Hz, 1 H), 7.19 (s, 1 H), 6.22 (m, 1 H), 5.76 (m, 1 H), 5.65 (d, *J* = 11.7, 1 H), 5.26 (d, *J* = 18.8 Hz, 1 H), 5.15 (d, *J* = 11.2 Hz, 1 H), 4.62 (m, 1 H), 4.46 (m, 3 H), 3.92 (dd, 1 H, J = 11.2 and 2.9 Hz), 3.73 (m, 1 H), 2.90 (m, 2 H), 2.70 (m, 1 H), 2.62 (m, 1 H), 2.51 (m, 1 H), 2.10 (m, 1 H), 1.96 (m, 1 H), 1.72 (m, 3 H), 1.48 (m, 2 H), 1.20-1.35 (m, 4 H), 1.07 (s, 9 H), 1.01 (m, 2 H).

EXAMPLE 12

(2R,4S,7S)-7-tert-butyl-N-((1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (III-37)

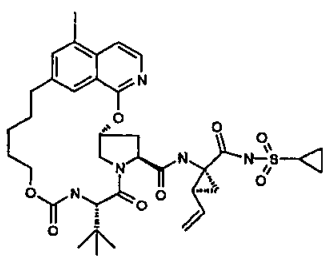


III-37

The title compound was prepared in a similar manner as described for the preparation of Example 10 Step 5 utilizing (1R,2R)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropanaminium chloride (Intermediate A3). LRMS (ESI) *m/z* 696 $[(M+H)^+$; calcd for $C_{35}H_{46}N_5O_8S$: 696]. ^{1}H NMR (500 MHz, ppm) (d_6-DMSO) δ 10.28 (s, 1 H), 8.66 (s, 1 H), 8.45 (s, 1 H), 7.94 (d, *J* = 5.9 Hz, 1 H), 7.81 (d, *J* = 8.3 Hz, 1 H), 7.62 (dd, *J* = 8.3 and 1.7 Hz, 1 H), 7.35 (d, *J* = 5.9 Hz, 1 H), 7.23 (d, *J* = 7.32 Hz, 1 H), 6.62 (d, *J* = 15.6 Hz, 1 H), 6.39 (m, 1 H), 5.68 (m, 1 H), 4.52 (d, *J* = 11.0 Hz, 1 H), 4.31 (m, 3 H), 3.95 (m, 1 H), 3.86 (dd, *J* = 11.7 and 3.2 Hz, 1 H), 2.93 (m, 1 H), 2.55 (m, 1 H), 2.28 (m, 2 H), 2.08 (m, 1 H), 1.84 (m, 1 H), 1.75 (m, 1 H), 1.46 (m, 1 H), 1.24-1.38 (m, 3 H), 1.00-1.15 (m, 5 H), 1.04 (s, 9 H), 0.85 (t, *J* = 7.3 Hz, 3 H).

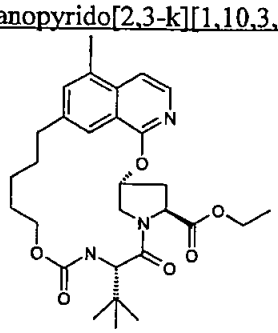
EXAMPLE 13

(2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (III-38)



III-38

Step 1: Ethyl (2R,4S,7S)-7-tert-butyl-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



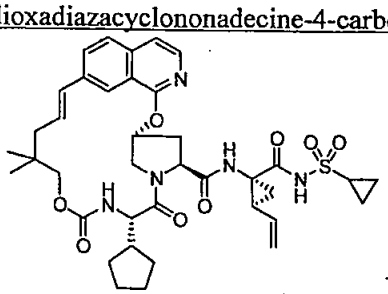
The ester from Example 11, Step 1 (0.79 gm, 1.55 mmol) was dissolved in triflic acid (5 mL) and added N-iodosuccinimide (0.90 gm, 4.0 mmol) in 4 portions over 4 h. Reaction was poured into a cold mixture of ethyl acetate and saturated sodium bicarbonate solution. Layers were separated and the organic layer was washed with saturated sodium bicarbonate solution and brine. Organics were dried over anhydrous sodium sulfate and the solvent was then evaporated to yield a crude oil. The crude product was purified by chromatography on silica (10-50% EtOAc hexane) to give the title compound (0.76 gm). LRMS (ESI) *m/z* 638 [$(M+H)^+$; calcd for $C_{28}H_{37}IN_3O_6$: 638].

Step 2: (2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide

The title compound was prepared in a similar manner as described for the preparation of Example 10 Step 5 utilizing the ester from step 1. LRMS (ESI) *m/z* 822 [$(M+H)^+$; calcd for $C_{35}H_{45}IN_5O_8S$: 822]: ^1H NMR (400 MHz, ppm) (CD_3OD) δ 9.17 (s, 1 H), 8.17 (s, 1 H), 8.01 (d, J = 6.1 Hz, 1 H), 7.95 (s, 1 H), 7.43 (d, J = 6.04 Hz, 1 H), 6.2 (s, 1 H), 5.73 (m, 1 H), 5.28 (d, J = 18.7 Hz, 1 H), 5.12 (dd, J = 10.2 and 1.6 Hz, 1 H), 4.57 (m, 1 H), 4.41 (m, 3 H), 3.99 (dd, J = 11.7 and 3.1 Hz, 1 H), 3.74 (m, 1 H), 2.93 (m, 2 H), 2.64 (m, 1 H), 2.55 (m, 1 H), 2.24 (m, 2 H), 1.88 (m, 1 H), 1.73 (m, 3 H), 1.49 (m, 1 H), 1.43 (m, 1 H), 1.25 (m, 4 H), 1.09 (m, 2 H), and 1.06 (s, 9 H).

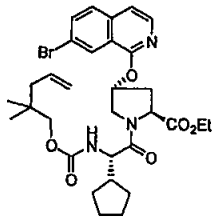
EXAMPLE 14

(2*R*,4*S*,7*S*,14*E*)-7-Cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-39**)



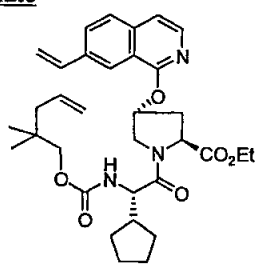
III-39

Step 1: Ethyl (4*R*)-4-[(7-bromoisoquinolin-1-yl)oxy]-1-[(2*S*)-2-cyclopentyl-2-({[(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl}amino)acetyl]-L-prolinate



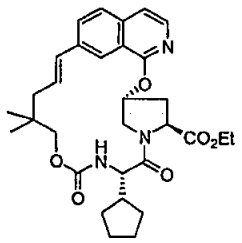
To a solution of ethyl (4R)-4-[7-bromoisoquinolin-1-yl)oxy]-L-prolinate hydrochloride (EXAMPLE 1, Step 1) (500 mg, 1.25 mmol) and (2*S*)-cyclopentyl({[(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl}amino)acetic acid (Intermediate B24) (353 mg, 1.25 mmol) in DMF (7 mL) at RT was added HATU (710 mg, 1.87 mmol) and DIPEA (0.87 mL, 5.00 mmol). After 2 h, the reaction mixture was poured into EtOAc, and extracted with 1 N HCl. The organic layer was washed with water and brine, dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified on silica (gradient elution, 5% to 75% EtOAc in hexanes) to yield 526 mg (67%) of the title compound. LRMS (ESI) *m/z* 630.3 $[(M+H)^+$; calcd for $C_{31}H_{41}BrN_3O_6$: 630.2].

Step 2: Ethyl (4*R*)-1-[(2*S*)-2-cyclopentyl-2-({[(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl}amino)acetyl]-4-[(7-vinylisoquinolin-1-yl)oxy]-L-prolinate



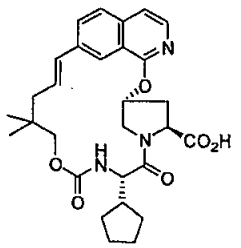
Ethyl (4*R*)-4-[(7-bromoisoquinolin-1-yl)oxy]-1-[(2*S*)-2-cyclopentyl-2-({[(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl}amino)acetyl]-L-prolinate (526 mg, 0.83 mmol) was dissolved in ethanol (10 mL) and nitrogen was bubbled through for 15 min. Potassium vinyltrifluoroborate (168 mg, 1.25 mmol) and dichloro [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) DCM adduct (34 mg, 0.04 mmol) were added and the reaction mixture heated to reflux under nitrogen. After 15 h, the reaction was complete and the volatiles were evaporated and the residue purified by silica gel chromatography (gradient elution, 10-75% EtOAc/hexane) to give a clear oil. LRMS (ESI) *m/z* 578.4 $[(M+H)^+$; calcd for $C_{33}H_{44}N_3O_6$: 578.3].

Step 3: Ethyl (2*R*,4*S*,7*S*,14*E*)-7-cyclopentyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



To a solution of the product from Step 2 (413 mg, 0.72 mmol) in degassed (nitrogen bubbling for 30 min) DCE (250 mL) was added Zhan 1B catalyst (Zhan catalyst 1B, RC-303, Zannan Pharma Ltd.) (52 mg, 0.07 mmol). The mixture was then stirred at 70 °C under an N_2 atmosphere. After 3 h, the reaction was complete and was concentrated in vacuo. The crude product was then directly purified on silica (gradient elution, 5% to 75% EtOAc in hexanes) to yield 325 mg (83%) of the title compound. LRMS (ESI) *m/z* 550.4 $[(M+H)^+$; calcd for $C_{31}H_{40}N_3O_6$: 550.3].

Step 4: (2*R*,4*S*,7*S*,14*E*)-7-Cyclopentyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylic acid



To a solution of the product from Step 3 (160 mg, 0.29 mmol) in THF (5 mL) and EtOH (0.5 mL) at RT was added LiOH (1 M, 2.9 mL, 2.9 mmol). After 1 h, the reaction mixture was partitioned between EtOAc and 1N HCl (x4). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was removed in vacuo to yield 144 mg (95%) of the title compound which was used without further purification. LRMS (ESI) *m/z* 522.3 $[(M+H)^+$; calcd for $C_{29}H_{36}N_3O_6$: 522.3].

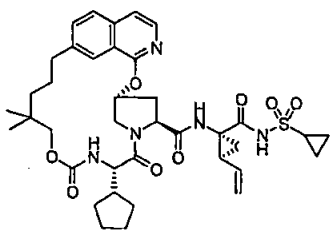
Step 5: (2*R*,4*S*,7*S*,14*E*)-7-Cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (III-39)

To a solution of the product from Step 4 (147 mg, 0.28 mmol) and (1*R*,2*S*)-1-amino-*N*-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide hydrochloride (Intermediate A1) (90 mg, 0.34 mmol) in DMF (2 mL) was added DIPEA (0.25 mL, 1.41 mmol), DMAP (3 mg, 0.03 mmol) and HATU (107 mg, 0.28 mmol). After full conversion (15 h), the reaction mixture was purified by reverse-phase

HPLC (gradient elution, 30% to 100% CH_3CN in 0.15% TFA/water) to yield 122 mg (59%) of the title compound as a white powder. ^1H NMR (500 MHz, CD_3OD) δ 9.16 (s, 1 H), 8.44 (s, 1 H), 7.87 (d, J = 5.9 Hz, 1 H), 7.72 (d, J = 8.3 Hz, 1 H), 7.56 (d, J = 8.3 Hz, 1 H), 7.27 (d, J = 6.1 Hz, 1 H), 6.47 (s, 2 H), 5.77 (s, 1 H), 5.70 (m, 1 H), 5.24 (d, J = 17.1 Hz, 1 H), 5.07 (d, J = 10.3 Hz, 1 H), 4.79 (d, J = 11.7 Hz, 1 H), 4.43 (d, J = 11.0 Hz, 1 H), 4.34 (m, 2 H), 4.03 (dd, J = 11.5 & 2.7 Hz, 1 H), 2.95 (m, 1 H), 2.65 (m, 1 H), 2.42 (m, 2 H), 2.22 (m, 1 H), 2.13 (q, J = 8.8 Hz, 1 H), 2.01 (m, 1 H), 1.92 (m, 1 H), 1.86 (m, 1 H), 1.80 - 1.60 (m, 5 H), 1.43 - 1.20 (m, 5 H), 1.15 (s, 3 H), 1.10 (m, 2 H), 0.89 (s, 3 H) ppm. LRMS (ESI) *m/z* 734.4 $[(M+H)^+$; calcd for $C_{38}H_{48}N_5O_8S$: 734.3].

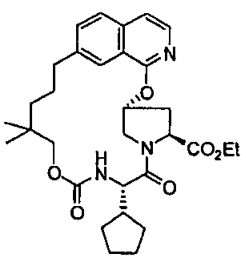
EXAMPLE 15

(2*R*,4*S*,7*S*)-7-Cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-40**)



III-40

Step 1: Ethyl (2*R*,4*S*,7*S*)-7-cyclopentyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



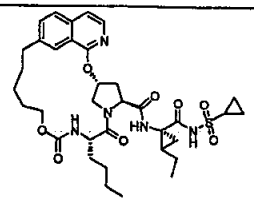
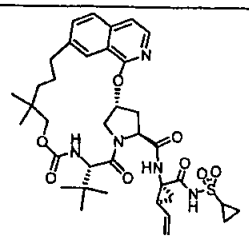
To a solution of ethyl (2*R*,4*S*,7*S*,14*E*)-7-cyclopentyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (EXAMPLE 14, Step 3) (160 mg, 0.29 mmol) in EtOAc (7 mL) at RT was added Pd/C (100 mg). An H_2 balloon was then placed on the reaction flask, the flask was evacuated quickly and filled with H_2. After 7 h, the reaction mixture was filtered through celite and washed with EtOAc. Concentration of the filtrate gave 147 mg (92%) of the title compound which was used without further purification. LRMS (ESI) *m/z* 552.4 $[(M+H)^+$; calcd for $C_{31}H_{42}N_3O_6S$: 552.3].

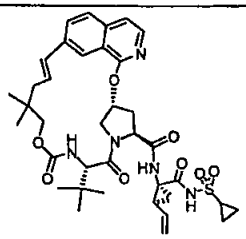
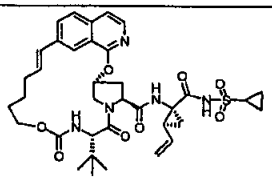
Step 2: (2*R*,4*S*,7*S*)-7-Cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-40**)

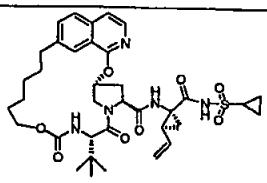
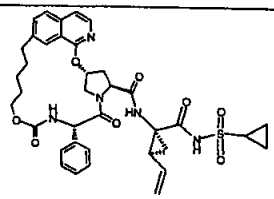
The title compound was prepared from ethyl (2*R*,4*S*,7*S*)-7-cyclopentyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate using the procedures described in EXAMPLE 14, Steps 4 and 5. ^{1}H NMR (500 MHz, CD_3OD) δ 9.26 (s, 1 H), 7.89 (s, 1 H), 7.87 (d, *J* = 5.9 Hz, 1 H), 7.71 (d, *J* = 8.3 Hz, 1 H), 7.55 (d, *J* = 8.3 Hz, 1 H), 7.29 (d, *J* = 5.9 Hz, 1 H), 6.03 (s, 1 H), 5.76 (m, 1 H), 5.28 (d, *J* = 15.6 Hz, 1 H), 5.10 (d, *J* = 8.5 Hz, 1 H), 4.58 (d, *J* = 11.5 Hz, 1 H), 4.46 (m, 1 H), 4.33 (d, *J* = 10.7 Hz, 2 H), 4.01 (dd, *J* = 11.5 & 2.7 Hz, 1 H), 3.28 (d, *J* = 10.7 Hz, 1 H), 2.97 (sep, *J* = 4.6 Hz, 1 H), 2.81 (m, 1 H), 2.64 (m, 1 H), 2.55 (q, *J* = 6.7 Hz, 1 H), 2.44 (m, 1 H), 2.26 (m, 1 H), 2.18 (q, *J* = 9.0 Hz, 1 H), 1.88 (m, 2 H), 1.70 (m, 4 H), 1.56 (m, 3 H), 1.40 (m, 3 H), 1.27 (m, 4 H), 1.07 (m, 4 H), 0.77 (s, 3 H) ppm. LRMS (ESI) *m/z* 736.4 [$(M+H)^+$; calcd for $C_{38}H_{50}N_5O_8S$: 736.3].

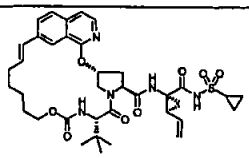
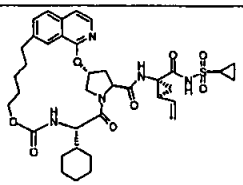
By using the appropriate procedures and the appropriate A and B intermediates in place of (1*R*,2*S*)-1-amino-*N*-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide hydrochloride (Intermediate A1) and (2*S*)-cyclopentyl({[(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl}amino)acetic acid (Intermediate B24), the following compounds were prepared.

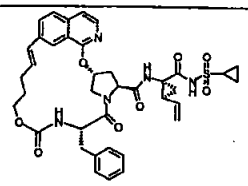
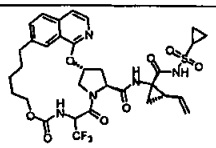
Ex.	Structure	Name	LRMS $(M+H)^+$	Prepared using the appropriate Intermediates according to the procedure below.	Int.

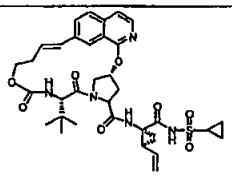
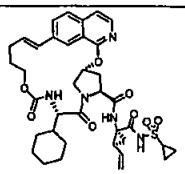
16, **III-41**		(2*R*,4*S*,7*S*)-7-butyl-*N*-((1*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	698.5	See Example 15	A3, B1
17, **III-15**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	724.4	See Example 15	A1, B4

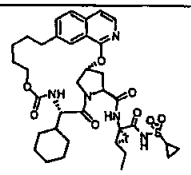
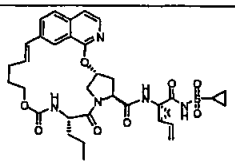
18, **III-29**		(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	722.3	See Example 14	A1, B4
19, **III-42**		(2*R*,4*S*,7*S*,15*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacycloicosine-4-carboxamide	708.6	See Example 14	A1, B5

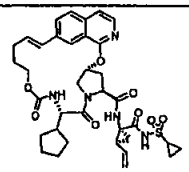
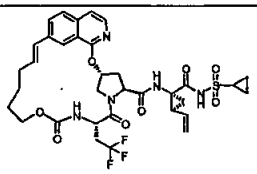
20, **III-43**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16-dodecahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooicosine-4-carboxamide	710.6	See Example 15	A1, B5
21, **III-44**		(2*R*,4*S*,7*S*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-7-phenyl-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	716.3	See Example 15	A1, B6

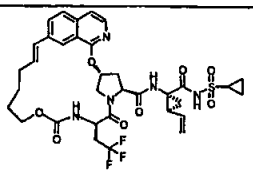
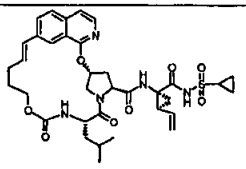
22, **III-45**		(2*R*,4*S*,7*S*,16*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-18,20-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	722.5	See Example 14	A1, B7
23, **III-10**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	708.3	See Example 15	A1, B8

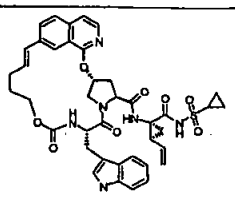
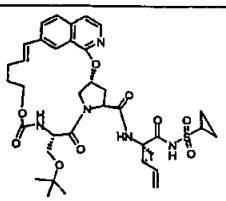
24, **III-46**		(2*R*,4*S*,7*S*,14*E*)-7-benzyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	728.4	See Example 14	A1, B9
25, **III-47**		(2*R*,4*S*)-*N*-((1*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-7-(trifluoromethyl)-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	708.2	See Example 15	A1, B10

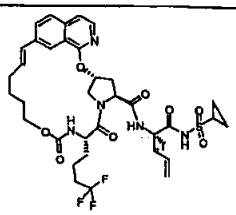
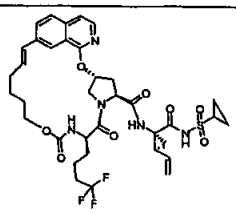
26, **III-48**		(2*R*,4*S*,7*S*,13*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12-octahydro-2*H*-15,17-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooctadecine-4-carboxamide	680.6	See Example 14	A1, B22
27, **III-24**		(2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	720.6	See Example 14	A1, B8

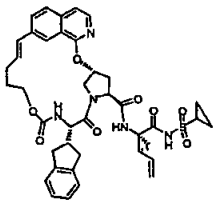
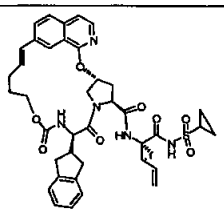
28, **III-49**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	724.5	See Example 15	A3, B8
29, **III-50**		(2*R*,4*S*,7*S*,14*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-7-propyl-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	680.5	See Example 14	A1, B12

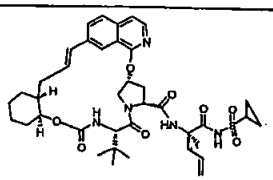
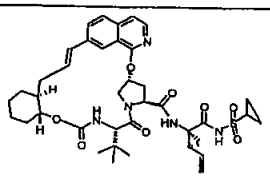
30, III-51		(2*R*,4*S*,7*S*,14*E*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	706.5	See Example 14	A1, B13
31, III-52		(2*R*,4*S*,7*S*,15*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-7-(2,2,2-trifluoroethyl)-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacycloicosine-4-carboxamide	734.4	See Example 14, separated diastereomers	A1, B14

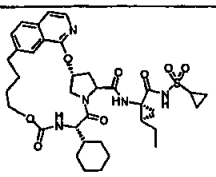
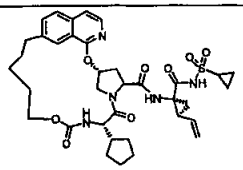
32, **III-53**		(2*R*,4*S*,7*R*,15*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-7-(2,2,2-trifluoroethyl)-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacycloicosine-4-carboxamide	734.4	See Example 14, separated diastereomers	A1, B14
33, **III-54**		(2*R*,4*S*,7*S*,14*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-7-isobutyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	694.5	See Example 14	A1, B15

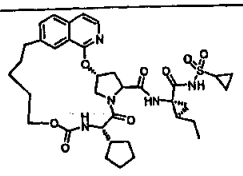
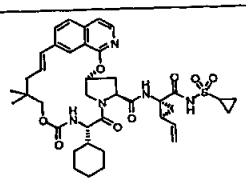
34, **III-55**		(2*R*,4*S*,7*S*,14*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-7-(1*H*-indol-3-ylmethyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	767.3	See Example 14	A1, B16
35, **III-56**		(2*R*,4*S*,7*S*,14*E*)-7-(*tert*-butoxymethyl)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	724.4	See Example 14	A1, B17

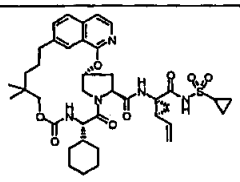
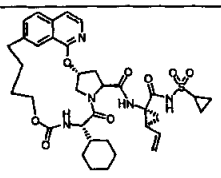
36, **III-57**		(2*R*,4*S*,7*S*,15*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-7-(4,4,4-trifluorobutyl)-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooicosine-4-carboxamide	762.3	See Example 14, separated diastereomers	A1, B18
37, **III-58**		(2*R*,4*S*,7*R*,15*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-7-(4,4,4-trifluorobutyl)-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooicosine-4-carboxamide	762.3	See Example 14, separated diastereomers	A1, B18

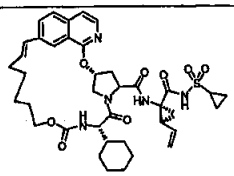
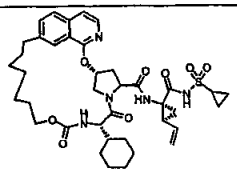
38, III-59		(2*R*,4*S*,7*S*,14*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-7-(2,3-dihydro-1*H*-inden-2-yl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	754.3	See Example 14, separated diastereomers	A1, B19
39, III-60		(2*R*,4*S*,7*R*,14*E*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-7-(2,3-dihydro-1*H*-inden-2-yl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	754.3	See Example 14, separated diastereomers	A1, B19

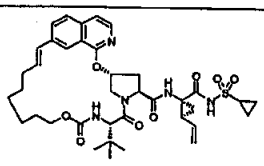
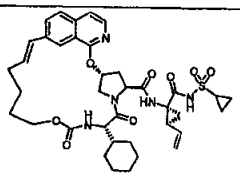
40, **III-61**		(6*R*,8*S*,11*S*,14a*S*,18a*R*,20*E*)-11-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,15,16,17,18,18a,19-dodecahydro-6*H*,14a*H*-1,22-etheno-6,9-methanopyrido[2,3-*k*][1,10,3,6]benzodioxadiazacyclononadecine-8-carboxamide	748.3	See Example 14, separated diastereomers	A1, B20
41, **III-62**		(6*R*,8*S*,11*S*,14a*R*,18a*S*,20*E*)-11-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,15,16,17,18,18a,19-dodecahydro-6*H*,14a*H*-1,22-etheno-6,9-methanopyrido[2,3-*k*][1,10,3,6]benzodioxadiazacyclononadecine-8-carboxamide	748.3	See Example 14, separated diastereomers	A1, B20

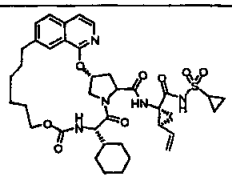
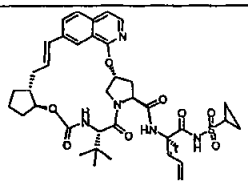
42, **III-63**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-15,17-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooctadecine-4-carboxamide	710.5	See Example 15	A3, B21
43, **III-64**		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	708.4	See Example 15	A1, B13

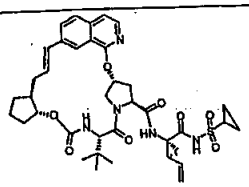
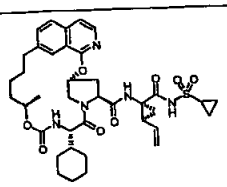
44, **III-65**		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	710.5	See Example 15	A3, B13
45, **III-66**		(2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	748.5	See Example 14	A1, B23

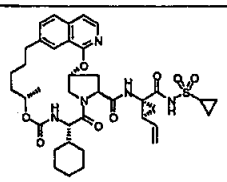
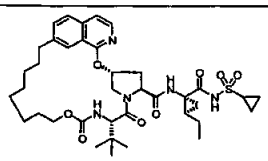
46, III-67		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	750.5	See Example 15	A1, B23
47, III-68		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-15,17-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooctadecine-4-carboxamide	708.3	See Example 15	A1, B21

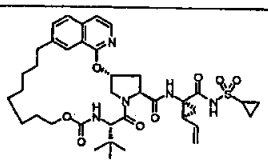
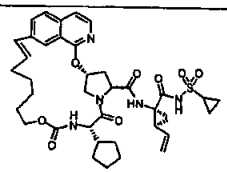
48, **III-69**		(2*R*,4*S*,7*S*,16*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-18,20-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	748.3	See Example 14	A1, B26
49, **III-70**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17-dodecahydro-2*H*,11*H*-18,20-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	750.5	See Example 15	A1, B26

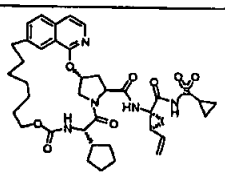
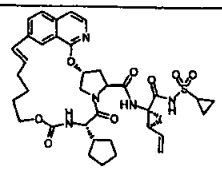
50, **III-71**		(2*R*,4*S*,7*S*,17*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16-dodecahydro-2*H*-19,21-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclodocosine-4-carboxamide	736.5	See Example 14	A1, B27
51, **III-72**		(2*R*,4*S*,7*S*,15*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooicosine-4-carboxamide	734.4	See Example 14	A1, B28

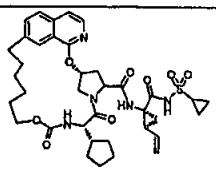
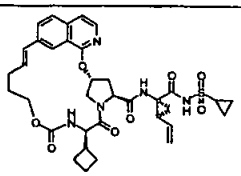
52, **III-73**		(2R,4S,7S)-7-cyclohexyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16-dodecahydro-2H-17,19-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclooicosine-4-carboxamide	736.5	See Example 15	A1, B28
53, **III-74**		(6*R*,8*S*,11*S*,14a*S*,17a*R*,19*E*)-11-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	734.3	See Example 14, separated diastereomers	A1, B29

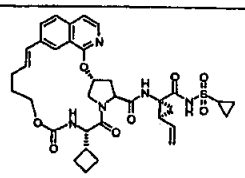
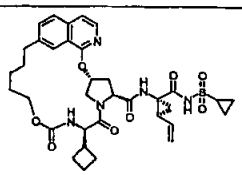
54, III-75		(6*R*,8*S*,11*S*,14a*R*,17a*S*,19*E*)-11-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	734.3	See Example 14, separated diastereomers	A1, B29
55, III-76		(2*R*,4*S*,7*S*,11*R*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-11-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	736.5	See Example 15, separated diastereomers	A1, B30

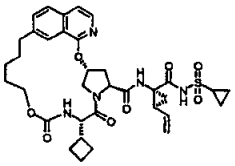
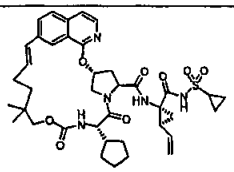
56, III-77		(2*R*,4*S*,7*S*,11*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-11-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	736.4	See Example 15, separated diastereomers	A1, B30
57, III-78		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16,17,18-tetradecahydro-2*H*-19,21-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclodocosine-4-carboxamide	740.6	See Example 15	A3, B27

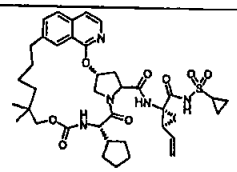
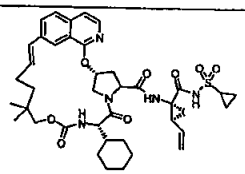
58, **III-79**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16,17,18-tetradecahydro-2*H*-19,21-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclodocosine-4-carboxamide	738.5	See Example 15	A1, B27
59, **III-80**		(2*R*,4*S*,7*S*,15*E*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacycloicosine-4-carboxamide	720.4	See Example 14	A1, B32

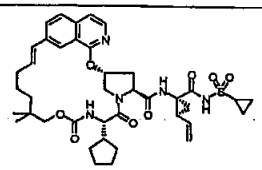
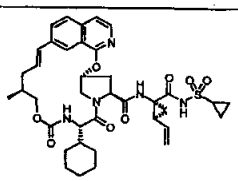
60, III-81		(2R,4S,7S)-7-cyclopentyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17-dodecahydro-2H,11H-18,20-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	722.4	See Example 15	A1, B32
61, III-82		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-18,20-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	734.4	See Example 14	A1, B31

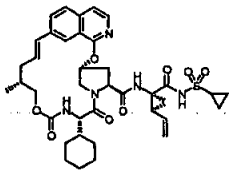
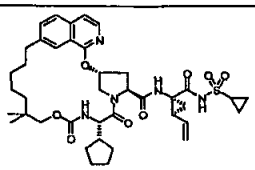
62, III-83		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17-dodecahydro-2*H*,11*H*-18,20-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	736.4	See Example 15	A1, B31
63, III-84		(2*R*,4*S*,7*R*,14*E*)-7-cyclobutyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	692.3	See Example 14, separated diastereomers	A1, B33

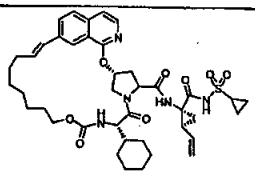
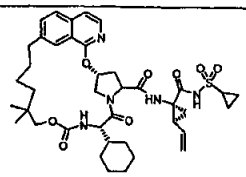
64, **III-85**		(2*R*,4*S*,7*S*,14*E*)-7-cyclobutyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	692.4	See Example 14, separated diastereomers	A1, B33
65, **III-86**		(2*R*,4*S*,7*R*)-7-cyclobutyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	694.3	See Example 15, separated diastereomers	A1, B33

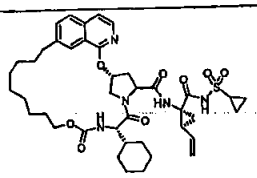
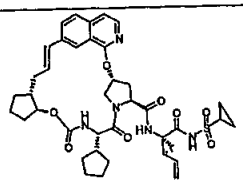
66, **III-87**		(2*R*,4*S*,7*S*)-7-cyclobutyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	694.3	See Example 15, separated diastereomers	A1, B33
67, **III-88**		(2*R*,4*S*,7*S*,15*E*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacycloicosine-4-carboxamide	748.4	See Example 14	A1, B34

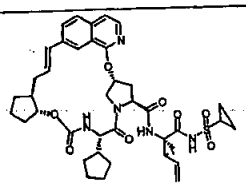
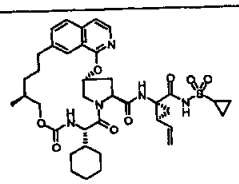
68, **III-89**		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16-dodecahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooicosine-4-carboxamide	750.4	See Example 15	A1, B34
69, **III-90**		(2*R*,4*S*,7*S*,15*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooicosine-4-carboxamide	762.4	See Example 14	A1, B35

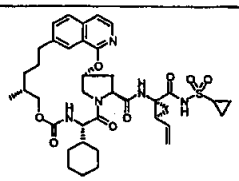
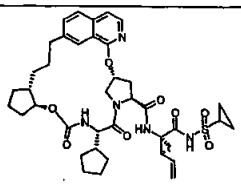
70, **III-91**		(2*R*,4*S*,7*S*,16*E*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-18,20-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	762.5	See Example 14	A1, B36
71, **III-92**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	734.4	See Example 14, separated diastereomers	A1, B39

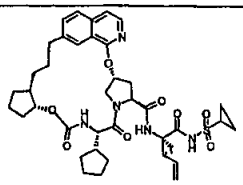
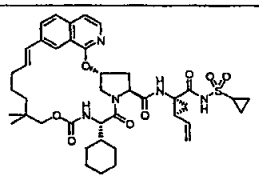
72, **III-93**		(2*R*,4*S*,7*S*,12*R*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	734.4	See Example 14, separated diastereomers	A1, B39
73, **III-94**		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17-dodecahydro-2*H*,11*H*-18,20-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	764.6	See Example 15	A1, B36

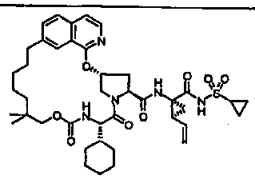
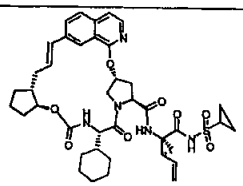
74, **III-95**		(2*R*,4*S*,7*S*,18*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17-dodecahydro-2*H*,11*H*-20,22-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclotricosine-4-carboxamide	776.5	See Example 14	A1, B37
75, **III-96**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16-dodecahydro-2*H*-17,19-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacycloicosine-4-carboxamide	764.4	See Example 15	A1, B35

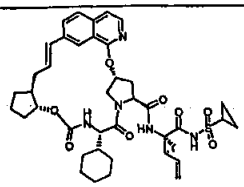
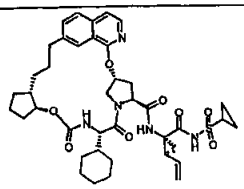
76, **III-97**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17,18,19-tetradecahydro-2*H*,11*H*-20,22-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclotricosine-4-carboxamide	778.5	See Example 15	A1, B37
77, **III-98**		(6*R*,8*S*,11*S*,14a*S*,17a*R*,19*E*)-11-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	746.4	See Example 14, separated diastereomers	A1, B38

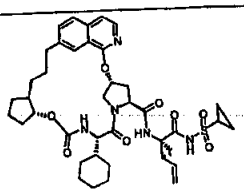
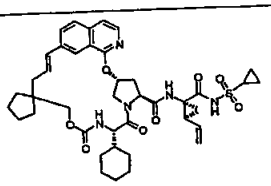
78, **III-99**		(6*R*,8*S*,11*S*,14a*R*,17a*S*,19*E*)-11-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	746.4	See Example 14, separated diastereomers	A1, B38
79, **III-100**		(2*R*,4*S*,7*S*,12*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	736.3	See Example 15, separated diastereomers	A1, B39

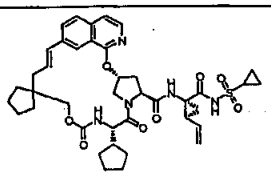
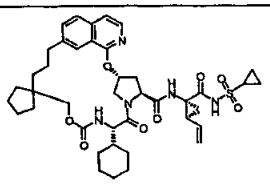
80, III-101		(2*R*,4*S*,7*S*,12*R*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	736.3	See Example 15, separated diastereomers	A1, B39
81, III-102		(6*R*,8*S*,11*S*,14a*S*,17a*S*)-11-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18,19,20-tetradecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	748.3	See Example 15, separated diastereomers	A1, B38

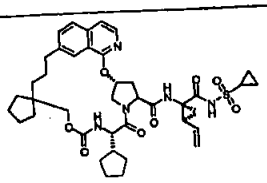
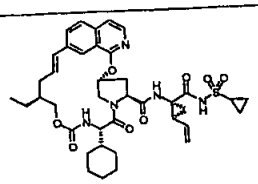
82, **III-103**		(6*R*,8*S*,11*S*,14a*R*,17a*R*)-11-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18,19,20-tetradecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	748.3	See Example 15, separated diastereomers	A1, B38
83, **III-104**		(2*R*,4*S*,7*S*,16*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-18,20-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	776.3	See Example 14	A1, B40

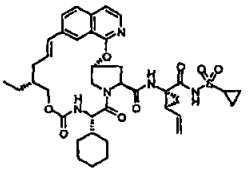
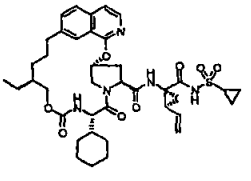
84, **III-105**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17-dodecahydro-2*H*,11*H*-18,20-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclohenicosine-4-carboxamide	778.4	See Example 15	A1, B40
85, **III-106**		(6*R*,8*S*,11*S*,14a*S*,17a*R*,19*E*)-11-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	760.5	See Example 14, separated diastereomers	A1, B41

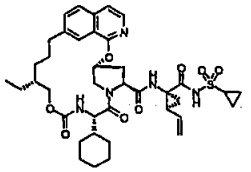
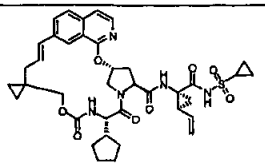
86, III-107		(6*R*,8*S*,11*S*,14a*R*,17a*S*,19*E*)-11-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	760.5	See Example 14, separated diastereomers	A1, B41
87, III-108		(6*R*,8*S*,11*S*,14a*S*,17a*S*)-11-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18,19,20-tetradecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	762.6	See Example 15, separated diastereomers	A1, B41

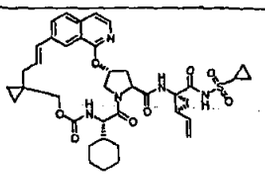
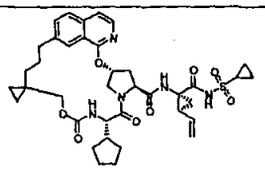
88, III-109		(6*R*,8*S*,11*S*,14a*R*,17a*R*)-11-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18,19,20-tetradecahydro-6*H*-1,21-etheno-6,9-methanocyclopenta[*r*]pyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-8-carboxamide	762.6	See Example 15, separated diastereomers	A1, B41
89, III-110		(2'*R*,4'*S*,7'*S*,14'*E*)-7'-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6',9'-dioxo-3',4',6',7',8',9'-hexahydro-2'*H*,13'*H*-spiro[cyclopentane-1,12'-[1,10]dioxa[5,8,21]triaza[16,18]etheno[2,5]methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine]-4'-carboxamide	774.2	See Example 14	A1, B42

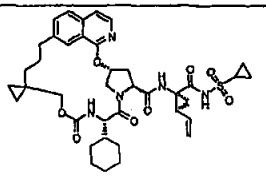
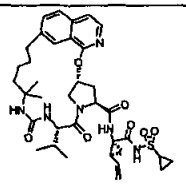
90, III-111		(2'*R*,4'*S*,7'*S*,14'*E*)-7'-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6',9'-dioxo-3',4',6',7',8',9'-hexahydro-2'*H*,13'*H*-spiro[cyclopentane-1,12'-[1,10]dioxa[5,8,21]triaza[16,18]etheno[2,5]methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine]-4'-carboxamide	760.3	See Example 14	A1, B47
91, III-112		(2'*R*,4'*S*,7'*S*)-7'-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6',9'-dioxo-3',4',6',7',8',9',14',15'-octahydro-2'*H*,13'*H*-spiro[cyclopentane-1,12'-[1,10]dioxa[5,8,21]triaza[16,18]etheno[2,5]methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine]-4'-carboxamide	776.4	See Example 15	A1, B42

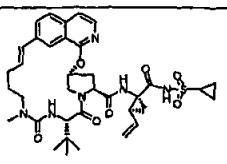
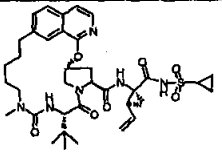
92, **III-113**		(2'*R*,4'*S*,7'*S*)-7'-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6',9'-dioxo-3',4',6',7',8',9',14',15'-octahydro-2'*H*,13'*H*-spiro[cyclopentane-1,12'-[1,10]dioxa[5,8,21]triaza[16,18]etheno[2,5]methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine]-4'-carboxamide	762.3	See Example 15	A1, B47
93, **III-114**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-ethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	748.4	See Example 14, separated diastereomers	A1, B43

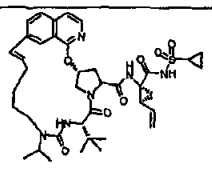
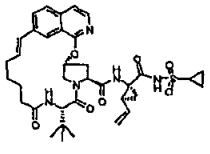
94, **III-115**		(2*R*,4*S*,7*S*,12*R*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-ethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	748.4	See Example 14, separated diastereomers	A1, B43
95, **III-116**		(2*R*,4*S*,7*S*,12*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-ethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	750.4	See Example 15, separated diastereomers	A1, B43

96, **III-117**		(2*R*,4*S*,7*S*,12*R*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-12-ethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	750.5	See Example 15, separated diastereomers	A1, B43
97, **III-118**		(2'*R*,4'*S*,7'*S*,14'*E*)-7'-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6',9'-dioxo-3',4',6',7',8',9'-hexahydro-2'*H*,13'*H*-spiro[cyclopropane-1,12'-[1,10]dioxa[5,8,21]triaza[16,18](ethanediylidene)[2,5]methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine]-4'-carboxamide	732.3	See Example 14	A1, B44

98, III-119		(2'*R*,4'*S*,7'*S*,14'*E*)-7'-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6',9'-dioxo-3',4',6',7',8',9'-hexahydro-2'*H*,13'*H*-spiro[cyclopropane-1,12'-[1,10]dioxa[5,8,21]triaza[16,18](ethanediylidene)[2,5]methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine]-4'-carboxamide	746.3	See Example 14	A1, B45
99, III-120		(2'*R*,4'*S*,7'*S*)-7'-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6',9'-dioxo-3',4',6',7',8',9',14',15'-octahydro-2'*H*,13'*H*-spiro[cyclopropane-1,12'-[1,10]dioxa[5,8,21]triaza[16,18](ethanediylidene)[2,5]methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine]-4'-carboxamide	734.3	See Example 15	A1, B44

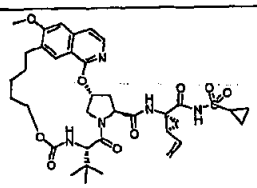
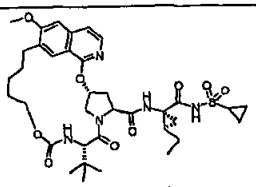
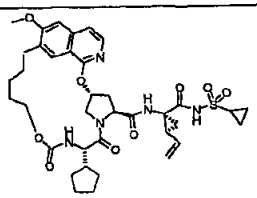
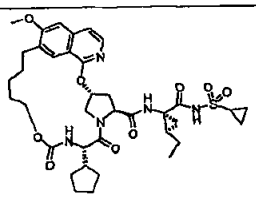
100, **III-121**		(2'*R*,4'*S*,7'*S*)-7'-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6',9'-dioxo-3',4',6',7',8',9',14',15'-octahydro-2'*H*,13'*H*-spiro[cyclopropane-1,12'-[1,10]dioxa[5,8,21]triaza[16,18](ethanediylidene)[2,5]methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine]-4'-carboxamide	748.3	See Example 15	A1, B45
101, **III-122**		(2*R*,4*S*,7*S*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-7-isopropyl-11,11-dimethyl-6,9-dioxo-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2*H*-16,18-etheno-2,5-methanopyrido[3,2-*r*][1,5,8,10]oxatriazacyclononadecine-4-carboxamide	709.4	See Example 15	A1, B50

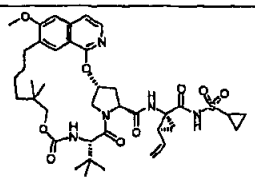
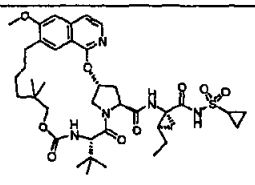
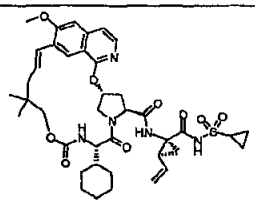
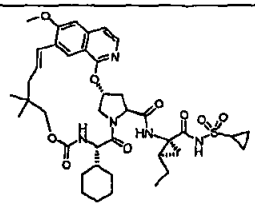
102, **III-28**		(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-methyl-6,9-dioxo-3,4,6,7,8,9,10,11,12,13-decahydro-2*H*-16,18-(ethanediylidene)-2,5-methanopyrido[3,2-*r*][1,5,8,10]oxatriazacyclononadecine-4-carboxamide	707.6	See Example 14	A1, B51
103, **III-14**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-methyl-6,9-dioxo-3,4,6,7,8,9,10,11,12,13,14,15-dodecahydro-2*H*-16,18-(ethanediylidene)-2,5-methanopyrido[3,2-*r*][1,5,8,10]oxatriazacyclononadecine-4-carboxamide	709.7	See Example 15	A1, B51

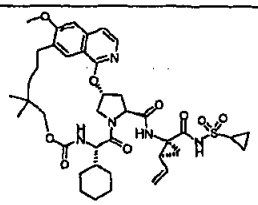
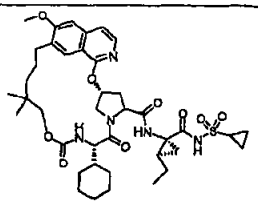
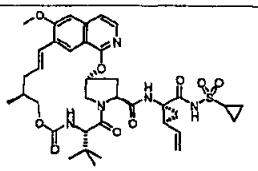
104, III-123		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-10-isopropyl-6,9-dioxo-3,4,7,8,9,10,11,12,13,14-decahydro-2*H*,6*H*-17,19-etheno-2,5-methanopyrido[3,2-*s*][1,5,8,10]oxatriazacycloicosine-4-carboxamide	749.4	See Example 14	A1, B52
105, III-25		(2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,10,11,12,13-decahydro-2H-16,18-ethanediylidene-2,5-methanopyrido[3,2-r][1,5,8]oxadiazacyclononadecine-4-carboxamide	692.6	See Example 14	A1, B53

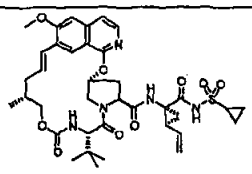
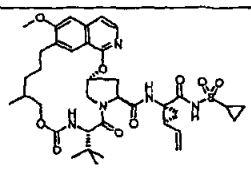
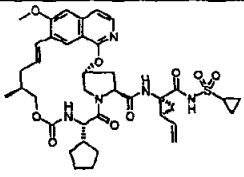
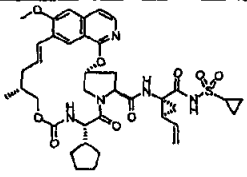
By using the appropriate procedures and the appropriate A, B and C intermediates the following compounds were prepared.

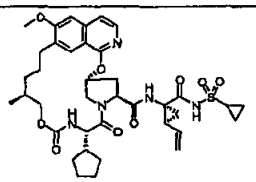
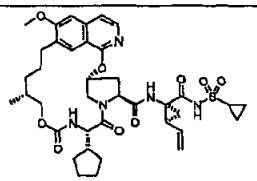
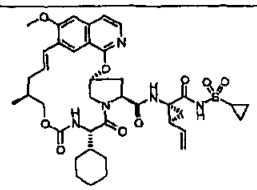
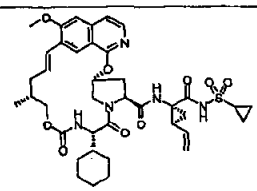
Ex.	Structure	Name	LRMS $(M+H)^+$	Prepared using the appropriate Intermediates according to the procedure below.	Int.

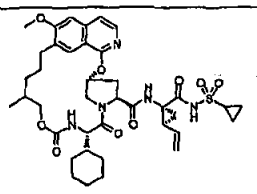
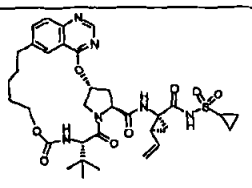
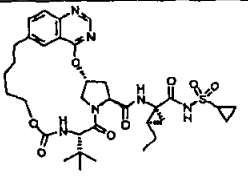
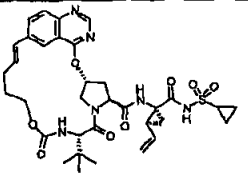
106, **III-12**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	726.5	See Example 15	A1, B2, C1
107, **III-124**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-23-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	728.6	See Example 15	A3, B2, C1
108, **III-125**		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	738.5	See Example 15	A1, B13, C1
109, **III-126**		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-23-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	740.6	See Example 15	A3, B13, C1

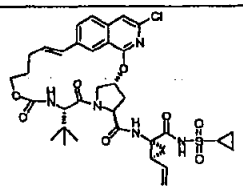
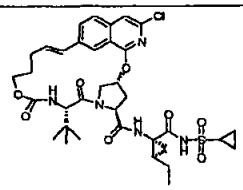
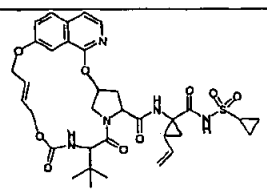
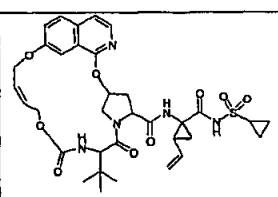
110, **III-127**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-24-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16-dodecahydro-2*H*-17,19-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacycloicosine-4-carboxamide	768.6	See Example 15	A1, B25, C1
111, **III-128**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-24-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16-dodecahydro-2*H*-17,19-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacycloicosine-4-carboxamide	770.7	See Example 15	A3, B25, C1
112, **III-129**		(2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	778.6	See Example 14	A1, B23, C1
113, **III-130**		(2*R*,4*S*,7*S*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	780.6	See Example 14	A3, B23, C1

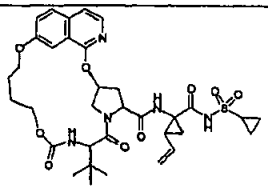
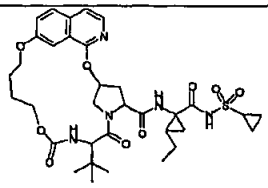
114, **III-131**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	780.5	See Example 15	A1, B23, C1
115, **III-132**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	782.6	See Example 15	A3, B23, C1
116, **III-133**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	738.3	See Example 14, separated diastereomers	A1, B46, C1

117, **III-134**		(2*R*,4*S*,7*S*,12*R*,14*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	738.3	See Example 14, separated diastereomers	A1, B46, C1
118, **III-135**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	740.2	See Example 15	A1, B46, C1
119, **III-136**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	750.4	See Example 14, separated diastereomers	A1, B48, C1
120, **III-137**		(2*R*,4*S*,7*S*,12*R*,14*E*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	750.4	See Example 14, separated diastereomers	A1, B48, C1

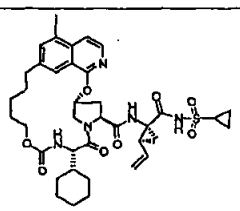
121, **III-138**		(2*R*,4*S*,7*S*,12*S*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	752.4	See Example 15, separated diastereomers	A1, B48, C1
122, **III-139**		(2*R*,4*S*,7*S*,12*R*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	752.5	See Example 15, separated diastereomers	A1, B48, C1
123, **III-140**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	764.3	See Example 14, separated diastereomers	A1, B39, C1
124, **III-141**		(2*R*,4*S*,7*S*,12*R*,14*E*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	764.3	See Example 14, separated diastereomers	A1, B39, C1

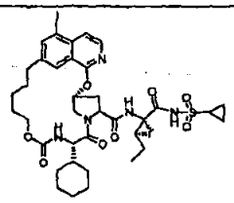
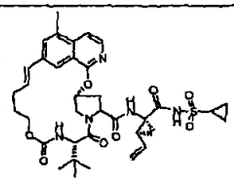
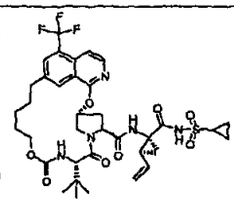
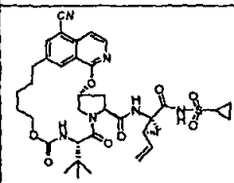
125, **III-142**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-23-methoxy-12-methyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	766.4	See Example 15	A1, B39, C1
126, **III-20**		(15*S*,18*S*,20*R*)-15-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-etheno-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxamide	697.5	See Example 15	A1, B2, C2
127, **III-143**		(15*S*,18*S*,20*R*)-15-*tert*-butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-etheno-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxamide	699.5	See Example 15	A3, B2, C2
128, **III-34**		(7*E*,15*S*,18*S*,20*R*)-15-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-13,16-dioxo-10,11,13,14,15,16,19,20-octahydro-9*H*,18*H*-4,6-etheno-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxamide	695.4	See Example 14	A1, B2, C2

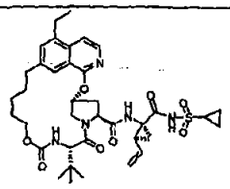
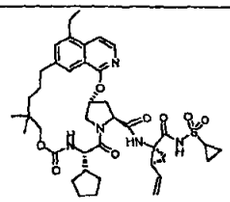
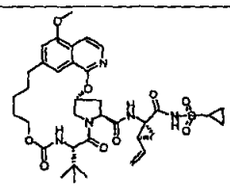
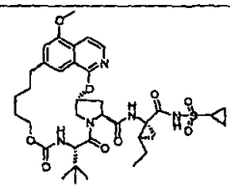
129, **III-31**		(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-20-chloro-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	728.5	See Example 14	A1, B2, C3
130, **III-32**		(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-20-chloro-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	730.5	See Example 14	A3, B2, C3
131, **III-144**		(2*R*,4*S*,7*S*,12*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,14-octahydro-2*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,15,3,6]trioxadiazacyclononadecine-4-carboxamide	696.5	See Example 14, separated olefin isomers	A1, B49, C4
132, **III-145**		(2*R*,4*S*,7*S*,12*Z*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,14-octahydro-2*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,15,3,6]trioxadiazacyclononadecine-4-carboxamide	696.5	See Example 14, separated olefin isomers	A1, B49, C4

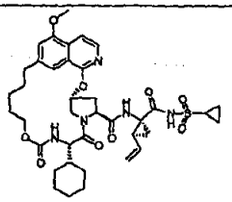
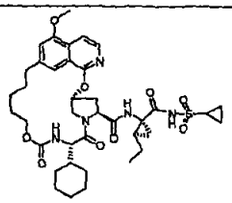
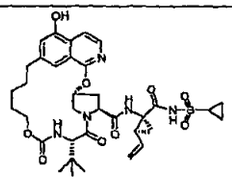
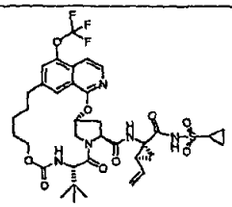
133, **III-146**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,15,3,6]trioxadiazacyclononadecine-4-carboxamide	698.4	See Example 15	A1, B49, C4
134, **III-147**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,15,3,6]trioxadiazacyclononadecine-4-carboxamide	700.5	See Example 15	A3, B49, C4

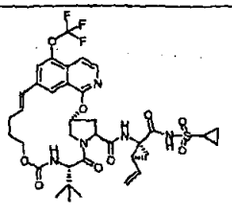
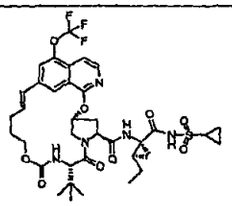
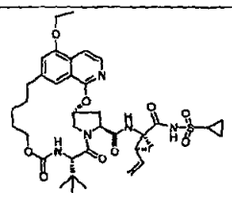
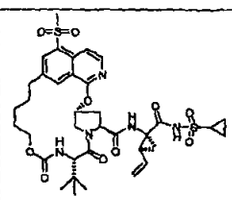
By using the appropriate procedures and the appropriate A, B and D intermediates, the following compounds were prepared.

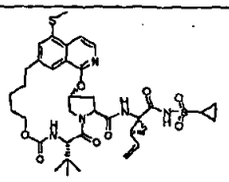
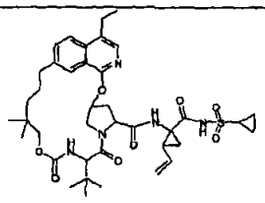
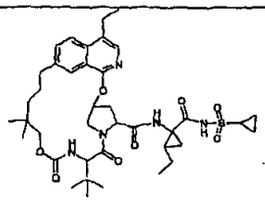
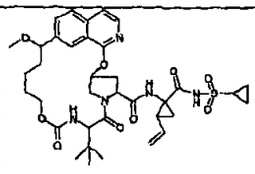
Ex.	Structure	Name	LRMS (M+H)$^+$	Prepared using the appropriate Intermediates according to the procedure below.	Int.
135, **III-148**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	848.4	See Example 13	A1, B8

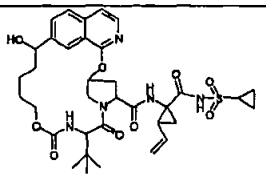
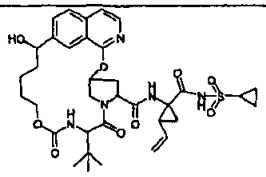
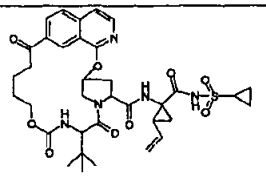
136, **III-149**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	850.5	See Example 13	A3, B8
137, **III-150**		(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	820.2	See Example 14, Step 5	A1, D1
138, **III-151**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-22-(trifluoromethyl)-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	764.3	See Example 14, Steps 4 and 5	A1, D5
139, **III-152**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-22-cyano-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	721.6	See Example 14, Steps 4 and 5	A1, D6

140, **III-153**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-ethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	724.7	See Example 14, Steps 4 and 5	A1, D7
141, **III-154**		(2*R*,4*S*,7*S*)-7-cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-ethyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	764.4	See Example 14, Steps 4 and 5	A1, D8
142, **III-155**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	726.7	See Example 14, Step 5	A1, D9
143, **III-156**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-22-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	728.5	See Example 14, Step 5	A3, D9

144, **III-157**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	752.5	See Example 14, Step 5	A1, D10
145, **III-158**		(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-22-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	754.5	See Example 14, Step 5	A3, D10
146, **III-159**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-hydroxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	712.5	See Example 14, Step 5	A1, D11
147, **III-160**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-22-(trifluoromethoxy)-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	780.5	See Example 15	A1, D15

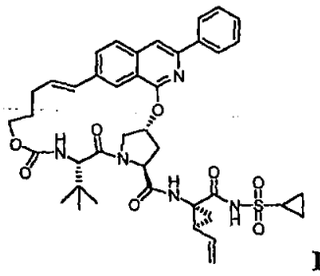
148, **III-161**		(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-22-(trifluoromethoxy)-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	778.4	See Example 14, Steps 4 and 5	A1, D15
149, **III-162**		(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-6,9-dioxo-22-(trifluoromethoxy)-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	780.5	See Example 14, Steps 4 and 5	A3, D15
150, **III-163**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-ethoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	740.5	See Example 14, Steps 4 and 5	A1, D12
151, **III-164**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-(methylsulfonyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	774.5	See Example 14, Steps 4 and 5	A1, D13

152, **III-165**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-(methylthio)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	742.5	See Example 14, Steps 4 and 5	A1, D14
153, **III-166**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-19-ethyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	752.6	See Example 14, Steps 4 and 5	A1, D16
154, **III-167**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-19-ethyl-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	754.5	See Example 14, Steps 4 and 5	A3, D16
155, **III-168**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-15-methoxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	726.3	See Example 14, Step 5	A1, D2

156, **III-169**		(2*R*,4*S*,7*S*,15*R*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-15-hydroxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	712.6	See Example 14, Steps 4 and 5, separated diastereomers	A1, D3
157, **III-170**		(2*R*,4*S*,7*S*,15*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-15-hydroxy-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	712.6	See Example 14, Steps 4 and 5, separated diastereomers	A1, D3
158, **III-171**		(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9,15-trioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide	710.5	See Example 14, Steps 4 and 5	A1, D4

EXAMPLE 159

(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-20-phenyl-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-172**)

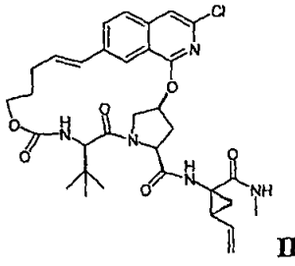


III-172

To a solution of (2R,4S,7S,14E)-7-tert-butyl-20-chloro-N-((1R,2S)-1-{[(cyclopropylsulfonyl) amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (EXAMPLE 129, **III-31**) (25 mg, 0.034 mmol) in THF (2 mL) was added phenylboronic acid (5.6 mg, 0.0447 mmol), cesium carbonate (56 mg, 0.16 mmol) and tricyclohexylphosphine (1.0 mg, 0.34 mmol). To this mixture was added $Pd_2(dba)_3$ (1.6 mg, 0.00172 mmol) and the mixture heated to 80°C for 2 hours. The reaction was concentrated and purified by reverse phase HPLC to give the title compound (20 mg) as a foam. LRMS (ESI) *m/z* 770.6 [$(M+H)^+$; calcd for $C_{41}H_{48}N_5O_8S$: 770.3].

EXAMPLE 160

(2*R*,4*S*,7*S*,14*E*)-7-*tert*-Butyl-20-chloro-*N*-{(1*R*,2*S*)-1-[(methylamino)carbonyl]-2-vinylcyclopropyl}-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-173**)

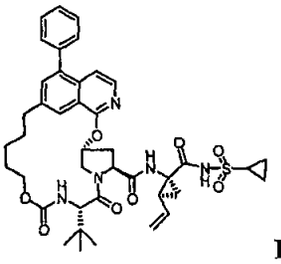


III-173

To a solution of (2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-20-chloro-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (EXAMPLE 129, **III-31**) (20 mg, 0.0275 mmol) in THF (1 mL) was added 40% aqueous methylamine and the mixture was heated in a microwave reactor at 180 °C for 30 min. The reaction mixture was concentrated and purified by reverse phase HPLC to give 2 mg product as foam. LRMS (ESI) m/z 638.5 [$(M+H)^+$; calcd for $C_{33}H_{41}ClN_5O_6$: 638.3].

EXAMPLE 161

(2*R*,4*S*,7*S*)-7-*tert*-butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-22-phenyl-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-174**)

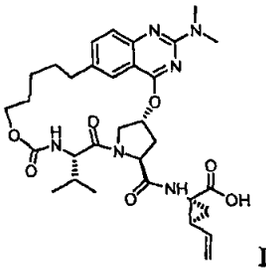


III-174

To a sealed tube containing (2R,4S,7S)-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-iodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-38**) (EXAMPLE 13) (17 mg, 0.021 mmol) in toluene (1 mL) was added phenylboronic acid (3 mg, 1.1 mmol), 2M sodium carbonate (0.021 mL, 0.041 mmol), and tetrakis(triphenylphosphine)palladium (1 mg, 0.001 mmol). The reaction mixture was heated at 80 C for 10 h. The reaction mixture was diluted with EtOAc, washed with 1N HCl, brine, dried the organics, and concentrated to a yellow oil. The resulting oil was purified by reverse phase HPLC to yield the title compound as a yellow solid. (5 mg). LRMS (ESI) m/z 772.7 $[(M+H)^+$; calcd for $C_{41}H_{50}N_5O_8S$: 772.3].

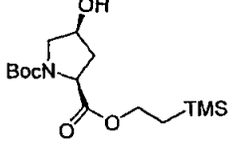
EXAMPLE 162

(1*R*,2*S*)-1-({[(15*S*,18*S*,20*R*)-2-(Dimethylamino)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecin-18-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid (**III-175**)



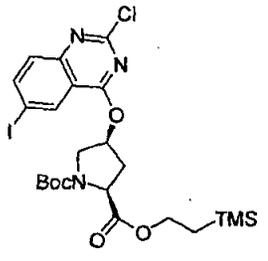
III-175

Step 1: 1-*tert*-Butyl 2-[2-(trimethylsilyl)ethyl] (2*S*,4*S*)-4-hydroxypyrrolidine-1,2-dicarboxylate



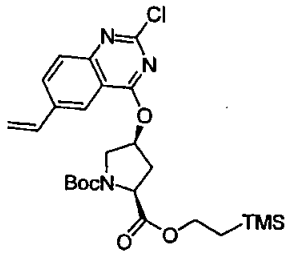
To a solution of 1-*tert*-butyl 2-methyl (2*S*,4*S*)-4-hydroxypyrrolidine-1,2-dicarboxylate (1.0 g, 4.08 mmol) in THF (30 mL) and water (6 mL) cooled to 0 °C was added a 1 M solution of NaOH (6.12 mL, 6.12 mmol). The mixture was stirred at this temperature for 2 h. At this time, TLC (100% Et_2O) indicated complete consumption of the starting material and formation of a more polar compound ($KMnO_4$ stain). The THF was then removed in vacuo, and the pH of the water layer was adjusted to 2-3 with 1 N HCl. The mixture was then extracted with EtOAc, dried over $MgSO_4$, and the solvent was removed in vacuo. LC-MS indicated that the major product had the desired mass. The crude compound was then taken up in PhMe (30 mL), O-2-trimethylsilyl-N,N'-diisopropylisourea (T. Eicher, M. Ott, A. Speicher *Synthesis*, 1996, 755-762)(1.99 g, 8.15 mmol) was added, and the mixture was refluxed for 2 h. At this time, 30% EtOAc/hexanes (10 mL) was added and the mixture was filtered. The solvent was then removed in vacuo, and the crude product was purified on silica (40% EtOAc/hex) to yield the title compound (1.23 g). LRMS $(M+H)^+ = 332.2$.

Step 2: 1-tert-Butyl 2-[2-(trimethylsilyl)ethyl] (2S,4S)-4-[(2-chloro-6-iodoquinazolin-4-yl)oxy]pyrrolidine-1,2-dicarboxylate



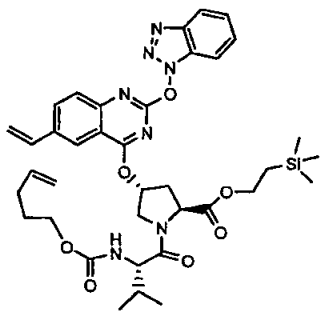
To a solution of the product from step 1 (1.02 g, 3.08 mmol) and 2,4-dichloro-6-iodoquinazoline (1.0 g, 3.08 mmol) (M. C. Venuti et al., *J. Med. Chem.* **1988**, *31*, 2136-2145) in toluene (25 mL) was added 60% sodium hydride (600 mg, excess) and the reaction mixture stirred at room temperature for 45 min. The reaction mixture was carefully partitioned between ice cold pH5.2 citrate buffer and EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4 and solvent evaporated. The crude product was purified by chromatography on silica (0-30% EtOAc hexane) to afford the title compound (1.61 g).

Step 3: 1-tert-Butyl 2-[2-(trimethylsilyl)ethyl] (2S,4S)-4-[(2-chloro-6-vinylquinazolin-4-yl)oxy]pyrrolidine-1,2-dicarboxylate



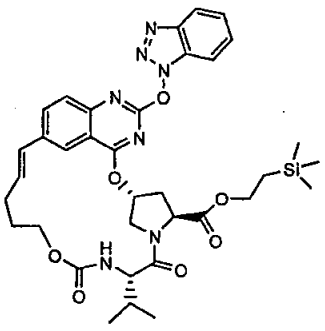
The title compound was prepared from 1-tert-butyl 2-[2-(trimethylsilyl)ethyl] (2S,4S)-4-[(2-chloro-6-iodoquinazolin-4-yl)oxy]pyrrolidine-1,2-dicarboxylate as described in Example 1 Step 3.

Step 4: 2-(trimethylsilyl)ethyl N-[(pent-4-en-1-yloxy)carbonyl]-L-valyl-(4R)-4-{[2-(1H-1,2,3-benzotriazol-1-yloxy)-6-vinylquinazolin-4-yl]oxy}-L-prolinate



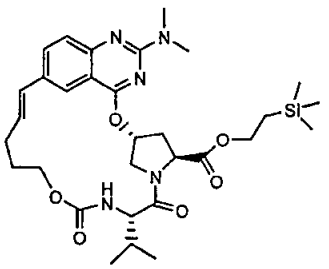
A solution of 1-tert-butyl 2-[2-(trimethylsilyl)ethyl] (2S,4S)-4-[(2-chloro-6-vinylquinazolin-4-yl)oxy]pyrrolidine-1,2-dicarboxylate (495 mg, 0.95 mmol) in EtOAC (10 mL) was cooled to 0 C and hydrogen chloride bubbled through for 30 min. Nitrogen was then bubbled through for 5 min, the solvent evaporated and the residue azeotroped with EtOAc (x3). The residue was dissolved in DMF (5 mL) and DIPEA (479 µL, 2.67 mmol), Intermediate B3 (307 mg, 1.34 mmol) and TBTU (472 mg, 1.47 mmol) added. The reaction mixture was stirred at room temperature overnight and partitioned between pH 5.2 citrate buffer and EtOAc. The organic phase was washed with water, saturated $NaHCO_3$, brine, dried over Na_2SO_4 and the solvent evaporated. The crude product was purified by chromatography on silica (5-50% EtOAc hexane) to afford the title compound (479 mg). LRMS $(M+H)^+ = 702.3$.

Step 5: 2-(Trimethylsilyl)ethyl (7*E*,15*S*,18*S*,20*R*)-2-(1*H*-1,2,3-benzotriazol-1-yloxy)-15-isopropyl-13,16-dioxo-10,11,13,14,15,16,19,20-octahydro-9*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxylate



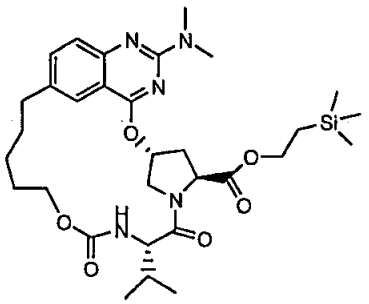
as the title compound was prepared from the product from Step 4 using the procedure described in Example 1 Step 4.

Step 6: 2-(Trimethylsilyl)ethyl (7*E*,15*S*,18*S*,20*R*)-2-(dimethylamino)-15-isopropyl-13,16-dioxo-10,11,13,14,15,16,19,20-octahydro-9*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxylate:



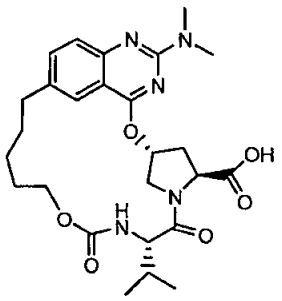
To a solution of the product from step 4 (130 mg, 0.185 mmol) in DCM (2 mL) was added a solution of 2.0M dimethylamine in THF (0.5 mL, 1.0 mmol) and the mixture was stirred at room temperature for 3 h. Additional 2.0M dimethylamine in THF (0.5 mL, 1.0 mmol) was added and the reaction was stirred for an additional 18 h. The reaction mixture was concentrated to an oil and chromatographed on silica using a gradient elution from dichloromethane to 5% acetone/dichloromethane to give the title compound as an oil (92 mg). LRMS $(M+H)^+ = 612.4$.

Step 7: 2-(Trimethylsilyl)ethyl (15*S*,18*S*,20*R*)-2-(dimethylamino)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxylate



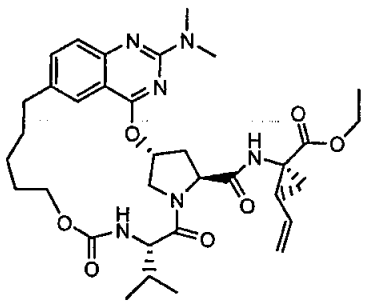
To a solution of the oil from step 5 (92 mg, 0.151 mmol) in ethyl acetate (20 mL) and under nitrogen was added 10 % palladium on carbon (20 mg) and the mixture stirred under hydrogen (1 atm) for 18 h. The reaction mixture was filtered and concentrated in vacuo to give the product as an oil (92 mg). LRMS $(M+H)^+ = 614.3$.

Step 8: (15*S*,18*S*,20*R*)-2-(Dimethylamino)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxylic acid



To a solution of the oil from step 6 (92 mg, 0.151 mmol) in THF (5 mL), under nitrogen, was added a solution of 1.0M tetrabutylammonium fluoride in THF (0.9 mL, 0.90 mmol). The reaction mixture was stirred for 0.5 hr and then concentrated in vacuo to give an oil. LRMS $(M+H)^+ = 514$.

Step 9: Ethyl (1*R*,2*S*)-1-({[(15*S*,18*S*,20*R*)-2-(dimethylamino)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecin-18-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylate

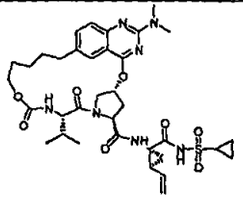
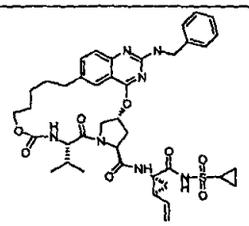


The oil from step 7 was dissolved in DMF (2 mL) and diisopropylamine (80 μL, 0.45 mmol), and (2R,3S)-3-vinyl-2-aminocyclopropyl carboxylic acid ethyl ester hydrochloride (Intermediate A2) (44 mg, 0.23 mmol) added, followed by TBTU (36 mg, 0.23 mmol) and the reaction mixture stirred at RT for 1 h. The mixture was diluted with EtOAc (20mL), washed with pH 5.2 citric acid (10 mL), 10% aqueous sodium bicarbonate (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give an oil, chromatographed on silica (30 to 100% ethyl acetate/hexanes) to give the title compound as an oil, (45 mg). LRMS $(M+H)^+ = 651.4$.

Step 10: (1*R*,2*S*)-1-({[(15*S*,18*S*,20*R*)-2-(Dimethylamino)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecin-18-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid (**III-175**)

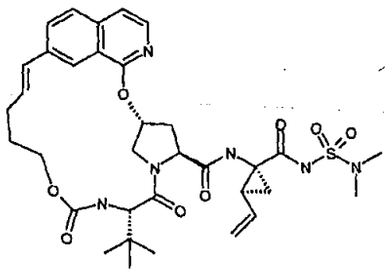
To a solution of the oil from step 8 (45 mg, 0.068 mmol) in THF (2 mL) was added a solution of lithium hydroxide (16 mg, 0.68 mmol) in water (0.4 mL) and the mixture stirred at 40 °C for 8 h. The reaction mixture was diluted with 1N hydrochloric acid (0.7 mL) and purified by reverse phase HPLC to give the title compound as a foam (45 mg) after concentration. ^{1}H NMR (500 Mhz, CD_3OD) δ 8.69 (s, 1H), 7.82 (d, 1H, J = 1.7 Hz), 7.79 (dd, 1H, J = 8.5 and 1.9 Hz), 7.68 (d, 1H, J = 8.5 Hz), 6.25 (m,1H), 5.84 (m, 1H), 5.27 (dd,1H, J = 16.8 and 1.5 Hz), 5.09 (dd, 1H, J = 10.3 and 1.7 Hz), 4.71 (d, 1H, J = 1.7 Hz), 4.66 (t, 1H, J = 10.0 Hz), 4.17 (m, 1H), 4.02 (m, 2H), 3.73 (m, 2H), 3.44 (brs, 6H), 2.86 (m, 1H), 2.69 (m, 1H), 2.19 (dd, 1H, J = 17.6 and 8.8 Hz), 2.02 (m, 1H), 1.80 (m,1H), 1.6 8(m, 2H), 1.40-1.55 (m, 3H), 1.10-1.30 (m, 2H), 1.02 (d, 6H) ppm; LRMS (ESI) *m/z* 623.3 $[(M+H)^+$; calcd for $C_{32}H_{43}N_6O_7$: 623.3].

By using the appropriate procedures and the appropriate A and B intermediates, the following compounds were prepared.

Ex.	Structure	Name	LRMS $(M+H)^+$	Prepared using the appropriate Intermediates according to the procedure below.	Int.
163, **III-176**		(15*S*,18*S*,20*R*)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-2-(dimethylamino)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxamide	726.6	Example 162	A1
164, **III-177**		(15*S*,18*S*,20*R*)-2-(benzylamino)-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-15-isopropyl-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahydro-7*H*,18*H*-4,6-(ethanediylidene)-17,20-methanopyrimido[4,5-*k*][1,10,3,6]dioxadiazacyclononadecine-18-carboxamide	788.6	Example 162	A1, benzylamine

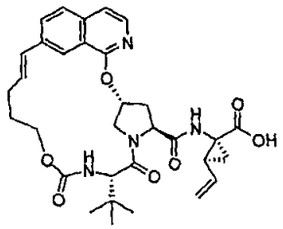
EXAMPLE 165

(2*R*,4*S*,7*S*,14*E*)-7-*tert*-Butyl-*N*-[(1*R*,2*S*)-1-({[(dimethylamino)sulfonyl]amino}carbonyl)-2-vinylcyclopropyl]-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-178**)



III-178

Step 1: (1R,2S)-1-({[(2R,4S,7S,14E)-7-tert-Butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-etheno-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid



Ethyl (2R,4S,7S)-7-tert-butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxodiazacyclononadecine-4-carboxylate (EXAMPLE 10, Step 4) (0.73 g, 0.1.43 mmol) was dissolved in THF (20 mL) and EtOH (10 mL) and a solution of LiOH in water (257 mg in 10 mL) added. The reaction mixture was stirred at room temperature for 1.5 h after which HPLC analysis indicated complete reaction,3M HCl (5.0 mL) was added and the mixture was evaporated to a solid. The solid was partitioned between EtOAc (20 mL) and water (20 mL),the organic phase, dried over Na_2SO_4, filtered and concentrated to a foam which was used without further purification.

LRMS $(M+H)^+ = 591.5$.

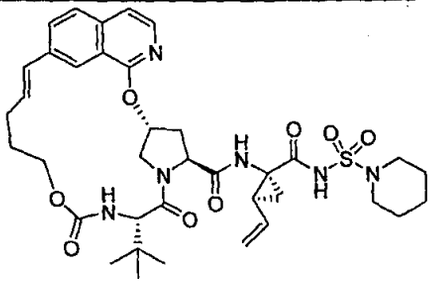
Step 2: (2*R*,4*S*,7*S*,14*E*)-7-*tert*-Butyl-*N*-[(1*R*,2*S*)-1-({[(dimethylamino)sulfonyl]amino}carbonyl)-2-vinylcyclopropyl]-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (III-178)

To the product from step 1 (100 mg, 0.169 mmol), N,N-dimethylsulfamide (84 mg, 0.677 mmol), DIPEA (0.148 mL, 0.847 mmol), and DMAP (83 mg, 0.677 mmol) in DMF (3 mL) was added DBU (0.115 mL, 0.762 mmol) and the mixture was stirred for 5 min. HATU (70.8 mg, 0.186 mmole) was added and mixture was stirred for 18 h. Additional HATU (15 mg) was added and the mixture stirred for an additional 3 h. The mixture was then purified by prep HPLC to give 65 mg of the title compound as a foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (s, 1H), 8.26 (s, 1H), 7.89 (d, 1H, J = 6.1 Hz), 7.64 (d, 1H, J = 8.3 Hz), 7.50 (dd, 1H, J = 1.7 and 8.3 Hz), 7.20 (d, 1H, J = 5.8 Hz), 7.17 (s, 1H), 6.50 (d,

1H, J = 15.8 Hz), 6.36 (m, 1H), 5.82 (m, 1H), 5.66 (m, 2H), 5.17 (dd, 1H, J = 0.8 and 17.1 Hz), 5.09 (dd, 1H, J = 0.8 and 10.3 Hz), 4.61(d, 1H, J = 10.3 Hz), 4.48 (m, 3H), 3.94 (m, 2H), 2.8 3(s, 6H), 2.73 (m, 1H), 2.46 (m, 1H), 2.38 (m, 2H), 2.00 (m, 2H), 1.85 (m, 2H), 1.34 (m, 1H), 1.08 (s, 9H). LRMS (ESI) *m/z* 697.5 [(M+H)$^+$; calcd for $C_{34}H_{45}N_6O_8S$: 697.3].

EXAMPLE 166

(2*R*,4*S*,7*S*,14*E*)-7-*tert*-butyl-6,9-dioxo-*N*-((1*R*,2*S*)-1-{[(piperidin-1-ylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-179**)

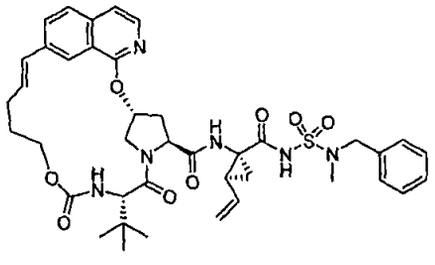


III-179

EXAMPLE 166 was prepared according to the procedure described for EXAMPLE 165 by using piperidine-1-sulfonamide in Step 2. LRMS (ESI) *m/z* 737.5 [(M+H)$^+$; calcd for $C_{37}H_{49}N_6O_8S$: 737.3].

EXAMPLE 167

(2*R*,4*S*,7*S*,14*E*)-*N*-{(1*R*,2*S*)-1-[({[benzyl(methyl)amino]sulfonyl}amino)carbonyl]-2-vinylcyclopropyl}-7-*tert*-butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-180**)

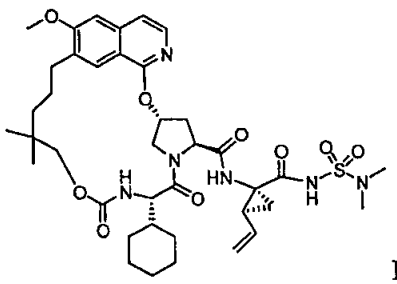


III-180

EXAMPLE 167 was prepared according to the procedure described for EXAMPLE 165 by using N-benzyl-N-methylsulfamide in Step 2. LRMS (ESI) *m/z* 773.6 [(M+H)$^+$; calcd for $C_{40}H_{49}N_6O_8S$: 773.3].

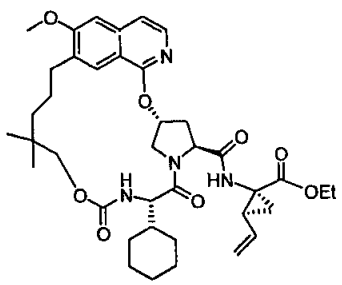
EXAMPLE 168

(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-[(1*R*,2*S*)-1-({[(dimethylamino)sulfonyl]amino}carbonyl)-2-vinylcyclopropyl]-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (III-181)



III-181

Step 1: Ethyl (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-cyclohexyl-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylate



Ethyl (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-cyclohexyl-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylate was prepared using the procedure described for EXAMPLE 15 using Intermediates A2, B23 and C1. LRMS $(M+H)^+ = 705.6$.

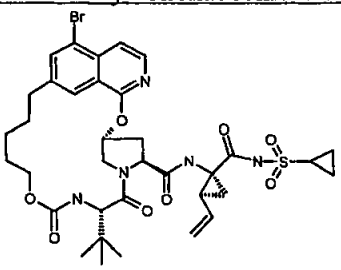
Step 2: (2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-[(1*R*,2*S*)-1-({[(dimethylamino)sulfonyl]amino}carbonyl)-2-vinylcyclopropyl]-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide

EXAMPLE 168 was prepared according to the procedure described for EXAMPLE 165 by using ethyl (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-cyclohexyl-23-methoxy-12,12-dimethyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-

k][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylate in Step 1. LRMS (ESI) *m/z* 783.6 [(M+H)$^+$; calcd for $C_{39}H_{55}N_6O_9S$: 783.4].

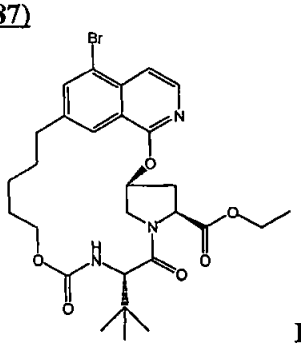
EXAMPLE 169

(2R,4S,7S)-22-bromo-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-182**)

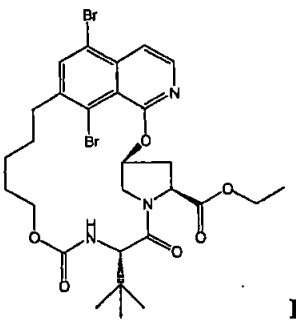


III-182

Step 1: Ethyl (2*R*,4*S*,7*S*)-22-bromo-7-*tert*-butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (**III-186**) and Ethyl (2*R*,4*S*,7*S*)-17,22-dibromo-7-*tert*-butyl-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate (**III-187**)



III-186



III-187

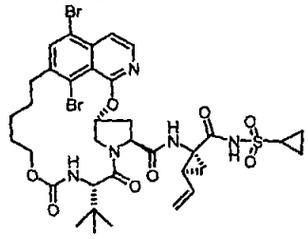
Compounds **III-186** and **III-187** were prepared according to the procedure given for EXAMPLE 13, Step 1 using N-bromosuccinimide. The mono- and di-brominated compounds were separated by reverse-phase HPLC. **III-186**: LRMS (M+H)$^+$ = 590.4. **III-187**: LRMS (M+H)$^+$ = 668.3.

Step 2: (2R,4S,7S)-22-bromo-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-ethanediylidene-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-182**)

EXAMPLE 169 was prepared from **III-186** using the procedure described for EXAMPLE 14, Steps 4 and 5. LRMS (ESI) *m/z* 774.5 [(M+H)$^+$; calcd for $C_{35}H_{45}BrN_5O_8S$: 774.2].

EXAMPLE 170

(2R,4S,7S)-17,22-dibromo-7-tert-butyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahydro-2H,11H-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-183**)

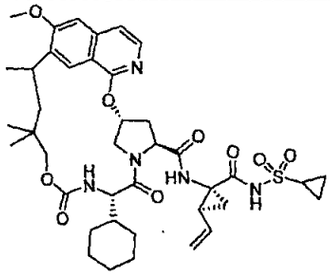


III-183

The title compound was prepared from **III-187** using the procedure described for EXAMPLE 14, Steps 4 and 5. LRMS (ESI) *m/z* 852.5 [(M+H)$^+$; calcd for $C_{35}H_{44}Br_2N_5O_8S$: 852.1].

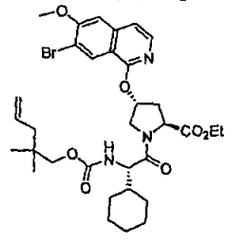
EXAMPLE 171

(2*R*,4*S*,7*S*)-7-cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-methoxy-12,12,14-trimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-15,17-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooctadecine-4-carboxamide (**III-184**)



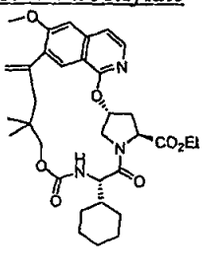
III-184

Step 1: Ethyl (4R)-4-[(7-bromo-6-methoxyisoquinolin-1-yl)oxy]-1-[(2S)-2-cyclohexyl-2-({[(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl}amino)acetyl]-L-prolinate



Ethyl (4R)-4-[(7-bromo-6-methoxyisoquinolin-1-yl)oxy]-1-[(2S)-2-cyclohexyl-2-({[(2,2-dimethylpent-4-en-1-yl)oxy]carbonyl}amino)acetyl]-L-prolinate was prepared according to the procedure given for EXAMPLE 14, Step 1 using intermediates B23 and C1. LRMS $(M+H)^+$ = 674.3

Step 2: Ethyl (2R,4S,7S)-7-cyclohexyl-22-methoxy-12,12-dimethyl-14-methylene-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2H-15,17-etheno-2,5-methanopyrido[2,3-k][1,10,3,6]dioxadiazacyclooctadecine-4-carboxylate



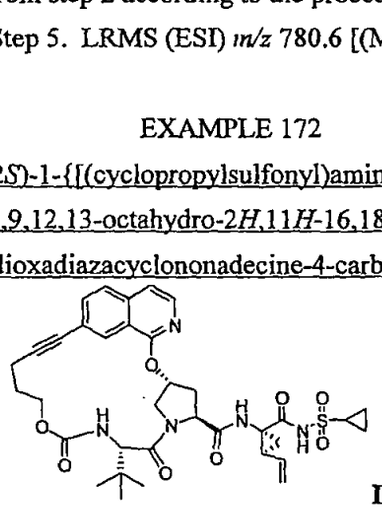
To a solution of the product from step 1 (448 mg, 0.664 mmol) dissolved in ethanol (10 mL) was added triethylamine (0.139 mL, 0.996 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) (24.3 mg, 0.033 mmol) and the reaction mixture heated to 90 °C. After 1 hour, additional catalyst (5mg) was added and reaction mixture was stirred an additional 18 h at 90 °C. The reaction mixture was concentrated in vacuo and chromatographed on silica (20 to 50% EtOAc/hexane) to give impure product. Prep HPLC purification gave the title compound (140 mg) as a foam. LRMS $(M+H)^+$ = 594.5.

Step 3: (2*R*,4*S*,7*S*)-7-Cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-methoxy-12,12,14-trimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-15,17-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooctadecine-4-carboxamide (**III-184**)

(2*R*,4*S*,7*S*)-7-Cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-22-methoxy-12,12,14-trimethyl-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahydro-2*H*-15,17-etheno-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclooctadecine-4-carboxamide (**III-184**) was prepared from the product from step 2 according to the procedure given for EXAMPLE 14, Steps 4 and 5 using intermediate A1 in Step 5. LRMS (ESI) *m/z* 780.6 [$(M+H)^+$; calcd for $C_{40}H_{53}N_5O_9S$: 780.4].

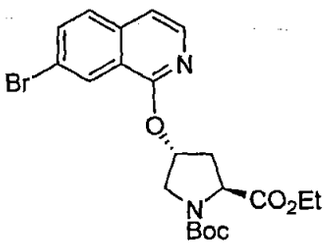
EXAMPLE 172

(2*R*,4*S*,7*S*)-7-*tert*-Butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-14,15-didehydro-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-185**)



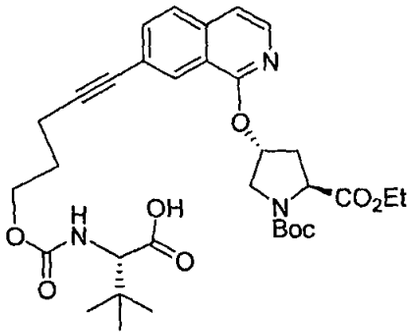
III-185

Step 1: 1,2-Pyrrolidinedicarboxylic acid, 4-[(7-bromo-1-isoquinolinyl)oxy]-, 1-(1,1-dimethylethyl) 2-ethyl ester, (2*S*,4*R*)-



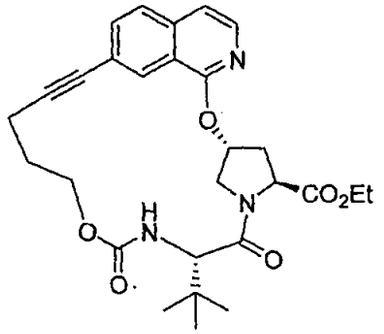
To a solution of di-*tert*-butyldicarbonate (1.14 g, 5.23 mmol) in CH_3CN (15 mL) was added Et_3N (2.08 mL, 14.9 mmol) and (4*R*)-4-[(7-bromoisoquinolin-1-yl)oxy]-L-prolinate hydrochloride (EXAMPLE 10, Step 1) (1.5 g, 3.73 mmol) at RT. After 15 min, DCM (150 mL) was added and the solution was extracted with 1 N HCl. The organic layer was dried over K_2CO_3 and the solvent was removed in vacuo. The crude material was purified on silica gel (gradient elution 0-30% EtOAc in hexanes) to yield the title compound as a foam (1.73 g). LRMS $(M+H)^+$ Calcd. = 465.1; found 465.2.

Step 2: *N*-({[5-(1-{[(3*R*,5*S*)-1-(*tert*-Butoxycarbonyl)-5-(ethoxycarbonyl)pyrrolidin-3-yl]oxy}isoquinolin-7-yl)pent-4-yn-1-yl]oxy}carbonyl)-3-methyl-L-valine



To a portion of the product from Step 1 (0.94 g, 2.02 mmol), in degassed THF (10 mL) and pyrrolidine (10 ml) was added intermediate B11, 3-methyl-*N*-[(pent-4-yn-1-yloxy)carbonyl]-L-valine (0.8 g, 3.33 mmol), $Pd(PPh_3)_4$ (58 mg, 0.05 mmol), and CuI (19 mg, 0.1 mmol). The mixture was then heated to 70 °C for 2h. The mixture was then poured into a mixture of water and EtOAc and the pH adjusted to ~1 with 1 N HCl. The organic layer was then separated, dried over $MgSO_4$, and the solvent evaporated. The crude product was purified on silica gel (20-100% EtOAc in hexanes) to yield the title compound as a foam (1.2 g). LRMS $(M+H)^+$ Calcd. = 626.3; found 626.4.

Step 3: 7-Ethyl (2*R*,4*S*,7*S*)-7-*tert*-butyl-6,9-dioxo-14,15-didehydro-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate



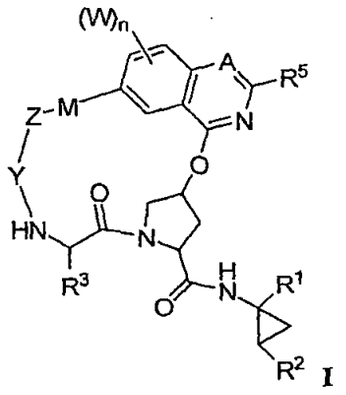
To a portion of the product from Step 2 (0.93 g, 1.49 mmol), was added HCl/dioxane (37 mL, 4M, 148 mmol). The mixture was stirred for 30 min and then the solvent was removed in vacuo. DCM (400 mL) was then added the mixture along with DIEA (1.3 mL, 7.4 mmol) and HATU (622 mg, 1.6 mmol). After 20 h, the solvent was removed in vacuo and the crude product was purified on silica gel (gradient elution 0-60% EtOAc in hexanes) to yield the title compound as a foam (0.11 g). LRMS $(M+H)^+$ Calcd. = 508.3; found 508.4.

Step 4: (2*R*,4*S*,7*S*)-7-*tert*-Butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-6,9-dioxo-14,15-didehydro-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxamide (**III-185**)

The title compound was prepared from 7-ethyl (2*R*,4*S*,7*S*)-7-*tert*-butyl-6,9-dioxo-14,15-didehydro-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-(ethanediylidene)-2,5-methanopyrido[2,3*k*][1,10,3,6]dioxadiazacyclononadecine-4-carboxylate and Intermediate A1 using the procedure described in EXAMPLE 14, Steps 4 and 5. LRMS (ESI) *m/z* 692.3 [$(M+H)^+$; calcd for $C_{35}H_{42}N_5O_8S$: 692.3].

WHAT IS CLAIMED IS:

1. A compound of formula (I):



I

wherein:

n is 1 or 2;

R^1 is CO_2R^{10}, $CONR^{10}SO_2R^6$, $CONR^{10}SO_2NR^8R^9$, or tetrazolyl;

R^2 is C_1-C_6 alkyl, C_2-C_6 alkenyl or C_3-C_8 cycloalkyl, wherein said alkyl, alkenyl or cycloalkyl is optionally substituted with 1 to 3 halo;

R^3 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8)alkyl, aryl(C_1-C_8)alkyl, or Het, wherein aryl is phenyl or naphthyl and said alkyl, cycloalkyl, or aryl is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), NO_2, CN, CF_3, $SO_2(C_1$-C_6 alkyl), $S(O)(C_1$-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$;

Het is a 5-6 membered saturated cyclic ring having 1, 2 or 3 heteroatoms selected from N, O and S, wherein said ring is optionally substituted with 1 to 3 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), NO_2, CN, CF_3, $SO_2(C_1$-C_6 alkyl), $S(O)(C_1$-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$;

R^4 is H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl(C_1-C_8)alkyl, or aryl(C_1-C_8)alkyl; wherein aryl is phenyl or naphthyl and said alkyl, cycloalkyl, or aryl is optionally substituted with 1 to 3 substituents selected from the

group consisting of halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1\text{-}C_6$ alkyl$)O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, halo($C_1\text{-}C_6$ alkoxy), NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $S(O)(C_1\text{-}C_6$ alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$;

R^5 is H, halo, OH, $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ alkyl, CN, CF_3, SR^{10}, $SO_2(C_1\text{-}C_6$ alkyl), $C_3\text{-}C_8$ cycloalkyl, $C_3\text{-}C_8$ cycloalkoxy, $C_1\text{-}C_6$ haloalkyl, $N(R^7)_2$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein said aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkoxy, alkyl or alkoxy is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^7)_2$, $N(C_1\text{-}C_6$ alkyl$)O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, halo($C_1\text{-}C_6$ alkoxy), $C_3\text{-}C_6$ cycloalkyl, $C_3\text{-}C_6$ cycloalkoxy, NO_2, CN, CF_3, $SO_2(C_1\text{-}C_6$ alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $S(O)(C_1\text{-}C_6$ alkyl), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$; wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

R^6 is $C_1\text{-}C_8$ alkyl, $C_3\text{-}C_8$ cycloalkyl, $C_3\text{-}C_8$ cycloalkyl($C_1\text{-}C_5$)alkyl, aryl, aryl($C_1\text{-}C_4$)alkyl, heteroaryl, heteroaryl($C_1\text{-}C_4$ alkyl), heterocyclyl, or heterocyclyl($C_1\text{-}C_8$ alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 W' substituents; and wherein each aryl is independently phenyl or naphthyl, each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen;

Y is C(=O), SO_2, or C(=N-CN);

Z is $C(R^{10})_2$, O, or $N(R^4)$;

M is $C_1\text{-}C_{12}$ alkylene or $C_2\text{-}C_{12}$ alkenylene or $C_2\text{-}C_{12}$ alkynylene, wherein said alkylene or alkenylene is optionally substituted with 1, 2 or 3 substituents selected from the group consisting of $C_1\text{-}C_8$ alkyl, $C_3\text{-}C_8$ cycloalkyl($C_1\text{-}C_8$ alkyl), and aryl($C_1\text{-}C_8$ alkyl); wherein 2 substituents on adjacent carbon atoms of M are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S, or 2 substituents on the same carbon atom of M are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

A is $C(R^{11})$ or N;

when R^5 is other than H, R^{11} is H, C_1-C_6 alkyl, halo, OR^{10}, SR^{10}, or $N(R^{10})_2$;

when R^5 is H, R^{11} is H, C_1-C_6 alkyl, halo, OH, C_1-C_6 alkoxy, CN, CF_3, SR^{10}, $SO_2(C_1$-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, $N(R^7)_2$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein said aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkoxy, alkyl or alkoxy is optionally substituted with 1 to 4 substituents selected from the group consisting of halo, OR^{10}, SR^{10}, $N(R^7)_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), C_3-C_6 cycloalkyl, C_3-C_6 cycloalkoxy, NO_2, CN, CF_3, $SO_2(C_1$-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $S(O)(C_1$-C_6 alkyl), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, and $CON(R^{10})_2$; wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

or R^5 and R^{11} are optionally taken together to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0-2 heteroatoms selected from N, O and S;

each R^7 is independently H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl(C_1-C_5)alkyl, aryl, aryl(C_1-C_4)alkyl, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl, or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 to 2 W' substituents; and wherein each aryl is independently phenyl or naphthyl, each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen;

each W is independently H, halo, OR^7, C_1-C_6 alkyl, CN, CF_3, NO_2, SR^7, CO_2R^7, $CON(R^7)_2$, $C(O)R^7$, $N(R^{10})C(O)R^7$, $SO_2(C_1$-C_6 alkyl), $S(O)(C_1$-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, $N(R^7)_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), halo(C_1-C_6 alkoxy), $NR^{10}SO_2R^7$, $SO_2N(R^7)_2$, $NHCOOR^7$, $NHCONHR^7$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached

through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein 2 adjacent W moieties are optionally taken together with the atoms to which they are attached to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0-2 heteroatoms selected from N, O and S;

each W' is independently halo, OR^{10}, C_1-C_6 alkyl, CN, CF_3, NO_2, SR^{10}, CO_2R^{10}, $CON(R^{10})_2$, $C(O)R^{10}$, $N(R^{10})C(O)R^{10}$, SO_2(C_1-C_6 alkyl), S(O)(C_1-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, $N(R^{10})_2$, N(C_1-C_6 alkyl)O(C_1-C_6 alkyl), halo(C_1-C_6 alkoxy), $NR^{10}SO_2R^{10}$, $SO_2N(R^{10})_2$, $NHCOOR^{10}$, $NHCONHR^{10}$, aryl, heteroaryl or heterocyclyl; wherein aryl is phenyl or naphthyl, heteroaryl is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen, and heterocyclyl is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein 2 adjacent W' moieties are optionally taken together with the atoms to which they are attached to form a 5- to 6-membered saturated, unsaturated non-aromatic, or aromatic cyclic ring having 0-2 heteroatoms selected from N, O and S;

R^8 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), aryl, aryl(C_1-C_4 alkyl), heteroaryl, heterocyclyl, heteroaryl(C_1-C_4 alkyl), or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, halo(C_1-C_6 alkoxy), halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(C_1-C_6 alkyl)O(C_1-C_6 alkyl), C_1-C_6 alkyl, $C(O)R^{10}$, C_1-C_6 haloalkyl, NO_2, CN, CF_3, SO_2(C_1-C_6 alkyl), S(O)(C_1-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, and $C(O)N(R^{10})_2$; wherein each aryl is independently phenyl or naphthyl; each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

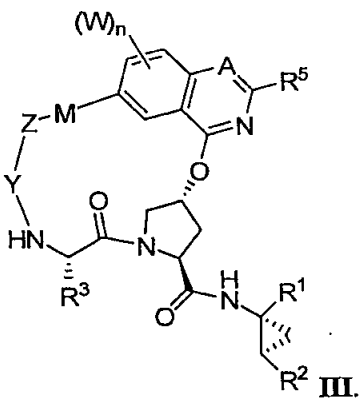
R^9 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, aryl, aryl(C_1-C_4 alkyl), heteroaryl, heterocyclyl, heteroaryl(C_1-C_4 alkyl), or heterocyclyl(C_1-C_8 alkyl), wherein said alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, heteroaryl or heterocyclyl is optionally substituted with 1 to 4 substituents selected from the group consisting of aryl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl,

C_1-C_6 alkyl, halo(C_1-C_6 alkoxy), halo, OR^{10}, SR^{10}, $N(R^{10})_2$, $N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, $C(O)R^{10}$, C_1-C_6 haloalkyl, NO_2, CN, CF_3, $SO_2(C_1$-C_6 alkyl), $S(O)(C_1$-C_6 alkyl), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, and $C(O)N(R^{10})_2$; wherein each aryl is independently phenyl or naphthyl; each heteroaryl is independently a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and each heterocyclyl is independently a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen; and wherein the 2 adjacent substituents of said cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3-6 membered cyclic ring containing 0-3 heteroatoms selected from N, O and S;

or R^8 and R^9 are optionally taken together, with the nitrogen atom to which they are attached, to form a 4-8 membered monocyclic ring containing 0-2 additional heteroatoms selected from N, O and S; and

each R^{10} is independently H or C_1-C_6 alkyl.

2. The compound of claim 1, wherein the compound is of formula III:



III.

3. The compound of claim 2, wherein R^1 is CO_2R^{10} or $CONR^{10}SO_2R^6$.

4. The compound of claim 3, wherein R^1 is CO_2H.

5. The compound of claim 3, wherein R^1 is $CONHSO_2R^6$.

6. The compound of claim 5, wherein R^1 is $CONHSO_2R^6$ wherein R^6 is C_3-C_8 cycloalkyl, C_1-C_8 alkyl, aryl, or aryl(C_1-C_4)alkyl.

7. The compound of claim 3, wherein R^2 is C_1-C_4 alkyl or C_2-C_4 alkenyl.

8. The compound of claim 7, wherein R^3 is C_5-C_6 cycloalkyl or C_1-C_8 alkyl optionally substituted with 1 to 3 halo substituents.

9. The compound of claim 8, wherein R^5 is H, halo, aryl, heteroaryl or $N(R^7)_2$.

10. The compound of claim 9, wherein R^5 is H or halo.

11. The compound of claim 9, wherein R^5 is aryl or heteroaryl.

12. The compound of claim 9, wherein Y is C=O.

13. The compound of claim 12, wherein Z is O, NH, $N(C_1$-C_8 alkyl) or $C(R^{10})_2$.

14. The compound of claim 13, wherein M is unsubstituted C_4-C_7 alkylene or unsubstituted C_4-C_7 alkenylene.

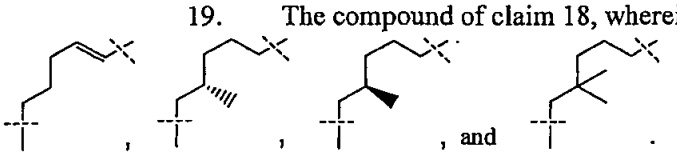
15. The compound of claim 14, wherein n is 1 and W is H, C_1-C_6 alkoxyl, C_1-C_6 alkyl, OH, halo, $N(R^7)_2$ wherein R^7 is H or C_1-C_6 alkyl.

16. The compound of claim 15, wherein A is N.

17. The compound of claim 15, wherein A is $C(R^{11})$ wherein R^{11} is H, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy or halo.

18. The compound of claim 10, wherein R^2 is C_2-C_4 alkenyl, R^5 is H, R^6 is C_3-C_8 cycloalkyl, W is R^7 or H, Y is C(=O), Z is O, and n is 1.

19. The compound of claim 18, wherein M is selected from the group consisting of:

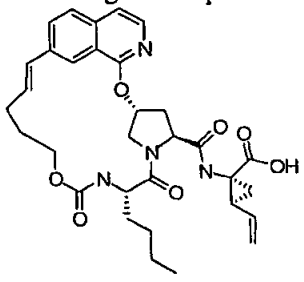


, and .

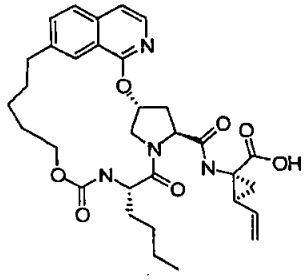
20. The compound of claim 19, wherein R^3 is C_5-C_6 cycloalkyl or C_3-C_5 alkyl.

21. The compound of claim 20, wherein R^6 is C_3-C_5 cycloalkyl.

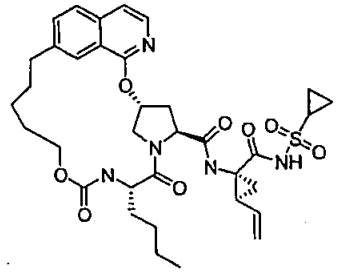
22. The compound of claim 1, wherein the compound is selected from the group consisting of compounds **III-1** to **III-38**:



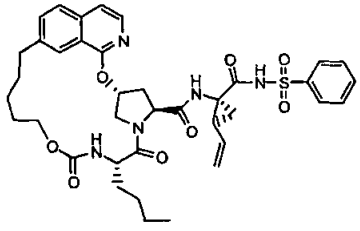
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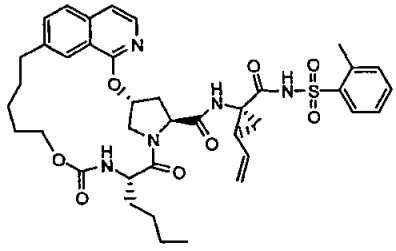
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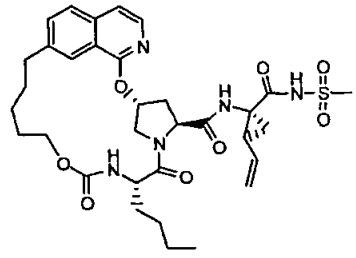
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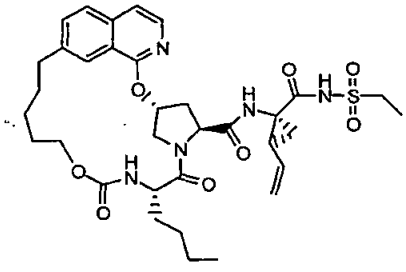
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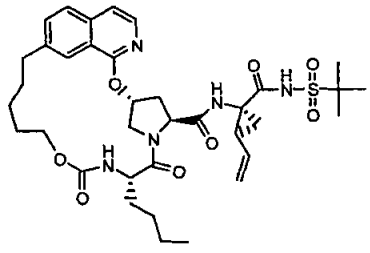
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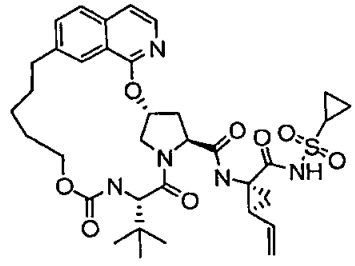
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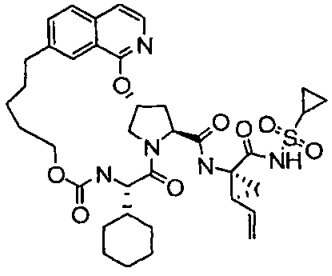
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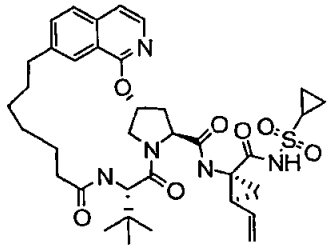
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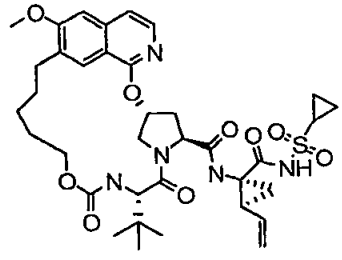
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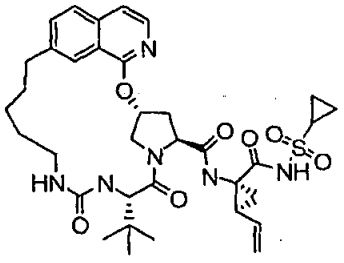
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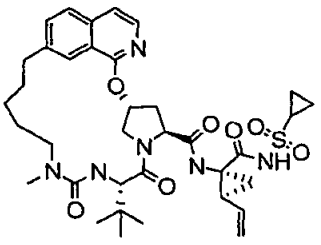
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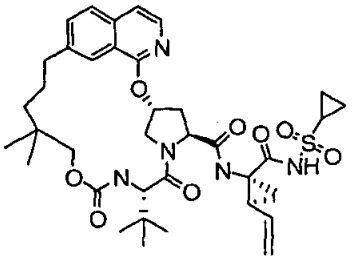
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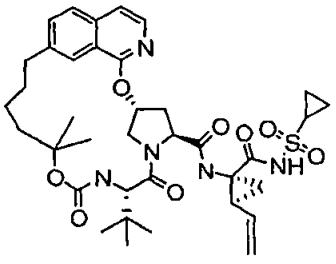
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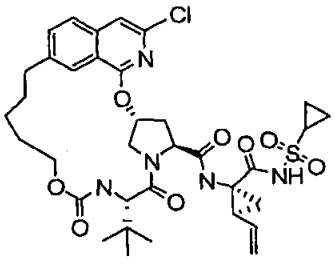
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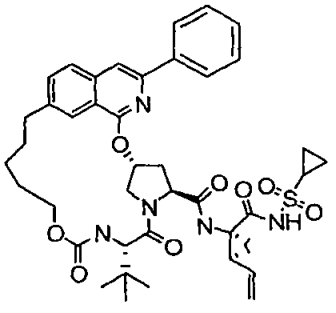
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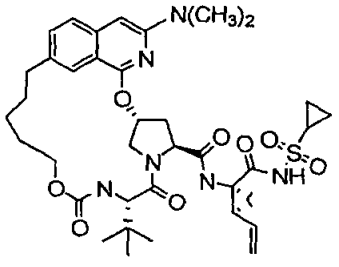
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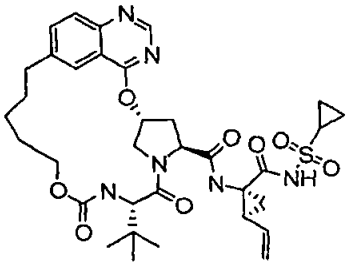
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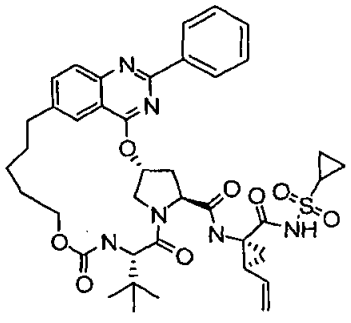
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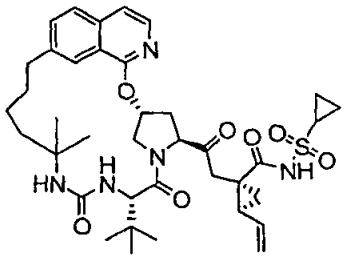
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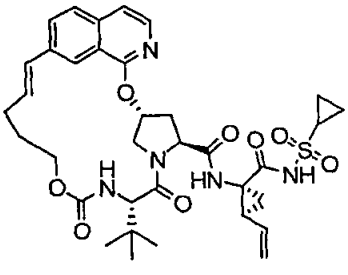
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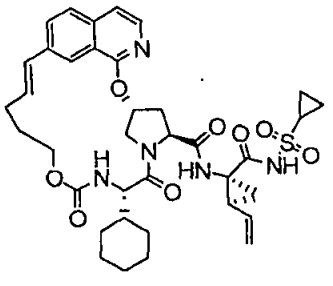
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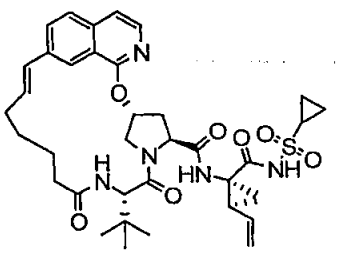
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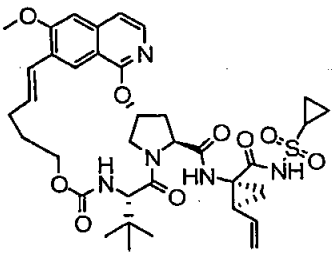
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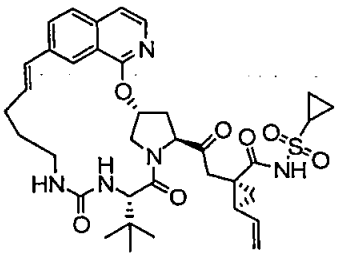
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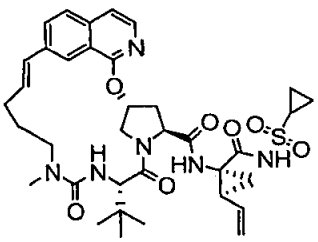
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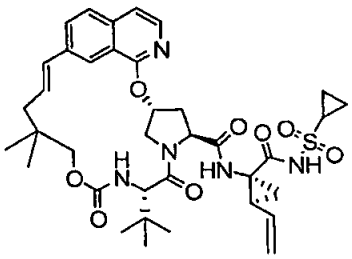
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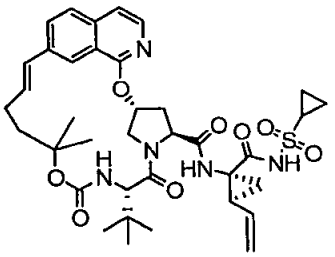
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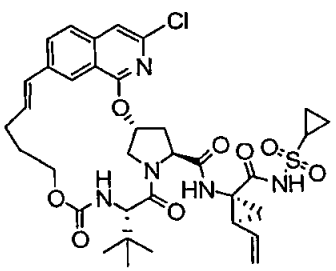
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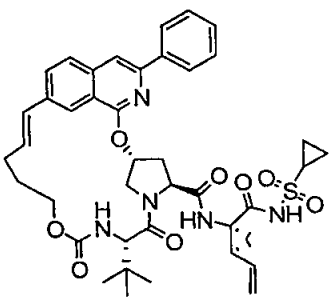
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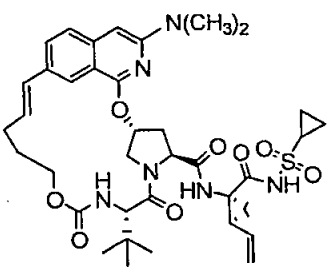
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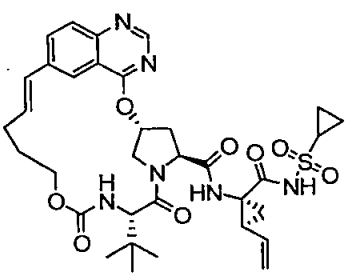
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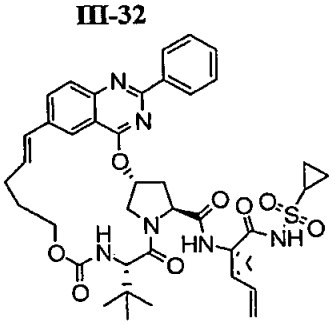
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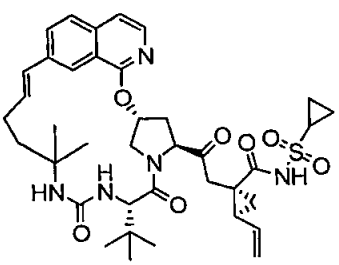
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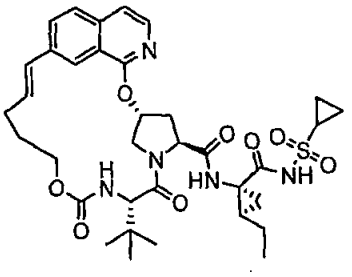
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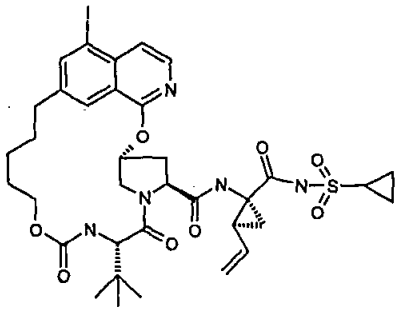
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III-36

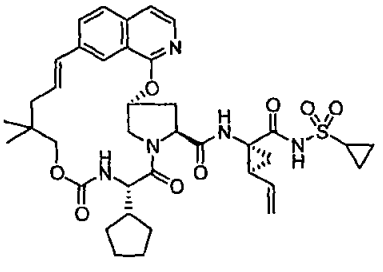


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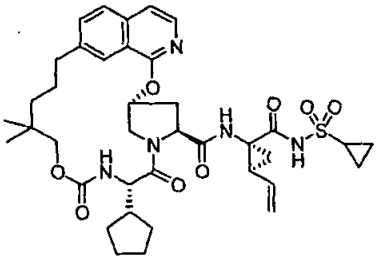


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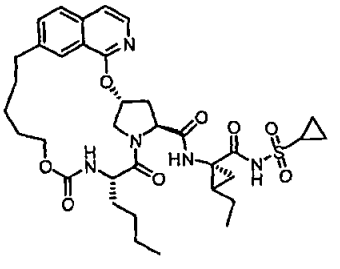
23. The compound of claim 1, wherein the compound is selected from the group consisting of compounds III-39 to III-187:



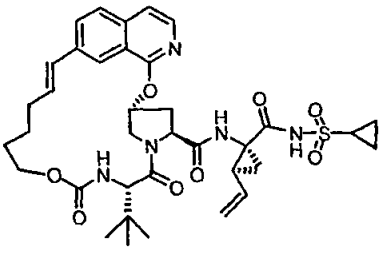
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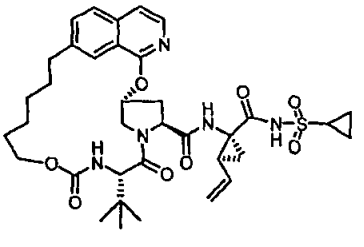
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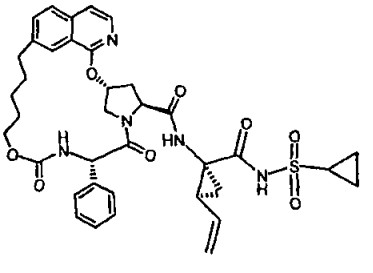
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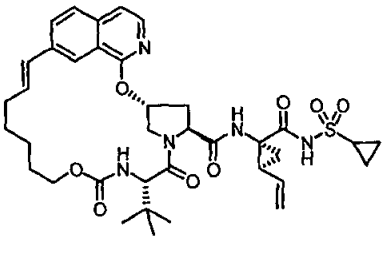
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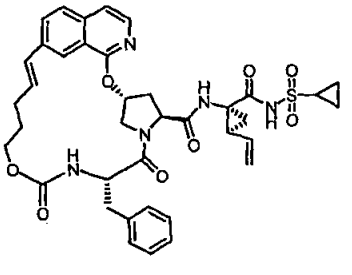
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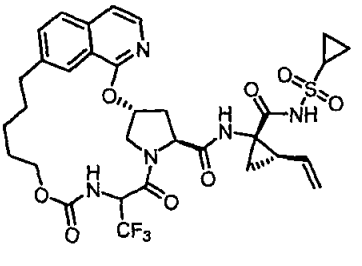
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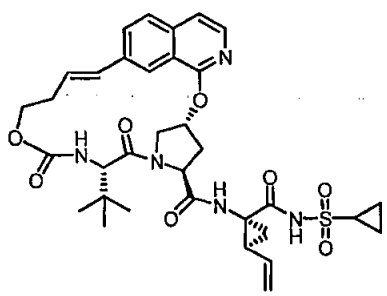
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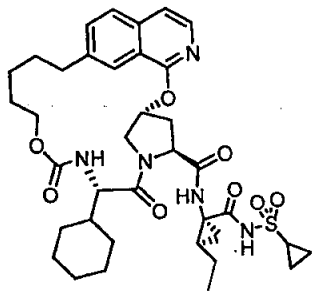
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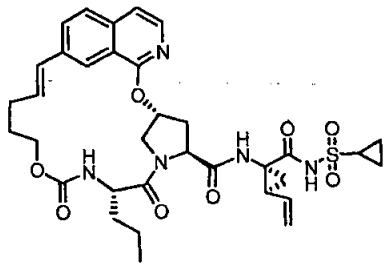
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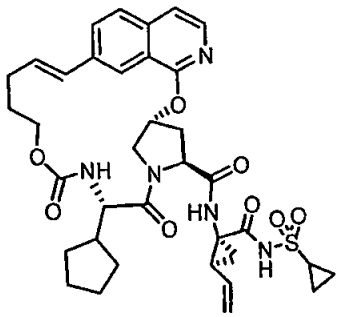
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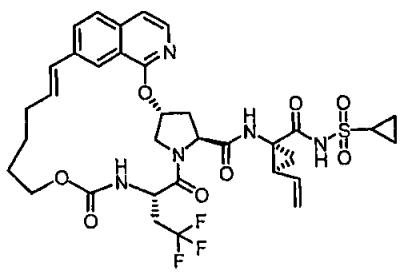
III-49



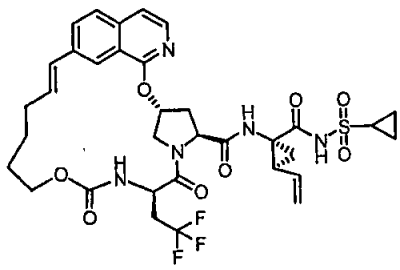
III-50



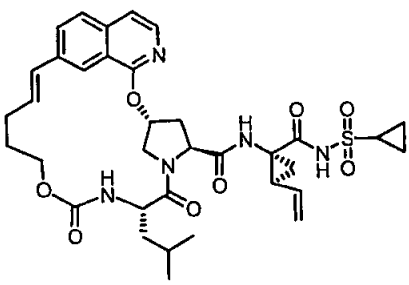
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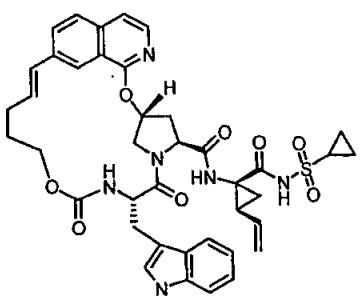
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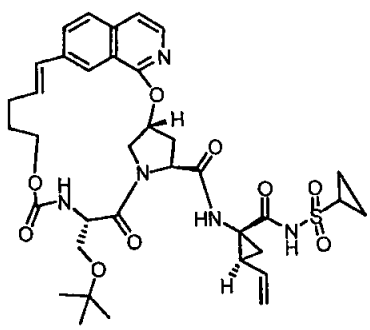
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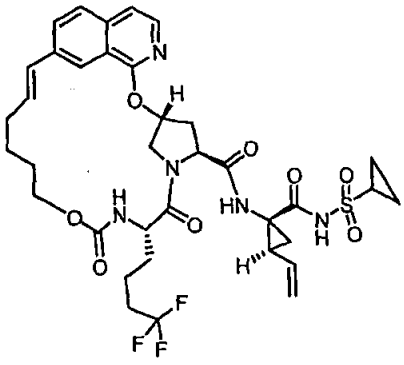
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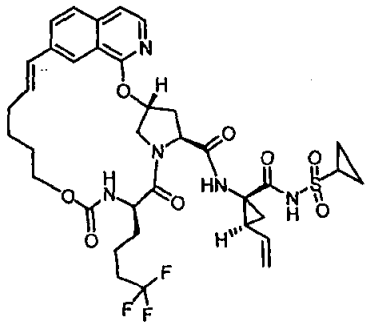
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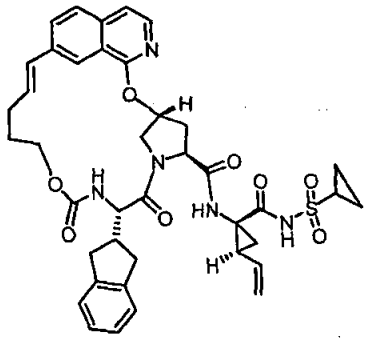
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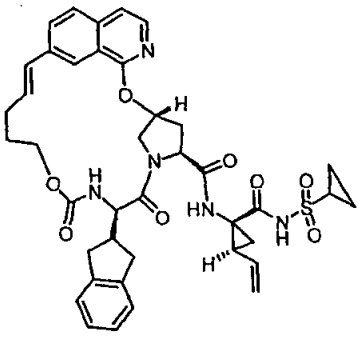
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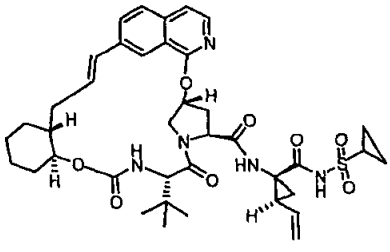
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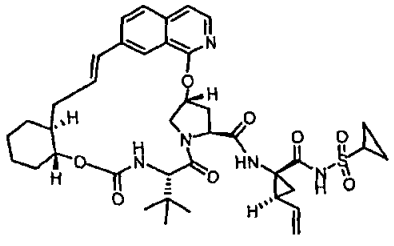
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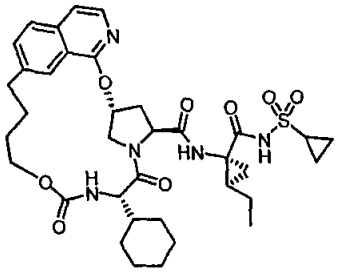
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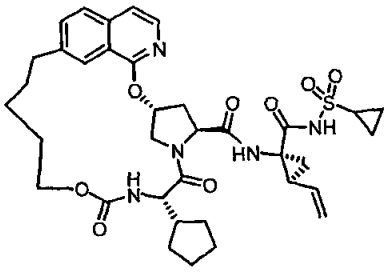
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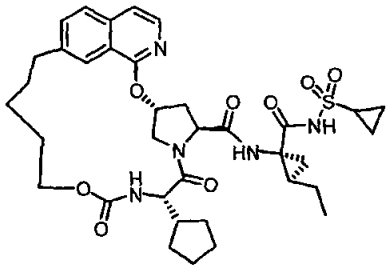
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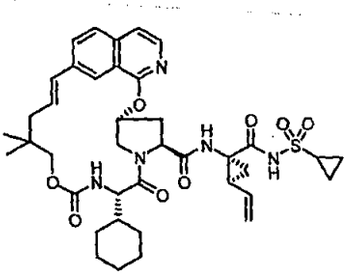
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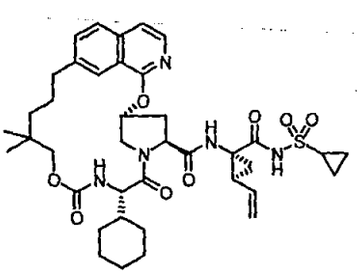
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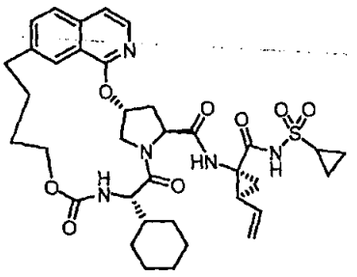
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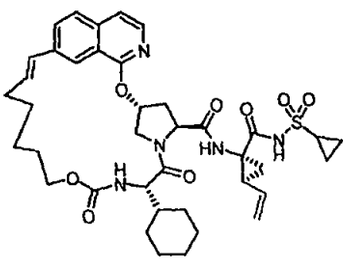
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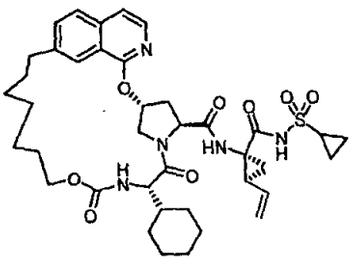
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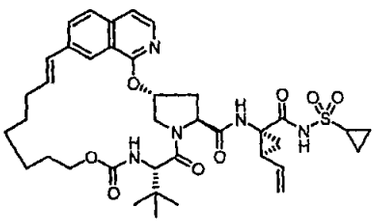
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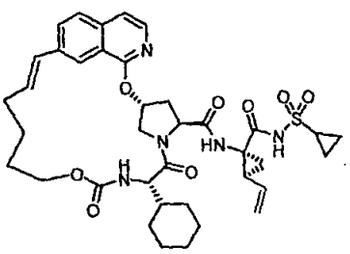
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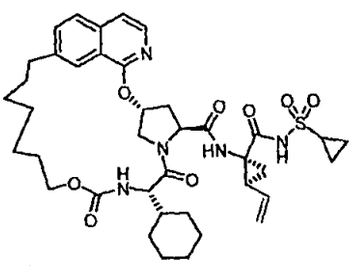
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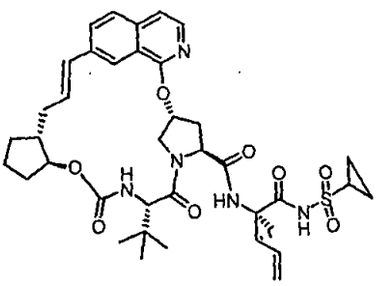
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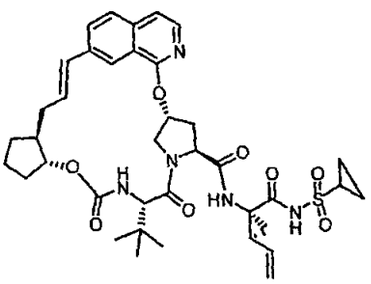
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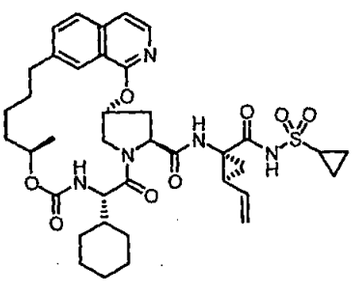
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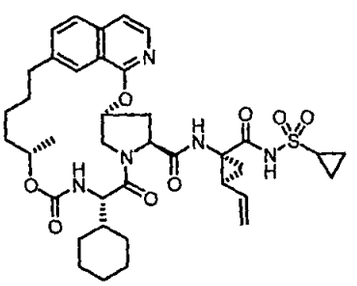
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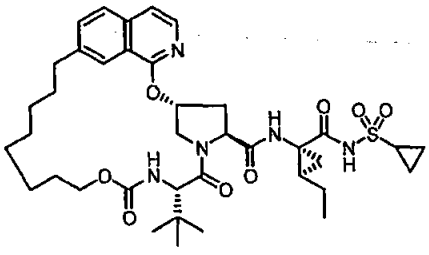
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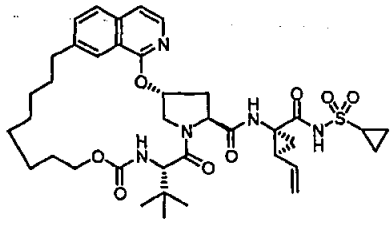
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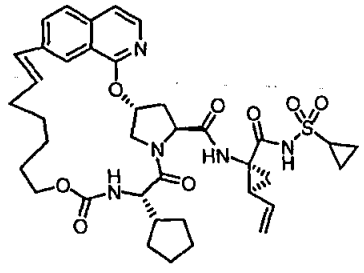
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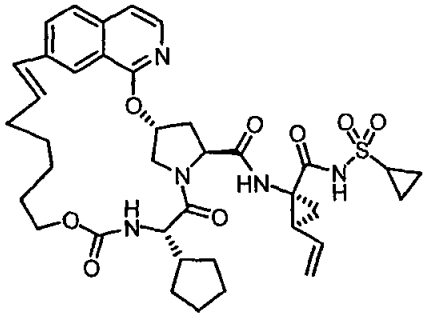
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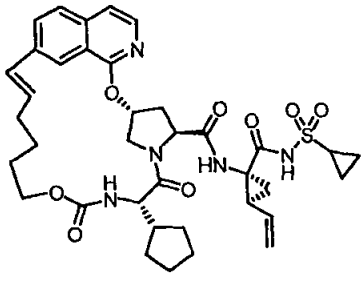
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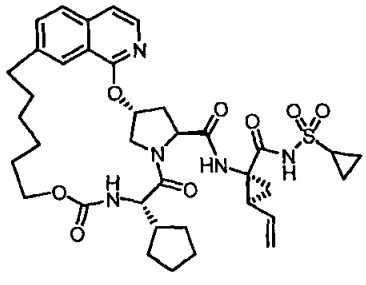
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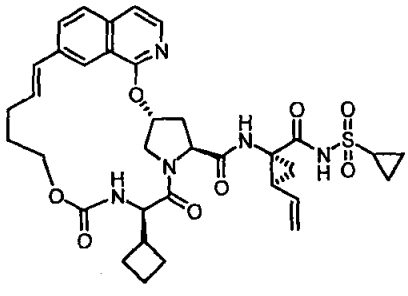
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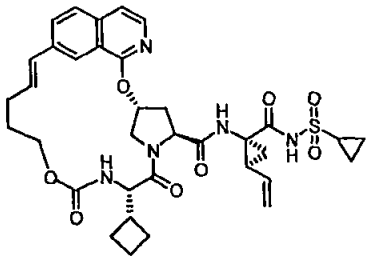
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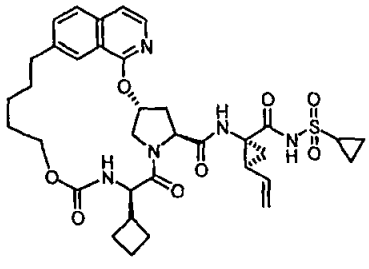
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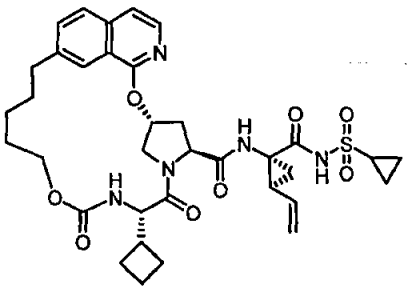
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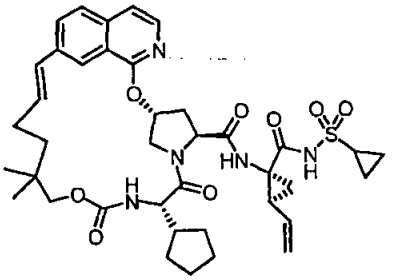
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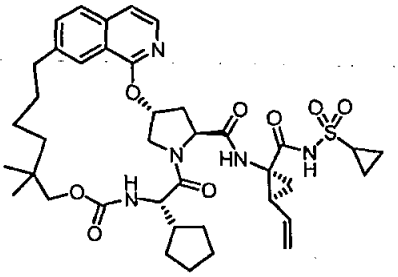
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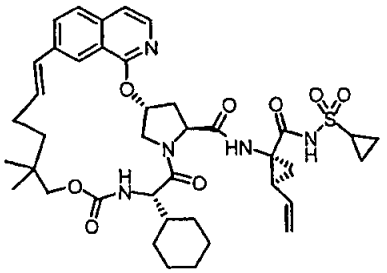
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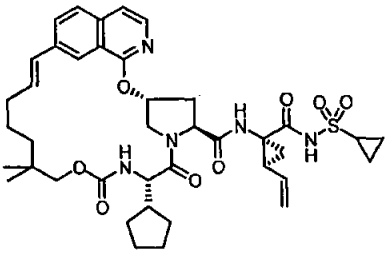
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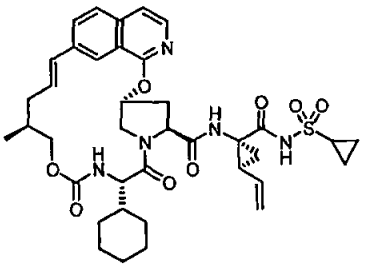
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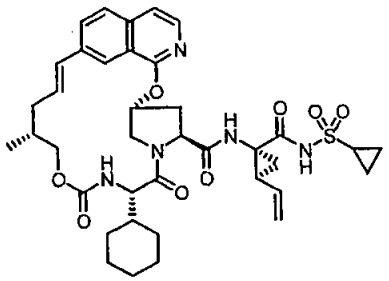
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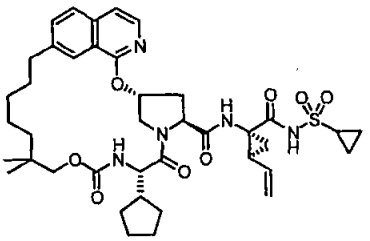
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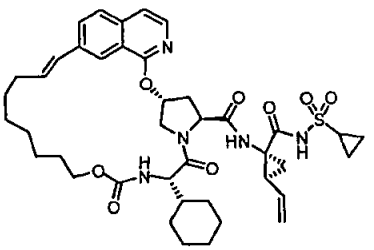
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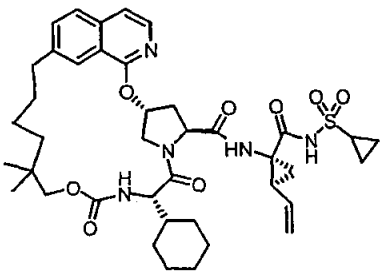
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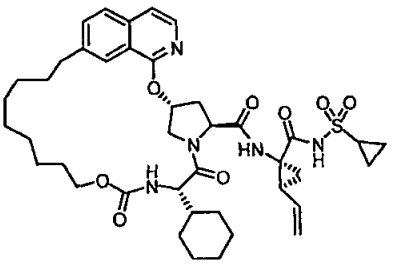
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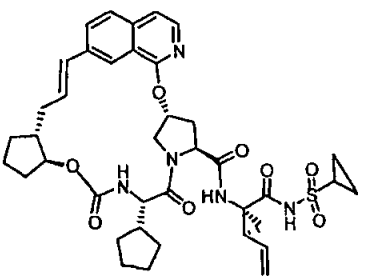
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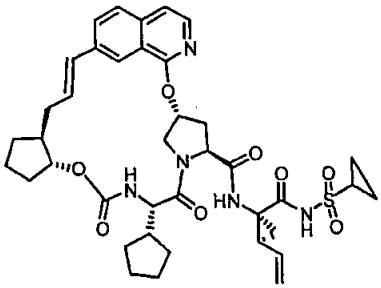
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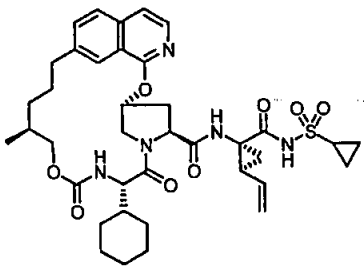
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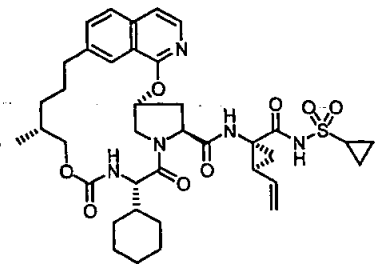
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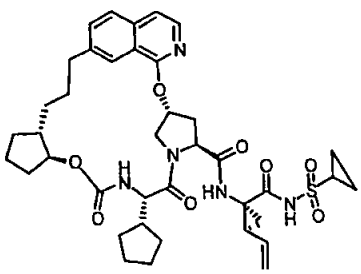
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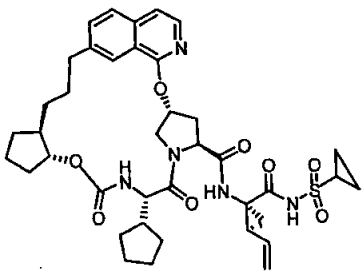
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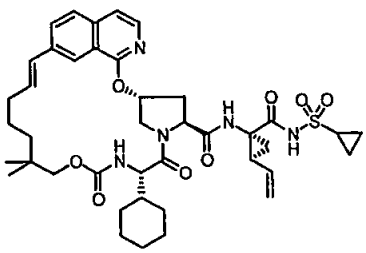
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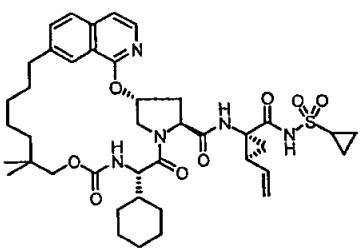
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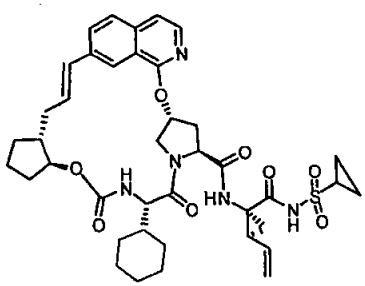
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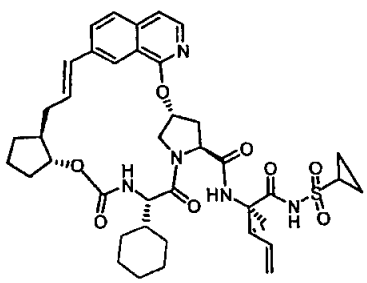
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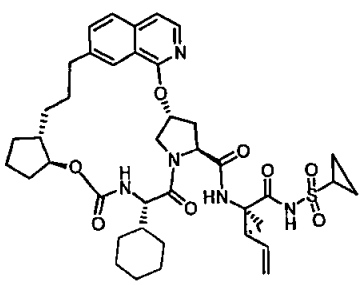
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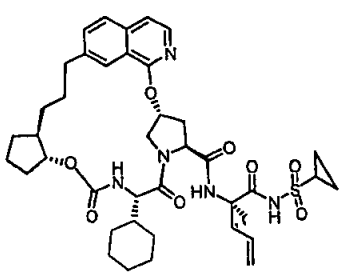
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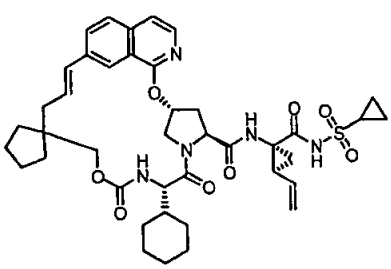
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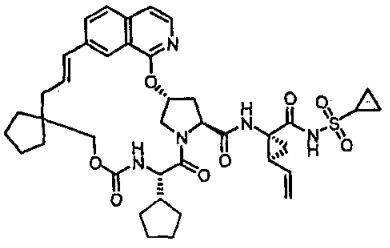
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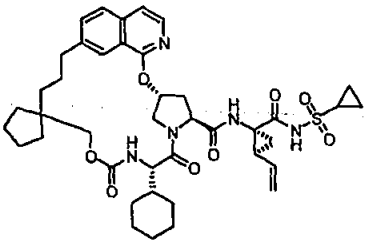
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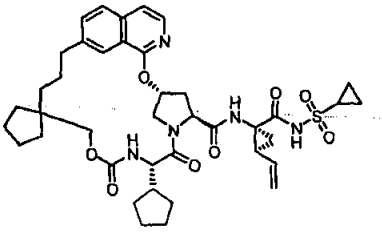
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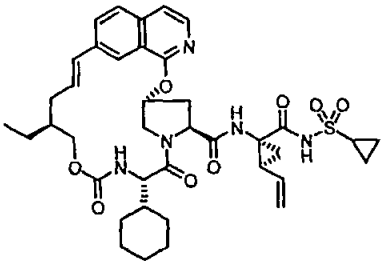
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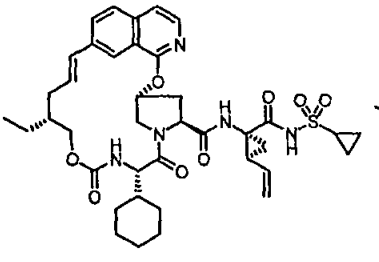
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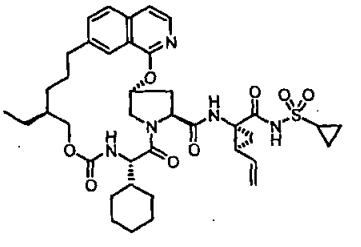
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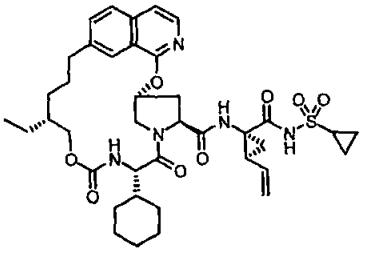
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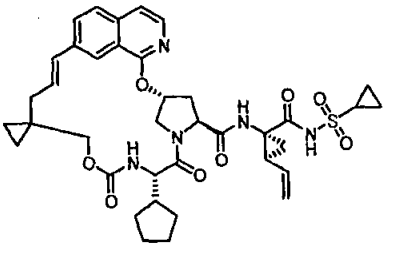
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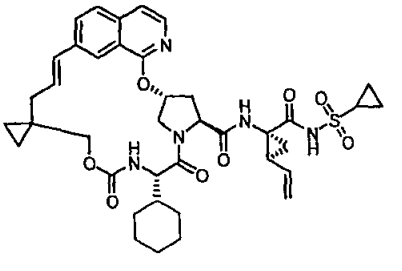
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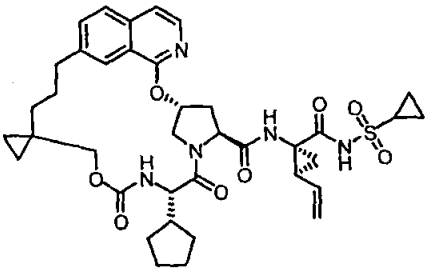
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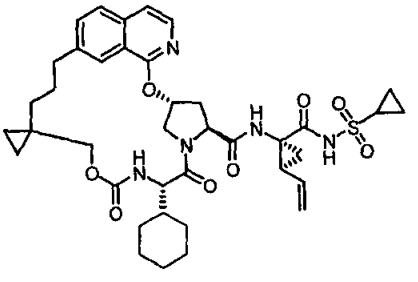
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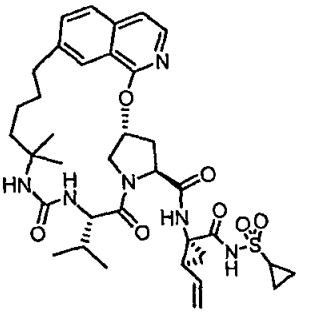
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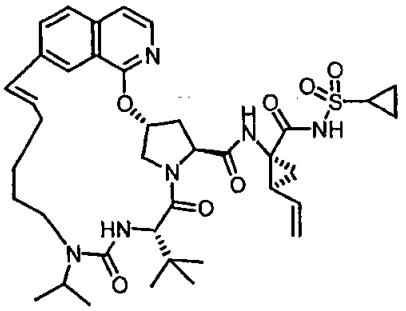
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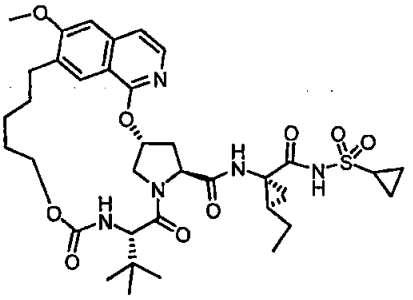
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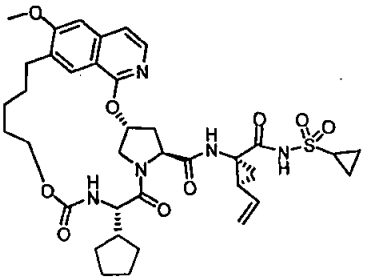
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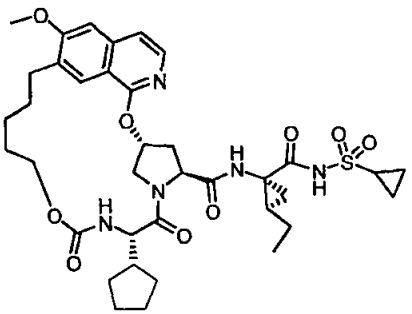
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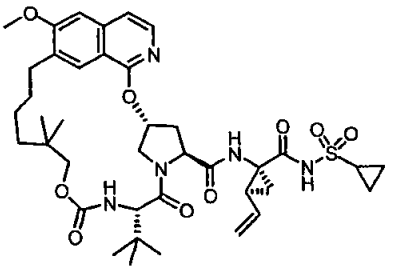
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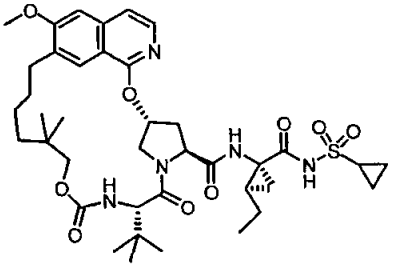
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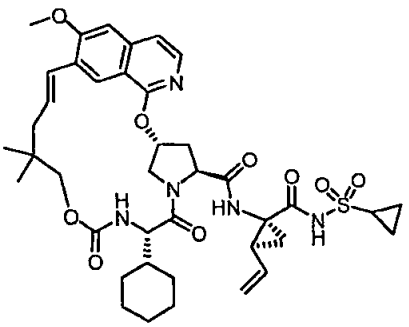
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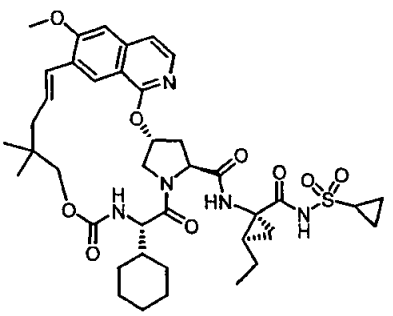
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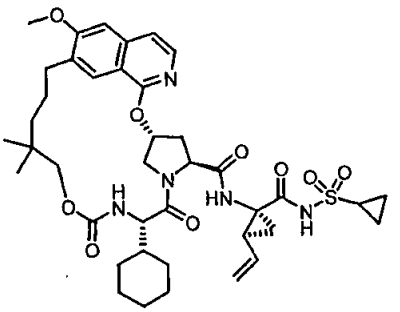
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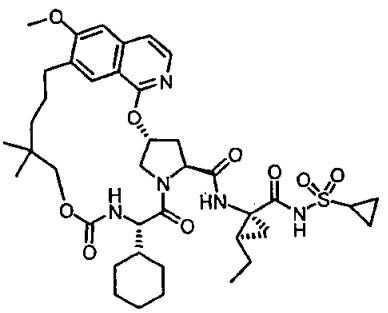
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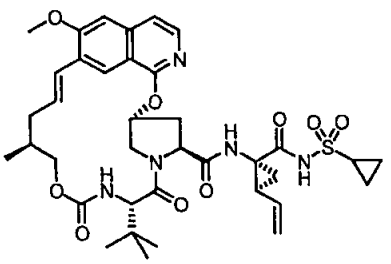
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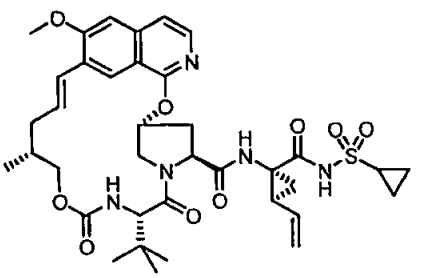
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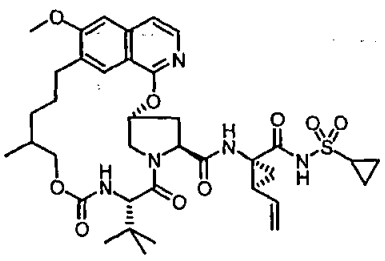
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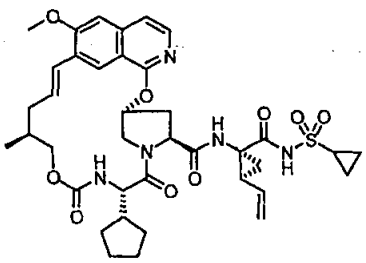
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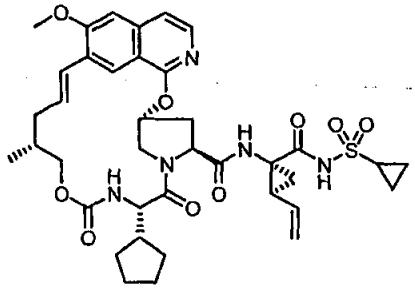
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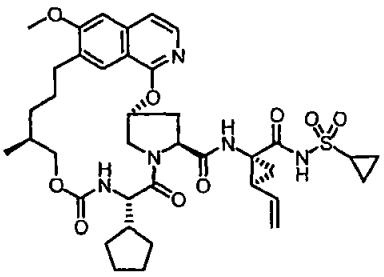
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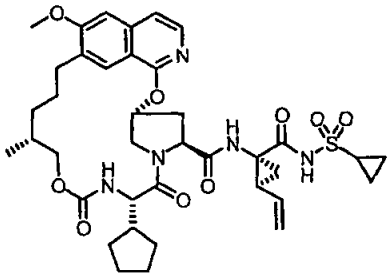
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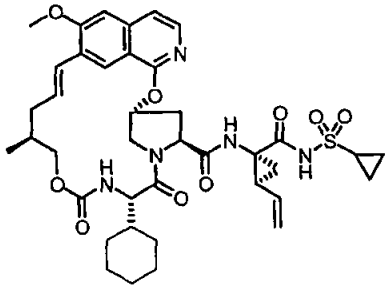
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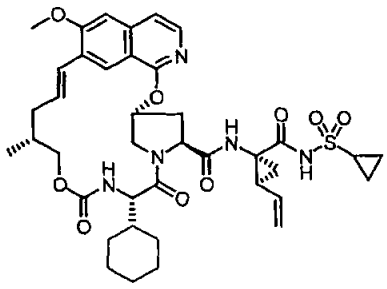
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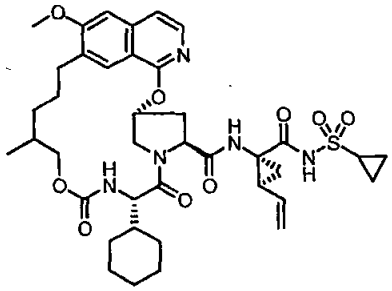
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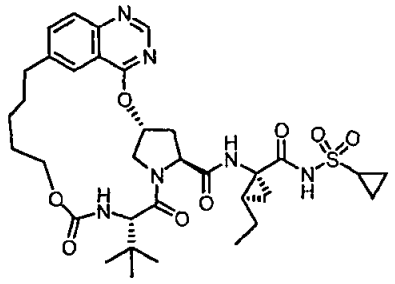
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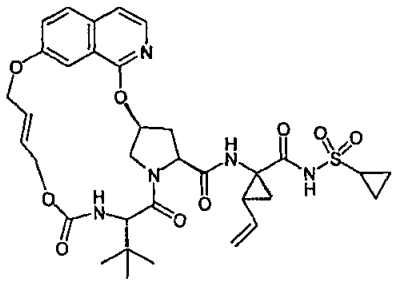
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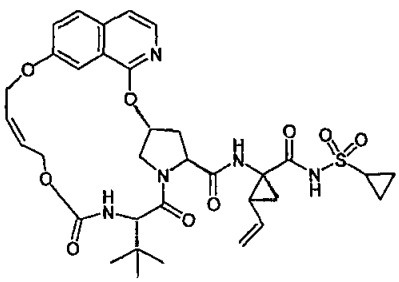
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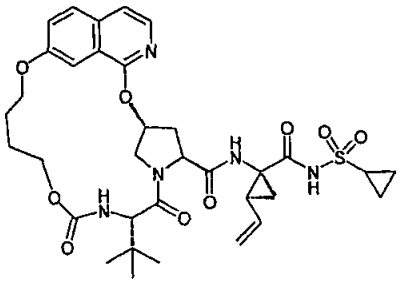
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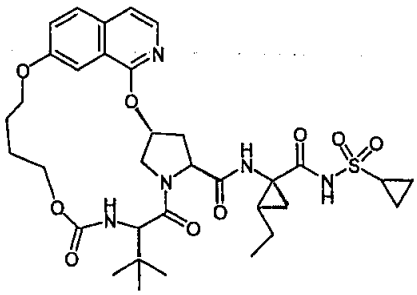
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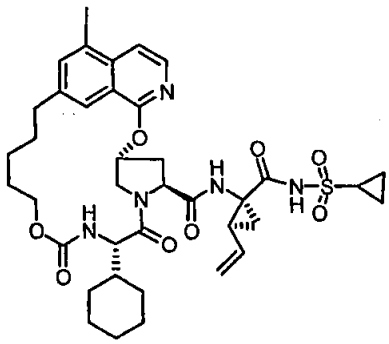
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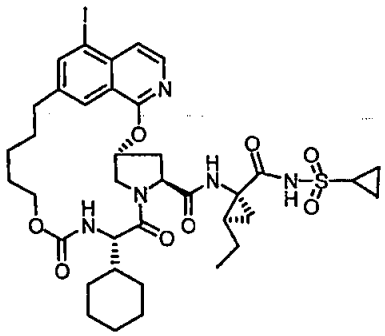
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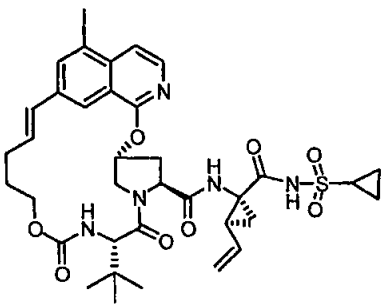
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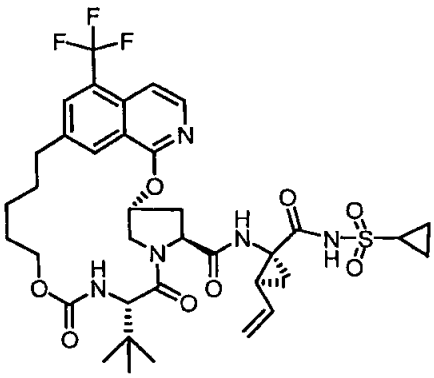
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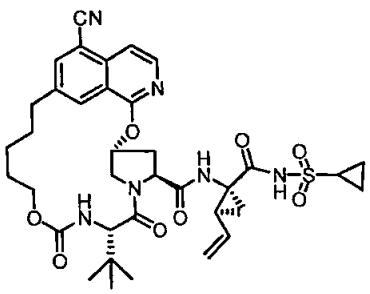
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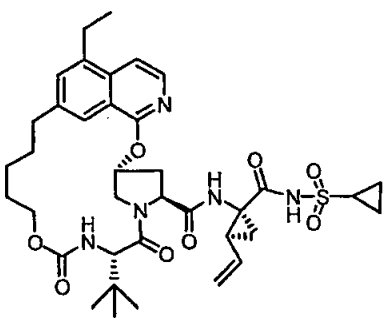
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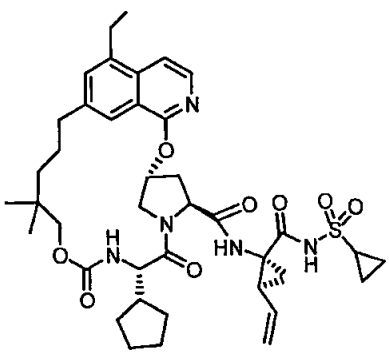
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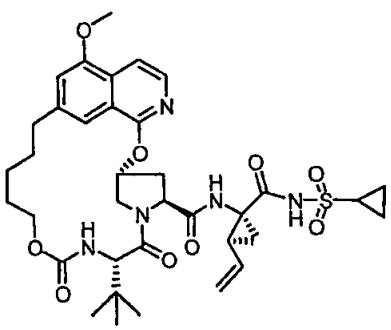
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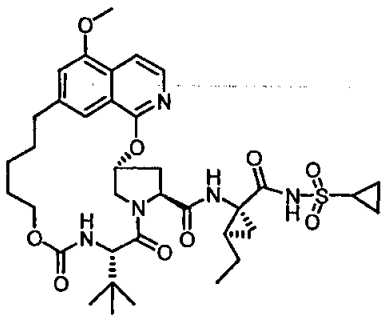
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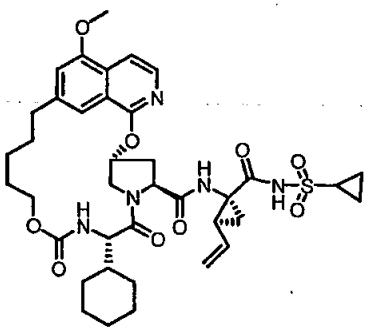
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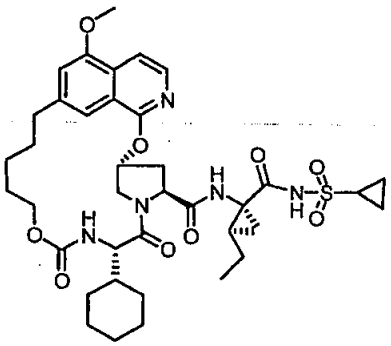
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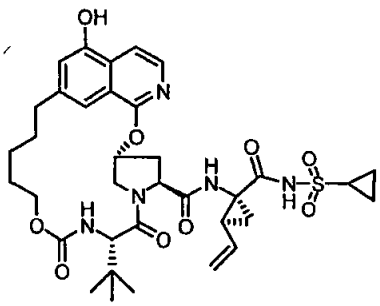
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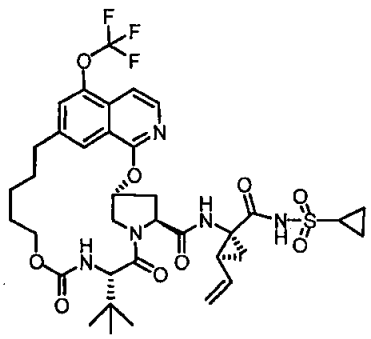
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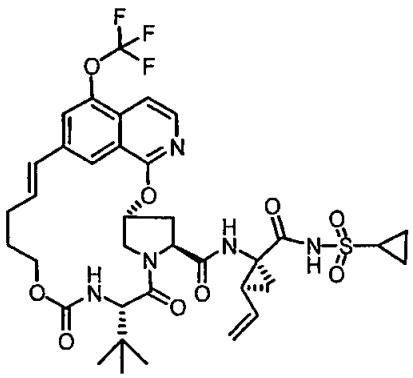
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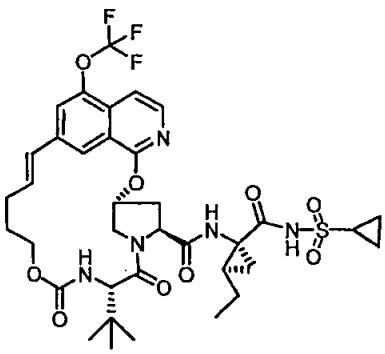
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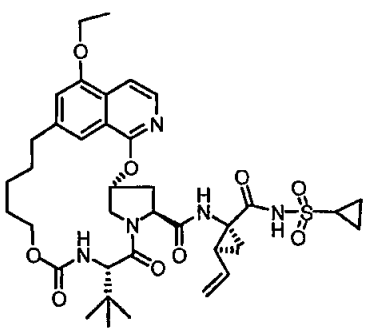
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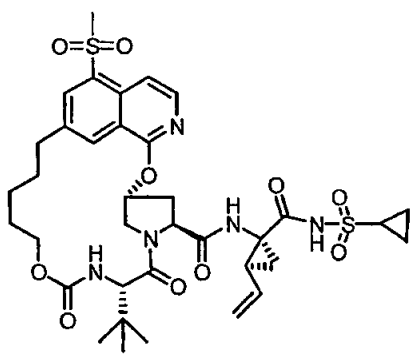
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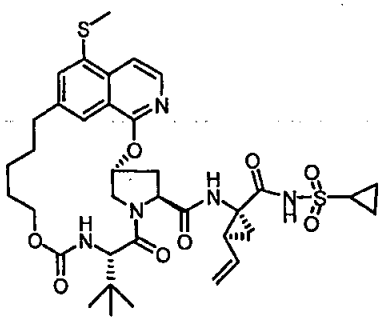
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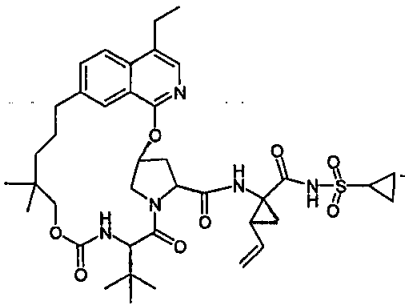
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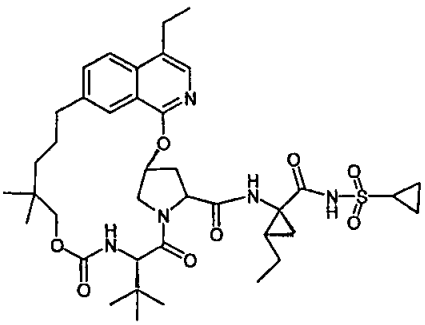
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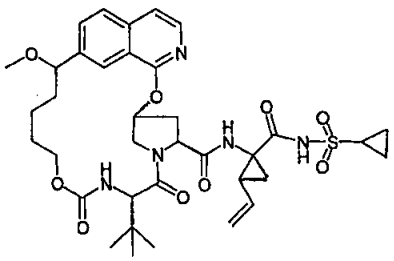
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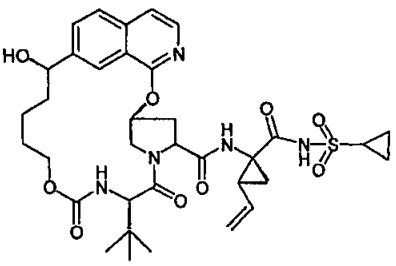
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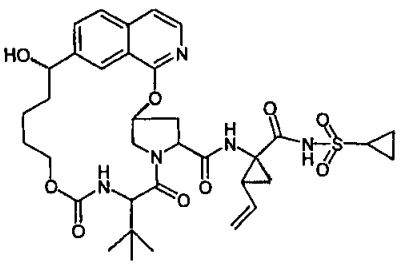
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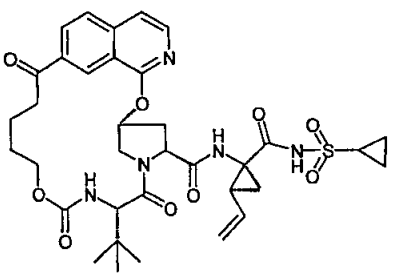
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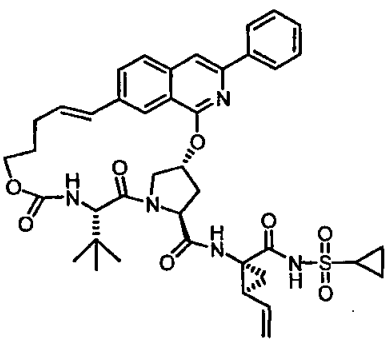
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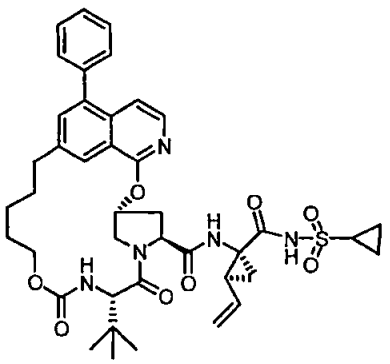
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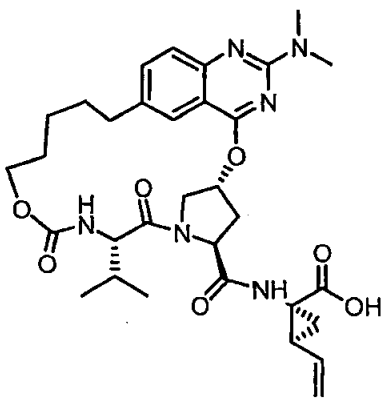


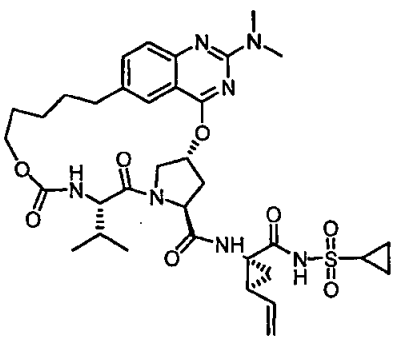
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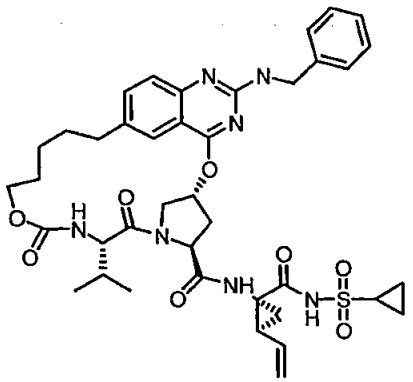
III-172

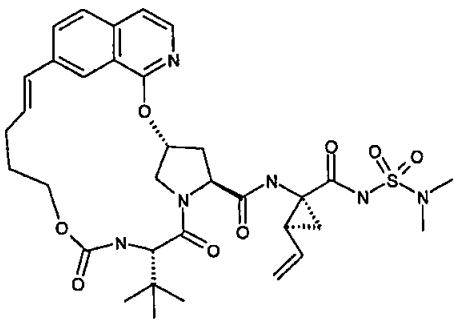




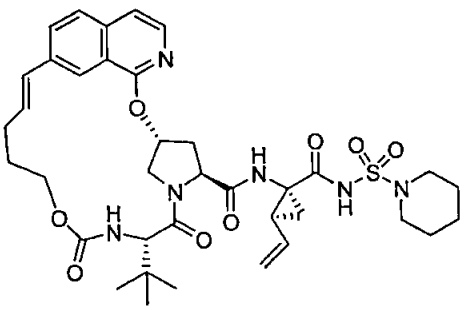


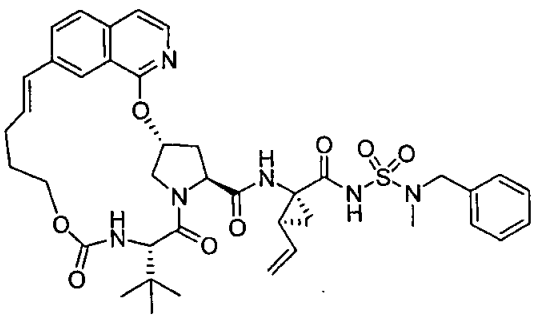
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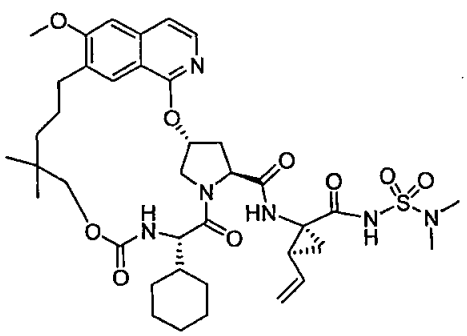


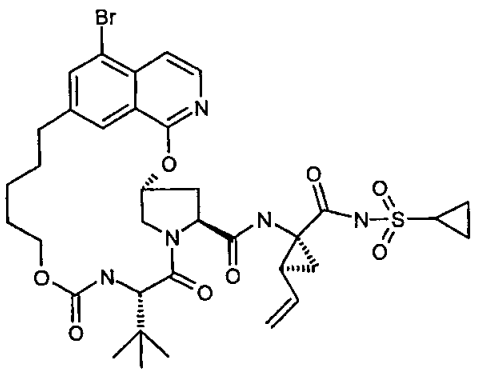
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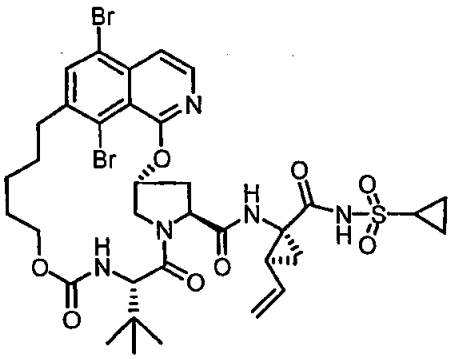


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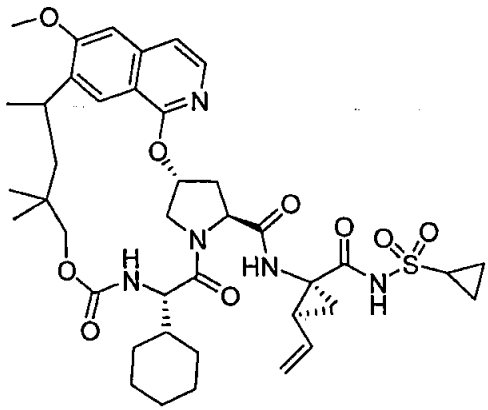




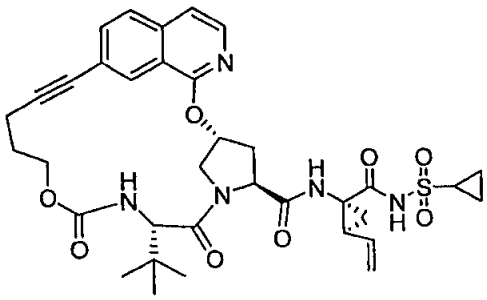
III-181 III-182



III-183



III-184



III-185

24. The compound of claim 1, wherein the compound is (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-tert-Butyl-6,9-dioxo-3,4,6,7,8,9,12,13-octahydro-2*H*,11*H*-16,18-ethanediylidene-2,5-methanopyrido[2,3-*k*][1,10,3,6]dioxadiazacyclononadecin-4-yl]carbonyl}amino)-2-vinylcyclopropanecarboxylic acid.

25. A pharmaceutical composition comprising an effective amount of a compound of any one of claims 1-24, and a pharmaceutically acceptable carrier.

26. The pharmaceutical composition of claim 25, further comprising a second therapeutic agent selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent.

27. The pharmaceutical composition of claim 26, wherein the HCV antiviral agent is an antiviral selected from the group consisting of a HCV protease inhibitor and a HCV NS5B polymerase inhibitor.

28. A use of a compound of any one of claims 1-24 in the preparation of a medicament for inhibiting HCV NS3 protease activity in a subject in need thereof.

29. A use of a compound of any one of claims 1-24 in the preparation of a medicament for preventing or treating infection by HCV in a subject in need thereof.

30. The use of claim 29, wherein said medicament further comprises at least one second therapeutic agent selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent.

31. The use of claim 30, wherein the HCV antiviral agent is an antiviral selected from the group consisting of a HCV protease inhibitor and a HCV NS5B polymerase inhibitor.

TÍTULO DE LA INVENCIÓN

INHIBIDORES DE PROTEASA NS3 DEL VHC

La presente invención se refiere a compuestos macrocíclicos que son útiles como inhibidores de la proteasa NS3 del virus de la hepatitis C (VHC), su síntesis, y su uso para tratar o prevenir la infección por VHC.

ANTECEDENTES DE LA INVENCIÓN

La infección por el virus de la hepatitis C (VHC) es un importante problema de salud que conduce a enfermedad crónica del hígado, tal como cirrosis y carcinoma hepatocelular, en un número sustancial de individuos infectados, estimándose en el 2-15% de la población mundial. Se estima que hay 3,9 millones de personas infectadas solo en los Estados Unidos, de acuerdo con el Centro para el Control de Enfermedades de los Estados Unidos, aproximadamente cinco veces el número de personas infectadas con el virus de la inmunodeficiencia humana (VIH). De acuerdo con la Organización Mundial de la Salud, hay más de 170 millones de individuos infectados por todo el mundo, infectándose al menos 3 a 4 millones de personas cada año. Una vez infectada, aproximadamente el 20% de la población elimina el virus, pero el resto alberga el VHC el resto de sus vidas. Del diez al veinte por ciento de los individuos crónicamente infectados desarrolla finalmente cirrosis que destruye el hígado o cáncer. La enfermedad viral se transmite parenteralmente a través de sangre contaminada y productos sanguíneos contaminados, agujas contaminadas, o por vía sexual y verticalmente de madres infectadas o madres portadoras a sus hijos.

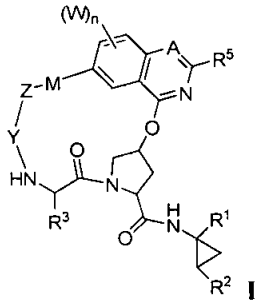
Los tratamientos actuales para infección por VHC, que están limitados a inmunoterapia con interferón-α recombinante solo o en combinación con el análogo nucleosídico ribavirina, son de beneficio clínico limitado. Además, no hay ninguna vacuna consolidada para VHC. Por consiguiente, hay una necesidad urgente de agentes terapéuticos mejorados que combatan de forma efectiva la infección crónica por VHC. El estado actual de la técnica en el tratamiento de la infección por VHC se ha descrito en las siguientes referencias: B. Dymock, y col., "Novel approaches to the treatment of hepatitis C virus infection," Antiviral Chemistry & Chemotherapy, 11: 79-96 (2000); H. Rosen, y col., "Hepatitis C virus: current understanding and prospects for future therapies," Molecular Medicine Today, 5: 393-399 (1999); D. Moradpour, y col., "Current and evolving therapies for hepatitis C," European J. Gastroenterol. Hepatol., 11: 1189-1202 (1999); R. Bartenschlager, "Candidate Targets for Hepatitis C Virus-Specific Antiviral Therapy," Intervirology, 40: 378-393 (1997); G.M. Lauer and B.D. Walker, "Hepatitis C Virus Infection," N. Engl. J. Med., 345: 41-52 (2001); B.W. Dymock, "Emerging therapies for hepatitis C virus infection," Emerging Drugs, 6: 13-42

(2001); y C. Crabb, "Hard-Won Advances Spark Excitement about Hepatitis C," Science: 506-507 (2001).

Varias enzimas codificadas viralmente son dianas teóricas para intervención terapéutica, incluyendo una metaloproteasa (NS2-3), una serina proteasa (NS3), una helicasa (NS3) y una RNA polimerasa dependiente de RNA (NS5B). La proteasa NS3 se localiza en el dominio N-terminal de la proteína NS3, y se considera un objetivo primordial de fármacos dado que es responsable de una escisión intramolecular en el sitio NS3/4A y de procesamiento intermolecular de moléculas posteriores en procesos biológicos en los empalmes de NS4A/4B, NS4B/5A y NS5A/5B. La investigación previa tiene clases identificadas de péptidos tales como hexapéptidos así como tripéptidos descritos en las solicitudes de Patente de los Estados Unidos US2005/0020503, US2004/0229818 y US2004/00229776, que muestran grados de actividad en inhibir la proteasa NS3. El objetivo de la presente invención es proporcionar otros compuestos que presenten actividad contra la proteasa NS3 de VHC.

SUMARIO DE LA INVENCIÓN

La presente invención se refiere a nuevos compuestos macrocíclicos de fórmula (**I**) y/o sales farmacéuticamente aceptables y/o hidratos de los mismos. Estos compuestos son útiles en la inhibición de la proteasa NS3 (no estructural 3) del VHC (virus de la hepatitis C), la prevención o tratamiento de uno o más de los síntomas de la infección por VHC, bien como compuestos o sus sales y/o hidratos farmacéuticamente aceptables (cuando sea apropiado), o como ingredientes de la composición farmacéutica, en combinación o no con otros antivirales contra el VCH, antiinfecciosos, inmunomoduladores, antibióticos o vacunas. Más particularmente, la presente invención se refiere a un compuesto de fórmula (**I**) y/o una sal y/o hidrato farmacéuticamente aceptable del mismo:



I

en la que:

n es 1 ó 2;

R^1 es CO_2R^{10}, $CONR^{10}SO_2R^6$, $CONR^{10}SO_2NR^8R^9$, o tetrazolilo;

R^2 es alquilo C_1-C_6, alquenilo C_2-C_6 o cicloalquilo C_3-C_8, en los que dicho alquilo, alquenilo o cicloalquilo está opcionalmente sustituido con 1 a 3 halo;

R^3 es alquilo C_1-C_8, cicloalquilo C_3-C_8, cicloalquil C_3-C_8(alquilo C_1-C_8), aril(alquiloC_1-C_8), o Het, en los que arilo es fenilo o naftilo y dicho alquilo, cicloalquilo, o arilo está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, y $CON(R^{10})_2$;

Het es un anillo cíclico saturado de 5-6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, en el que dicho anillo está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, y $CON(R^{10})_2$;

R^4 es H, alquilo C_1-C_8, cicloalquil C_3-C_8(alquil C_1-C_8), o aril(alquiloC_1-C_8); en los que arilo es fenilo o naftilo y dicho alquilo, cicloalquilo, o arilo está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)^2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO^2R10, C(O)R10, y $CON(R^{10})_2$;

R^5 es H, halo, OH, alcoxi C_1-C_6, alquilo C_1-C_6, CN, CF_3, SR^{10}, SO_2(alquilo C_1-C_6), cicloalquilo C_3-C_8, cicloalcoxi C_3-C_8, haloalquilo C_1-C_6, $N(R^7)_2$, arilo, heteroarilo o heterociclilo; en el que arilo es fenilo o naftilo, heteroarilo es un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y heterociclilo es un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en los que dicho arilo, heteroarilo, heterociclilo, cicloalquilo, cicloalcoxi, alquilo o alcoxi está opcionalmente sustituido con 1 a 4 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^7)_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), cicloalquilo C_3-C_6, cicloalcoxi C_3-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, S(O)(alquilo C_1-C_6), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, y $CON(R^{10})_2$; en los que los 2 sustituyentes adyacentes de dicho cicloalquilo,

cicloalcoxi, arilo, heteroarilo o heterociclilo se toman opcionalmente conjuntamente para formar un anillo cíclico de 3-6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S;

R^6 es alquilo C_1-C_8, cicloalquilo C_3-C_8, cicloalquil C_3-C_8(alquilo C_1-C_5), arilo, aril(alquilo C_1-C_4), heteroarilo, heteroaril(alquilo C_1-C_4), heterociclilo, o heterociclil(alquilo C_1-C_8), en los que dicho alquilo, cicloalquilo, arilo, heteroarilo, o heterociclilo está opcionalmente sustituido con 1 a 2 sustituyentes W'; y en los que cada arilo es independientemente fenilo o naftilo, cada heteroarilo es independientemente un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y cada heterociclilo es independientemente un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un anillo de carbono o nitrógeno;

Y es C(=O), SO_2, o C(=N-CN);

Z es $C(R^{10})_2$, O, o $N(R^4)$;

M es alquileno C_1-C_{12} o alquenileno C_2-C_{12} o alquinileno C_2-C_{12}, en el que dicho alquileno o alquenileno está opcionalmente sustituido con 1, 2 ó 3 sustituyentes seleccionados del grupo constituido por alquilo C_1-C_8, cicloalquil C_3-C_8(alquilo C_1-C_8), y aril(alquilo C_1-C_8); en los que 2 sustituyentes en átomos de carbono adyacentes de M se toman opcionalmente conjuntamente para formar un anillo cíclico de 3-6 miembros que contienen 0-3 heteroátomos seleccionados de N, O y S, o 2 sustituyentes en el mismo átomo de carbono de M opcionalmente se toman conjuntamente para formar un anillo cíclico de 3-6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S;

A es $C(R^{11})$ o N;

cuando R^5 es distinto de H, R^{11} es H, alquilo C_1-C_6, halo, OR^{10}, SR^{10}, o $N(R^{10})_2$;

cuando R^5 es H, halo, R^{11} es H, alquilo C_1-C_6, halo, OH, alcoxi C_1-C_6,CN, CF_3, SR^{10}, SO_2(alquilo C_1-C_6), cicloalquilo C_3-C_8, cicloalcoxi C_3-C_8, haloalquilo C_1-C_6, $N(R^7)_2$, arilo, heteroarilo o heterociclilo; en el que arilo es fenilo o naftilo, heteroarilo es un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y heterociclilo es un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en los que dicho arilo, heteroarilo,

heterociclilo, cicloalquilo, cicloalcoxi, alquilo o alcoxi está opcionalmente sustituido con 1 a 4 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^7)_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), cicloalquilo C_3-C_6, cicloalcoxi C_3-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, S(O)(alquilo C_1-C_6), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, y $CON(R^{10})_2$; en los que los 2 sustituyentes adyacentes de dicho cicloalquilo, cicloalcoxi, arilo, heteroarilo o heterociclilo se toman opcionalmente conjuntamente para formar un anillo cíclico de 3-6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S;
o R^5 y R^{11} se toman opcionalmente conjuntamente parar formar un anillo cíclico saturado, no aromático insaturado, o aromático de 5 a 6 miembros, que tiene 0-2 heteroátomos seleccionados de N, O y S;

cada R^7 es independientemente H, alquilo C_1-C_6, cicloalquilo C_3-C_6, cicloalquil C_3-C_6(alquilo C_1-C_5), arilo, aril(alquilo C_1-C_4), heteroarilo, heteroaril(alquilo C_1-C_4), heterociclilo, o heterociclil(alquilo C_1-C_8), en los que dicho alquilo, cicloalquilo, arilo, heteroarilo, o heterociclilo está opcionalmente sustituido con 1 a 2 sustituyentes W'; y en los que cada arilo es independientemente fenilo o naftilo, cada heteroarilo es independientemente un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y cada heterociclilo es independientemente un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo;

cada W es independientemente halo, OR^7, alquilo C_1-C_6, CN, CF_3, NO_2, SR^7, CO_2R^7, $CON(R^7)_2$, $C(O)R^7$, $N(R^{10})C(O)R^7$, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), cicloalquilo C_3-C_8, cicloalcoxi C_3-C_8, haloalquilo C_1-C_6, $N(R^7)_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), halo(alcoxi C_1-C_6), $NR^{10}SO_2R^7$, $SO_2N(R^7)_2$, $NHCOOR^7$, $NHCONHR^7$, arilo, heteroarilo o heterociclilo; en los que arilo es fenilo o naftilo, heteroarilo es un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y heterociclilo es un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en los que 2 restos W adyacentes se toman opcionalmente conjuntamente con los átomos a los que están unidos para formar un anillo cíclico no aromático insaturado, saturado, o aromático de 5 ó 6 miembros que tiene 0-2 heteroátomos seleccionados de N, O y S;

cada W' es independientemente H, halo, OR^{10}, alquilo C_1-C_6, CN, CF_3, NO_2, SR^{10}, CO_2R^{10}, $CON(R^{10})_2$, $C(O)R^{10}$, $N(R^{10})C(O)R^{10}$, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), cicloalquilo C_3-C_8, cicloalcoxi C_3-C_8, haloalquilo C_1-C_6, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), halo(alcoxi

C_1-C_6), $NR^{10}SO_2R^{10}$, $SO_2N(R^{10})_2$, $NHCOOR^{10}$, $NHCONHR^{10}$, arilo, heteroarilo o heterociclilo; en los que arilo es fenilo o naftilo, heteroarilo es un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y heterociclilo es un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en los que 2 restos W' adyacentes se toman opcionalmente conjuntamente con los átomos a los que están unidos para formar un anillo cíclico no aromático, o aromático saturado, insaturado que tiene 0-2 heteroátomos seleccionados de N, O y S;

R^8 es alquilo C_1-C_8, cicloalquilo C_3-C_8, cicloalquil C_3-C_8 cicloalquil(alquilo C_1-C_8), arilo, aril(alquilo C_1-C_4), heteroarilo, heterociclilo, heteroaril(alquilo C_1-C_4), o heterociclil(alquilo C_1-C_8), en los que dicho alquilo, cicloalquilo, arilo, heteroarilo o heterociclilo está opcionalmente sustituido con 1 a 4 sustituyentes seleccionados del grupo constituido por arilo, cicloalquilo C_3-C_8, heteroarilo, heterociclilo, alquilo C_1-C_6, halo(alcoxi C_1-C_6), halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, $C(O)R^{10}$, haloalquilo C_1-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, y $C(O)N(R^{10})_2$; en el que cada arilo es independientemente fenilo o naftilo; cada heteroarilo es independientemente un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y cada heterociclilo es independientemente un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en el que los 2 sustituyentes adyacentes de dicho cicloalquilo, cicloalcoxi, arilo, heteroarilo o heterociclilo se toman opcionalmente conjuntamente para formar un anillo cíclico de 3 a 6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S;

R^9 es alquilo C_1-C_8, cicloalquilo C_3-C_8, cicloalquil C_3-C_8 (alquilo C_1-C_8), alcoxi C_1-C_8, cicloalcoxi C_3-C_8, arilo, aril(alquilo C_1-C_4), heteroarilo, heterociclilo, heteroaril(alquilo C_1-C_4), o heterociclil(alquilo C_1-C_8), en los que dicho alquilo, cicloalquilo, alcoxi, cicloalcoxi, arilo, heteroarilo o heterociclilo está opcionalmente sustituido con 1 a 4 sustituyentes seleccionados del grupo constituido por arilo, cicloalquilo C_3-C_8, heteroarilo, heterociclilo, alquilo C_1-C_6, halo(alcoxi C_1-C_6), halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, $C(O)R^{10}$, haloalquilo C_1-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R_{10}, y $C(O)N(R^{10})_2$; en el que cada arilo es independientemente fenilo o naftilo; cada heteroarilo es independientemente un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y cada heterociclilo es independientemente

un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en la que los 2 sustituyentes adyacentes de dicho cicloalquilo, cicloalcoxi, arilo, heteroarilo o heterociclilo se toman opcionalmente conjuntamente para formar un anillo cíclico de 3 a 6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S;

o R^8 y R^9 se toman opcionalmente conjuntamente, con el átomo de nitrógeno al que están unidos, para formar un anillo monocíclico de 4-8 miembros que contienen 0-2 heteroátomos adicionales seleccionados de N, O y S; y

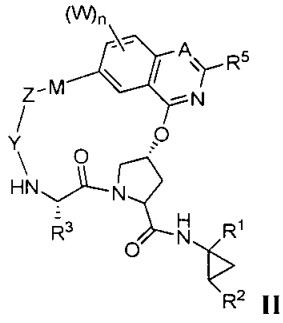
cada R^{10} es independientemente H o alquilo C_1-C_6.

La presente invención también incluye composiciones farmacéuticas que contienen un compuesto de la presente invención y procedimientos de preparar tales composiciones farmacéuticas. La presente invención incluye adicionalmente procedimientos de tratar o prevenir uno o más síntomas de infección por VHC.

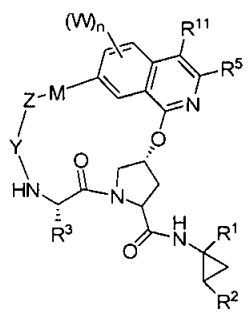
Otras realizaciones, aspectos y características de la presente invención bien se describen adicionalmente en ella o bien serán patentes a partir de la descripción, ejemplos y reivindicaciones adjuntas subsiguientes.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

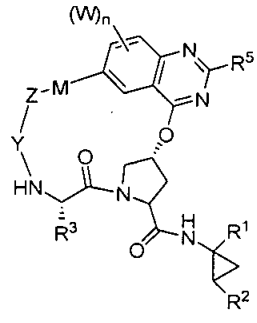
La presente invención incluye compuestos de fórmula **I** anteriores, y sales y/o hidratos farmacéuticamente aceptables de los mismos. Estos compuestos y sus sales y/o hidratos farmacéuticamente aceptables son inhibidores de proteasa de VHC (por ejemplo, inhibidores de proteasa NS3 de VHC). La presente invención también incluye compuestos de fórmulas **II**, **II-A**, **II-B**, **III**, **III-A** y **III-B** en las que las variables n, R^1, R^2, R^3, Y, Z, M, W, A, R^5 y R^{11} son como se definen para fórmula **I**.



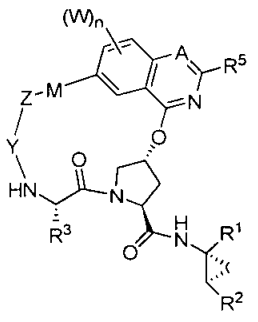
II



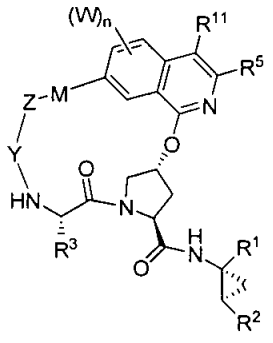
II-A



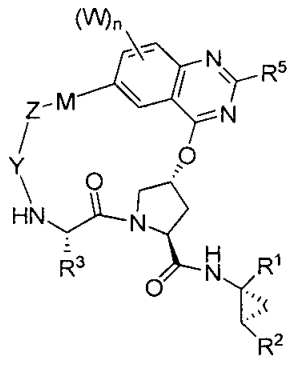
II-B



III



III-A



III-B

Una primera realización de la presente invención es un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B**, o una sal o hidrato farmacéuticamente aceptable del mismo, en la que R^1 es CO_2R^{10} o $CONR^{10}SO_2R^6$, y todas las otras variables son como se definen originalmente (es decir, como se definen en el Sumario de la Invención). En un primer aspecto de la primera realización, R^1 es $CONR^{10}SO_2R^6$; y todas las otras variables son como se definen en la primera realización. En una característica del primer aspecto de la primera realización, R^1 es $CONHSO_2R^6$ en el que R^6 es cicloalquilo C_3-C_8, alquilo C_1-C_8, arilo, aril(alquilo C_1-C_4), en los que dicho alquilo, cicloalquilo, o arilo está opcionalmente sustituido con 1 to 2 sustituyentes W'; y todas las otras variables son como se definen en la primera realización. En una segunda característica del primer aspecto de la primera realización, R^1 es $CONHSO_2R^6$ en el que R^6 es ciclopropilo; y todas las otras variables son como se definen en la primera realización. En una tercera característica del primer aspecto de la primera realización, R^1 es $CONHSO_2R^6$ en el que R^6 es fenilo; y todas las otras variables son como se definen en la primera realización. En una cuarta característica del primer aspecto de la primera realización, R^1 es $CONHSO_2R^6$ en el que R^6 es bencilo; y todas las otras variables son como se definen en la primera realización. En una quinta característica del primer aspecto de la primera realización, R^1 es $CONHSO_2R^6$ en el que R^6 es metilo, etilo, n-propilo, i-propilo, n-butilo, i-butilo o t-butilo; y todas las otras variables son como se definen en la primera realización. En un segundo aspecto de la primera realización, R^1 es CO_2R^{10}; y todas las otras variables son como se definen en la primera realización. En una característica del segundo aspecto de la primera realización, R^{10} es CO_2H; y todas las otras variables son como se definen en la primera realización.

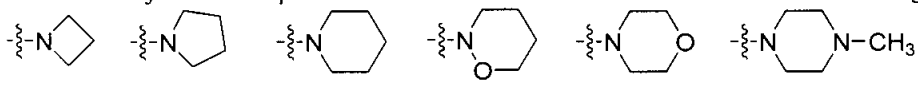
Una segunda realización de la presente invención es un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B**, o una sal o hidrato farmacéuticamente aceptable del mismo, en la que R^1 es $CONHSO_2NR^8R^9$; y todas las otras variables son como se definen originalmente. En un primer aspecto de la segunda realización, R^8 es alquilo C_1-C_8, cicloalquilo C_3-C_8, cicloalquil C_3-C_8(alquilo C_1-C_8), arilo, aril(alquilo C_1-C_4), heteroarilo, o heteroaril(alquilo C_1-C_4); y R^9 es alquilo C_1-C_8, cicloalquilo C_3-C_8, cicloalquil C_3-C_8(alquilo C_1-C_8), alcoxi C_1-C_8, arilo, aril(alquilo C_1-C_4), heteroarilo, o heteroaril(alquilo C_1-C_4), en los que dicho alquilo, cicloalquilo, alcoxi, arilo, o heteroarilo tanto en R^8 como en R^9 está opcionalmente sustituido

con de 1 a 4 sustituyentes seleccionados del grupo constituido por arilo, heteroarilo, alquilo C_1-C_6, halo(alcoxi C_1-C_6), halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6l)O(alquilo C_1-C_6), alquilo C_1-C_6, $C(O)R^{10}$, haloalquilo C_1-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, y $C(O)N(R^{10})_2$, en los que cada arilo es independientemente fenilo o naftilo y cada heteroarilo es independientemente un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y en los que los 2 sustituyentes adyacentes de dicho cicloalquilo, arilo o heteroarilo se toman opcionalmente conjuntamente para formar un anillo cíclico de 3-6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S; o R^8 y R^9 se toman opcionalmente conjuntamente, con el átomo de nitrógeno al que están unidos, para formar un anillo monocíclico de 4-8 miembros que contiene 0-2 heteroátomos adicionales seleccionados de N, O y S; y todas las otras variables son como se definen en la segunda realización.

En un segundo aspecto de la segunda realización, R^8 es alquilo C_1-C_8, cicloalquil C_3-C_8(alquilo C_1-C_8), arilo, aril(alquilo C_1-C_4), heteroarilo, o heteroaril(alquilo C^1-C_4); y R^9 es alquilo C1-C8, cicloalquil C_3-C_8(alquilo C_1-C_8), alcoxi C_1-C_8, arilo, aril(alquilo C_1-C_4), heteroarilo, o heteroaril(alquilo C_1-C_4), en los que dicho alquilo, cicloalquilo, alcoxi, arilo, o heteroarilo tanto en R^8 como en R^9 está opcionalmente sustituido con de 1 a 4 sustituyentes seleccionados del grupo constituido por arilo, cicloalquilo C_3-C_8, heteroarilo, heterocicliclo, alquilo C_1-C_6, halo(alcoxi C_1-C_6), halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, $C(O)R^{10}$, haloalquilo C_1-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)^2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, y $C(O)N(R^{10})_2$, en los que cada arilo es independientemente fenilo o naftilo y cada heteroarilo es independientemente un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y en los que los 2 sustituyentes adyacentes de dicho cicloalquilo, arilo o heteroarilo se toman opcionalmente conjuntamente para formar un anillo cíclico de 3-6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S; o R^8 y R^9 se toman opcionalmente conjuntamente, con el átomo de nitrógeno al que están unidos, para formar un anillo monocíclico de 4-6 miembros que contiene 0-2 heteroátomos adicionales seleccionados de N, O y S; y todas las otras variables son como se definen en la segunda realización.

En una primera característica del segundo aspecto de la segunda realización, R^8 es alquilo C_1-C_3, en el que dicho alquilo está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, $C(O)R^{10}$, haloalquilo C_1-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, y $C(O)N(R^{10})_2$; y R^9 es alquilo C_1-C_3, alcoxi C_1-C_3, fenilo, o -$(CH_2)_{1-2}$-fenilo, en los que dicho alquilo o alcoxi

está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, $C(O)R^{10}$, haloalquilo C_1-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, y $C(O)N(R^{10})_2$; o R^8 y R^9 se toman opcionalmente conjuntamente con el átomo de nitrógeno al que están unidos, para formar un anillo saturado monocíclico de 4-6 miembros que contienen 0-1 heteroátomos adicionales seleccionados de N y O; y todas las otras variables son como se definen en la segunda realización. En una segunda característica del segundo aspecto de la segunda realización, R^8 es metilo; y todas las otras variables son como se definen en la segunda realización. En una tercera característica del segundo aspecto de la segunda realización, R^9 es metilo, metoxi, etilo, i-propilo, fenilo, o bencilo; y todas las otras variables son como se definen en la tercera realización. En una cuarta característica del segundo aspecto de la segunda realización, R^8 y R^9 se toman conjuntamente para formar un anillo heterocíclico seleccionado de los siguientes:



; y todas las otras variables son como se definen en la segunda realización. En una quinta característica del segundo aspecto de la segunda realización, R^8 es metilo y R^9 es metoxi; y todas las otras variables son como se definen en la segunda realización.

Una tercera realización de la presente invención es un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B**, o una sal o hidrato farmacéuticamente aceptable del mismo, en el que R^2 es alquilo C_1-C_6 o alquenilo C_2-C_6; y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes. En un primer aspecto de la tercera realización, R^2 es alquilo C_1-C_4 o alquenilo C_2-C_4; y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes. En un segundo aspecto de la tercera realización, R^2 es alquenilo C_2-C_4; y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes. En una característica del segundo aspecto de la tercera realización, R^2 es vinilo; y todas las otras variables son como se definen en la segunda realización o como se definen en una cualquiera de las realizaciones precedentes. En un tercer aspecto de la tercera realización, R^2 es alquilo C_1-C_4; y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes. En una característica del tercer aspecto de la tercera realización, R^2 es etilo; y todas las otras variables son como se definen en la tercera realización o como se definen en una cualquiera de las realizaciones precedentes.

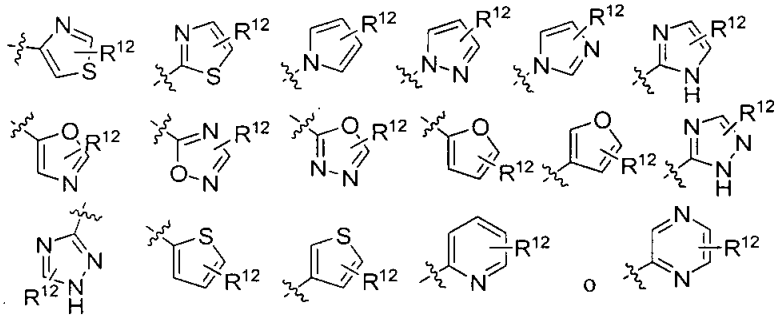
Una cuarta realización de la presente invención es un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B**, o una sal o hidrato farmacéuticamente aceptable del mismo, en la que R^3 es cicloalquilo C_3-C_8, Het, o alquilo C_1-C_8 opcionalmente sustituido con 1 a 3

sustituyentes halo; y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes. En un primer aspecto de la cuarta realización, R^3 es cicloalquilo C_5-C_7, piperidinilo, pirrolidinilo, tetrahidrofuranilo, tetrahidropiranilo, o alquilo C_1-C_8 opcionalmente sustituido con 1 a 3 sustituyentes halo; y todas las otras variables son como se definen en la cuarta realización o como se definen en una cualquiera de las realizaciones precedentes. En un segundo aspecto de la cuarta realización, R^3 es cicloalquilo C_5-C_6 o alquilo C_1-C_8 opcionalmente sustituido con 1 a 3 sustituyentes halo; y todas las otras variables son como se definen en la cuarta realización o como se definen en una cualquiera de las realizaciones precedentes. En un tercer aspecto de la cuarta realización, R^3 es propilo; y todas las otras variables son como se definen en la cuarta realización o como se definen en una cualquiera de las realizaciones precedentes. En una característica del tercer aspecto de la cuarta realización, R^3 es i-propilo, n-butilo, i-butilo o t-butilo; y todas las otras variables son como se definen en la cuarta realización o como se definen en una cualquiera de las realizaciones precedentes. En un cuarto aspecto de la cuarta realización, R^3 es ciclopentilo o ciclohexilo; y todas las otras variables son como se definen en la cuarta realización o como se definen en una cualquiera de las realizaciones precedentes. En un quinto aspecto de la cuarta realización, R^3 is CH_2CF_3 o CH_2CHF_2; y todas las otras variables son como se definen en la cuarta realización o como se definen en una cualquiera de las realizaciones precedentes.

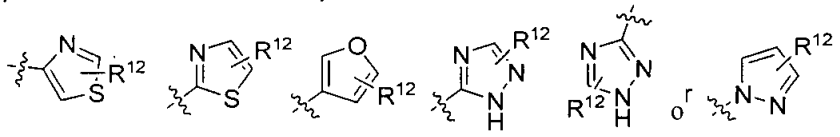
Una quinta realización de la presente invención es un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B**, o una sal o hidrato farmacéuticamente aceptable del mismo, en el que R^5 es H o halo; y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes. En un aspecto de la quinta realización, R^5 es H, F, o Cl; y todas las otras variables se definen en la quinta realización o como se definen en una cualquiera de las realizaciones precedentes. En otro aspecto de la quinta realización, R^5 es H; y todas las otras variables se definen en la quinta realización o como se definen en una cualquiera de las realizaciones precedentes.

Una sexta realización de la presente invención es un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B**, o una sal o hidrato farmacéuticamente aceptable del mismo, en la que R^5 es arilo o heteroarilo; en los que arilo es fenilo o naftilo y heteroarilo es un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en los que dicho arilo o heteroarilo está opcionalmente sustituido con 1 to 4 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^7)_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), cicloalquilo C_3-C_6, cicloalcoxi C_3-C_6 cicloalcoxi, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, S(O)(alquilo C_1-C_6), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, y $CON(R^{10})_2$; y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes.

En un primer aspecto de la sexta realización, R^5 es arilo en el que arilo está opcionalmente sustituido con 1 to 4 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^7)_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), cicloalquilo C_3-C_6, cicloalcoxi C_3-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, S(O)(alquilo C_1-C_6), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, y $CON(R^{10})_2$; y todas las otras variables son como se definen en la sexta realización o como se definen en una cualquiera de las realizaciones precedentes. En un segundo aspecto de la sexta realización, R^5 es



; en la que R^{12} es H, alquilo C_1-C_6, alcoxi C_1-C_6, $N(R^7)_2$, $NHCOR^{13}$, $NHCONHR^{13}$ o $NHCOOR^{13}$ y cada R^{13} es independientemente alquilo C_1-C_6 o cicloalquilo C_3-C_6; y todas las otras variables son como se definen en la sexta realización o como se definen en una cualquiera de las realizaciones precedentes. En un tercer aspecto de la sexta realización, R^5 es



; en la que R^{12} es H, alquilo C_1-C_6, alcoxi C_1-C_6, $N(R^7)_2$, $NHCOR^{13}$, $NHCONHR^{13}$ o $NHCOOR^{13}$ y cada R^{13} es independientemente alquilo C_1-C_6 o cicloalquilo C_3-C_6; y todas las otras variables son como se definen en la sexta realización o como se definen en una cualquiera de las realizaciones precedentes.

En un cuarto aspecto de la sexta realización, R^5 es fenilo insustituido; y todas las otras variables son como se definen en la sexta realización o como se definen en una cualquiera de las realizaciones precedentes.

Una decimoséptima realización de la presente invención es un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B**, o una sal o hidrato farmacéuticamente aceptable del mismo, en la que R^5 es alquilo C_1-C_6, cicloalquilo C_3-C_8, haloalquilo C_1-C_6, o heterociclilo en los que heterociclilo es un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un átomo de carbono o nitrógeno; y en los que dicho heterociclilo, cicloalquilo, o alquilo está opcionalmente sustituido con 1 to 4 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^7)_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6),

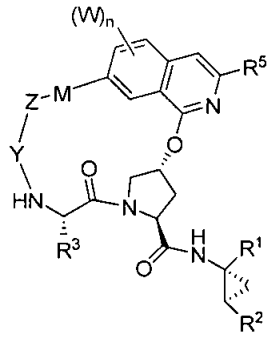
cicloalquilo C_3-C_6, cicloalcoxi C_3-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, S(O)(alquilo C_1-C_6), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, y $CON(R^{10})_2$; en los que los 2 sustituyentes adyacentes de dicho cicloalquilo o heterociclilo se toman opcionalmente conjuntamente para formar un anillo cíclico de 3-6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S; y todas las otras variables son como se definen originalmente en una cualquiera de las realizaciones precedentes. En un quinto aspecto de la séptima realización, R^5 es alquilo C_1-C_6; y todas las otras variables son como se definen en la séptima realización o como se definen en una cualquiera de las realizaciones precedentes. En una característica del primer aspecto de la séptima realización, R^5 es metilo; y todas las otras variables son como se definen en la séptima realización o como se definen en una cualquiera de las realizaciones precedentes. En un segundo aspecto de la séptima realización, R^5 es heterociclilo en el que heterociclilo es un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de una carbono o nitrógeno de anillo; y en el que dicho heterociclilo, cicloalquilo, o alquilo está opcionalmente sustituido con 1 a 4 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^7)_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), cicloalquilo C_3-C_6, cicloalquil, cicloalcoxi C_3-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, S(O)(alquilo C_1-C_6), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, y $CON(R^{10})_2$; en los que los dos sustituyentes adyacentes de dicho heterociclilo se toman opcionalmente conjuntamente para formar un anillo cíclico de 3-6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S; y todas las otras variables son como se definen en la séptima realización o como se definen en una cualquiera de las realizaciones precedentes. En una característica del segundo aspecto de la séptima realización, R^5 es N-morfolinilo; y todas las otras variables son como se definen en la séptima realización o como se definen en una cualquiera de las realizaciones precedentes. En un tercer aspecto de la séptima realización, R^5 es haloalquilo C1-C_6; y todas las otras variables son como se definen en la séptima realización o como se definen en una cualquiera de las realizaciones precedentes. En una característica del tercer aspecto de la séptima realización, R^5 es metilo; y todas las otras variables son como se definen en la séptima realización o como se definen en una cualquiera de las realizaciones precedentes.

Una octava realización de la presente invención es un compuesto de fórmula **I, II, II-A, II-B, III, III-A, o III-B,** o una sal o hidrato farmacéuticamente aceptable del mismo, en el que R^5 es es $N(R^7)_2$; y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes. En un aspecto de las octava realización, R^5 es $N(R^7)_2$ en el que R^7 es H o alquilo C_1-C_6; y todas las otras variables son como se definen en la octava realización o como se definen en una cualquiera de las realizaciones precedentes.

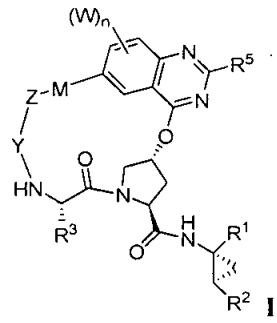
Una novena realización de la presente invención es un compuesto de fórmula **I**, **II**, **II-A**, **III**, o **III-A**, o una sal o hidrato farmacéuticamente aceptable del mismo, en la que R^{11} es H, alquilo C_1-C_6, alcoxi C_1-C_6, hidroxi o halo; y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes. En un primer aspecto de la novena realización, R^{11} es alcoxi C_1-C_6; y todas las otras variables son como se definen en la novena realización o como se definen en una cualquiera de las realizaciones precedentes. En una característica del primer aspecto de la novena realización, R^{11} es metoxi; y todas las otras variables son como se definen en la novena realización o como se definen en una cualquiera de las realizaciones precedentes. En un segundo aspecto de la novena realización, R^{11} es alquilo C_1-C_6; y todas las otras variables son como se definen en la novena realización o como se definen en una cualquiera de las realizaciones precedentes. En una característica del segundo aspecto de la novena realización, R^{11} es metilo; y todas las otras variables son como se definen en la novena realización o como se definen en una cualquiera de las realizaciones precedentes. En un tercer aspecto de la novena realización, R^{11} es halo o hidroxi; y todas las otras variables son como se definen en la novena realización o como se definen en una cualquiera de las realizaciones precedentes. En una característica del tercer aspecto de la novena realización, R^{11} es OH, Cl o Br; y todas las otras variables son como se definen en la novena realización o como se definen en una cualquiera de las realizaciones precedentes. En un cuarto aspecto de la novena realización, R^{11} es H; y todas las otras variables son como se definen en la novena realización o como se definen en una cualquiera de las realizaciones precedentes.

Una décima realización de la presente invención es un compuesto de fórmula **I**, **II**, **II-A**, **III**, o **III-A**, o una sal o hidrato farmacéuticamente aceptable del mismo, en el que R^5 y R^{11} se toman conjuntamente para formar un anillo cíclico aromático, no aromático insaturado o saturado de 5 a 6 miembros que tiene 1-2 átomos de oxígeno; y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes.

Una undécima realización de la presente invención es un compuesto de fórmula **IV-A** o **IV-B**, o una sal o hidrato farmacéuticamente aceptable del mismo, en el que R^5 es H, halo, arilo, heteroarilo, o $N(R^7)_2$; R^1 es CO_2R^{10} o $CONHSO_2R^6$ en los que R^6 es cicloalquilo C_3-C_6, alquilo C_1-C_6, fenilo o bencilo; y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes.



IV-A



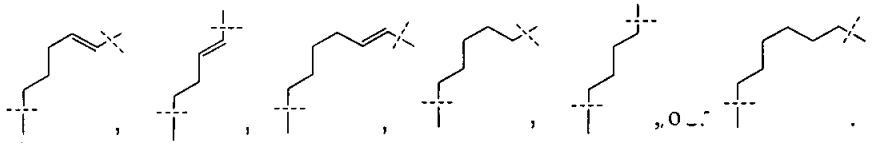
IV-B

Una duodécima realización de la presente invención es un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B**, o una sal o hidrato farmacéuticamente aceptable del mismo, en el que Y es C=O o SO_2; y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes. En un aspecto de la duodécima realización, Y is C=O; y todas las otras variables son como se definen en la duodécima realización o como se definen en una cualquiera de las realizaciones precedentes.

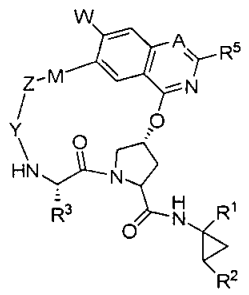
Una decimotercera realización de la presente invención es un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B**, o una sal o hidrato farmacéuticamente aceptable del mismo, en la que Z es O, NH, N(alquilo C_1-C_8) o $C(R^{10})_2$; y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes. En un aspecto de la decimotercera realización, Z es O, NH, $N(CH_3)$, o CH_2; y todas las otras variables son como se definen en la realización trece o como se definen en una cualquiera de las realizaciones precedentes.

Una realización decimocuarta de la presente invención es un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B**, o una sal o hidrato farmacéuticamente aceptable de la misma, en la que M es alquileno C_1-C_8 o alquenileno C_2-C_8, en el que dicho alquileno o alquenileno está opcionalmente sustituido con 1 ó 2 sustituyentes seleccionados de alquilo C_1-C_8, cicloalquil C_3-C_8(alquilo C_1-C_8), o aril(alquilo C_1-C_8); y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes. En un primer aspecto de la decimocuarta realización, M es alquileno C_1-C_8 insustituido o alquenileno C_2-C_8 insustituido; y todas las otras variables son como se definen en la decimocuarta realización o como se definen en una cualquiera de las realizaciones precedentes. En un segundo aspecto de la decimocuarta realización, M es alquileno C_4 insustituido o alquenileno C_4 insustituido; y todas las otras variables son como se definen en la decimocuarta realización o como se definen en una cualquiera de las realizaciones precedentes. En un tercer aspecto de la decimocuarta realización, M es alquileno C_5 insustituido o alquenileno C_5 insustituido; y todas las otras variables son como se definen en la decimocuarta realización o como se definen en una cualquiera de las realizaciones precedentes. En un cuarto aspecto de la

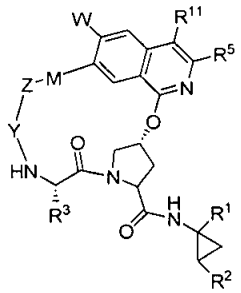
decimocuarta realización, M es alquileno C_6 insustituido o alquenileno C_6 insustituido; y todas las otras variables son como se definen en la decimocuarta realización o como se definen en una cualquiera de las realizaciones precedentes. En un quinto aspecto de la decimocuarta realización, M es alquileno C_7 insustituido o alquenileno C_7 insustituido; y todas las otras variables son como se definen en la decimocuarta realización o como se definen en una cualquiera de las realizaciones precedentes. En una característica del primer aspecto de la realización decimocuarta, M es:



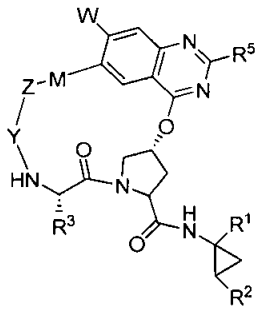
Una decimoquinta realización de la presente invención es un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B**, o una sal o hidrato farmacéuticamente aceptable del mismo, en el que n es 1; y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes. En un aspecto de la decimoquinta realización, W está en posición orto con respecto a la variable M como se representa en las fórmulas **Ia**, **IIa**, **II-Aa**, **II-Ba**, **IIIa**, **III-Aa**, **III-Ba**, **IV-Aa** y **IV-Ba**.



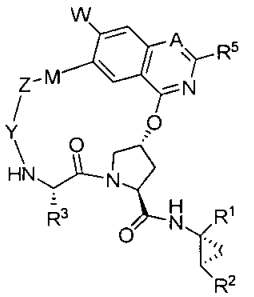
IIa



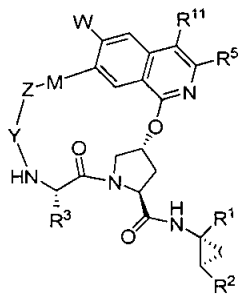
II-Aa



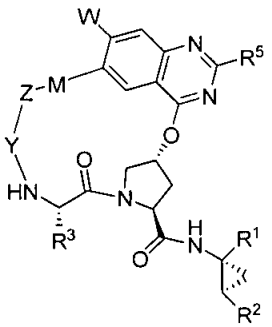
II-Ba



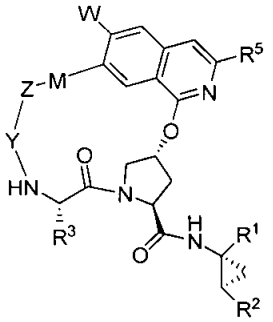
IIIa



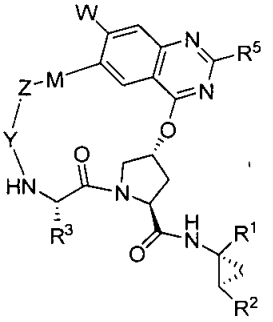
III-Aa



III-Ba



IV-Aa



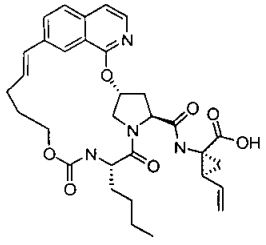
IV-Ba

Una decimosexta realización de la presente invención es un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B**, o una sal o hidrato farmacéuticamente aceptable del mismo, en el que n es 2; y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes. En un aspecto de la realización decimosexta, se toman los 2 restos W adyacentes para formar un anillo cíclico aromático, no aromático insaturado, o saturado de 5 a 6 miembros que tiene 0-2 heteroátomos seleccionados de N, O y S. En otro aspecto de la realización decimosexta, se toman los 2 restos W adyacentes para formar un anillo cíclico saturado de 5 miembros que tiene 0-2 heteroátomos seleccionados de N, O y S.

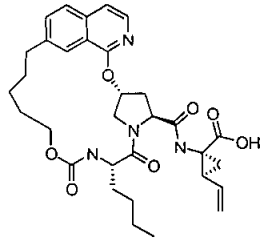
Una decimoséptima realización de la presente invención es un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B**, o una sal o hidrato farmacéuticamente aceptable del mismo, en el que W es H, alquilo C_1-C_6, alcoxi C_1-C_6, OH, halo, halo(alcoxi C_1-C_6), $C(O)N(R^7)_2$, $C(O)R^7$, $N(R^7)_2$, o heterociclilo; y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes. En un primer aspecto de la decimoséptima realización, W es H; y todas las otras variables son como se definen en la decimoséptima realización o como se definen en una cualquiera de las realizaciones precedentes. En un segundo aspecto de la decimoséptima realización, W es alcoxi C_1-C_6; y todas las otras variables son como se definen en la decimoséptima realización o como se definen en una cualquiera de las realizaciones precedentes. En una característica del segundo aspecto de la decimoséptima realización, W es metoxi; y todas las otras variables son como se definen en la decimoséptima realización o como se definen en una cualquiera de las realizaciones precedentes. En un tercer aspecto de la decimoséptima realización, W es alquilo C_1-C_6, halo, OH, o $N(R^7)_2$ en el que R^7 es H o alquilo C_1-C_6; y todas las otras variables son como se definen en la realización decimoséptima o como se definen en una cualquiera de las realizaciones precedentes. En una característica del tercer aspecto de la decimoséptima realización, W es metilo; y todas las otras variables son como se definen en la decimoséptima realización o como se definen en una cualquiera de las realizaciones precedentes. En un cuarto aspecto de la decimoséptima realización, W es halo(alcoxi C_1-C_6); y todas las otras variables son como se definen en la decimoséptima realización o como se definen en una cualquiera de

las realizaciones precedentes. En una característica del quinto aspecto de la decimoséptima realización, W es OCF_3, $OCHF_2$, $OC(CH_3)_3$, o $OCH(CH_3)_2$; y todas las otras variables son como se definen en la realización decimoséptima o como se definen en una cualquiera de las realizaciones precedentes. En un sexto aspecto de la decimoséptima realización, W es $C(O)N(R^7)_2$, $C(O)R^7$, o heterociclilo; y todas las otras variables son como se definen en la realización decimoséptima o como se definen en una cualquiera de las realizaciones precedentes. En una característica del sexto aspecto de la decimoséptima realización, W es $C(O)N(R^7)_2$ en el que R^7 es H o alquilo C_1-C_6; $C(O)R^7$ en el que R^7 es un heteroarilo de 5 miembros que tiene 1 heteroátomo O o S; o heterociclilo en el que heterociclilo es un anillo saturado de 6 miembros que tiene 1 ó 2 heteroátomos seleccionados de N, O y S; y todas las otras variables son como se definen en una cualquiera de las realizaciones precedentes.

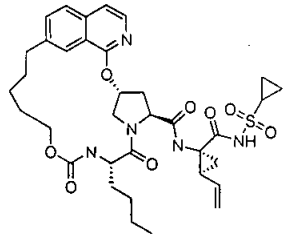
Una decimooctava realización de la presente invención es un compuesto, o una sal o hidrato farmacéuticamente aceptable del mismo, seleccionado del grupo constituido por los compuestos **III-1** a **III-38**.



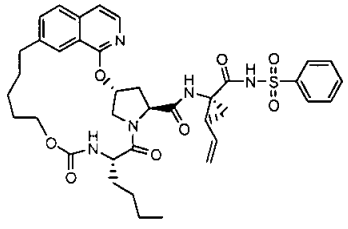
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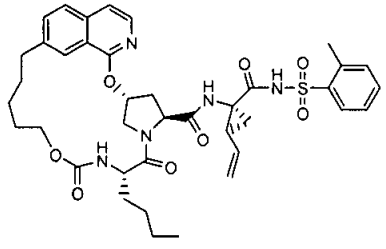
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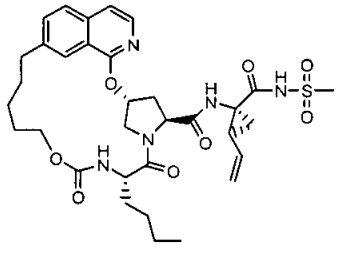
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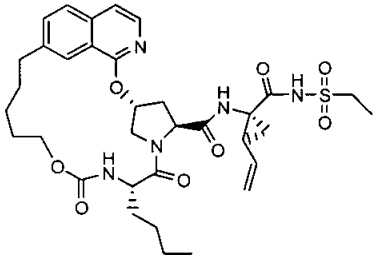
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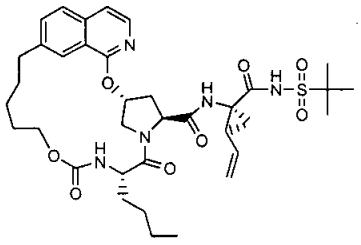
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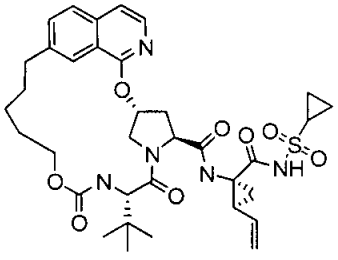
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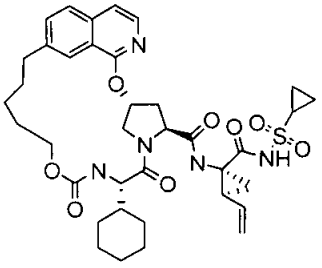
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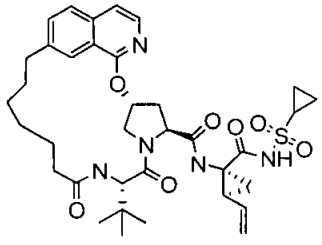
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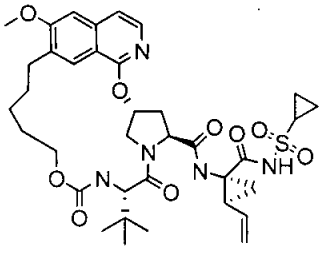
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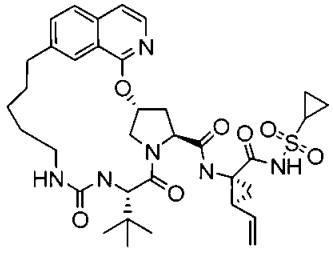
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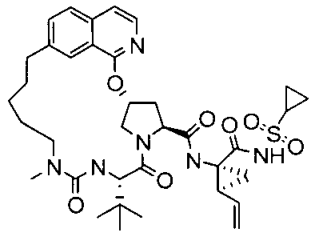
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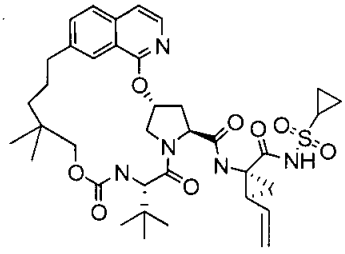
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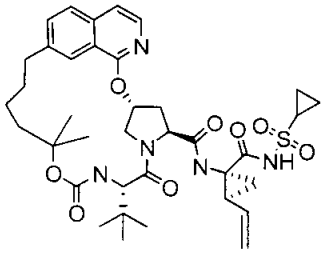
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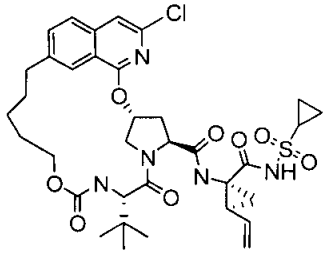
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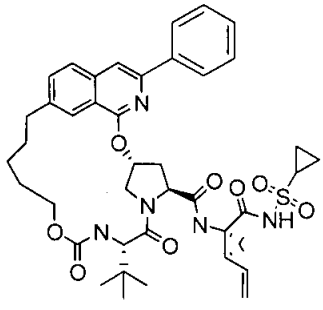
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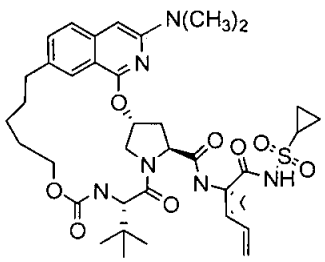
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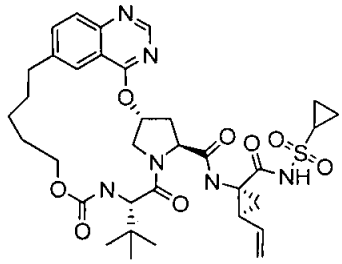
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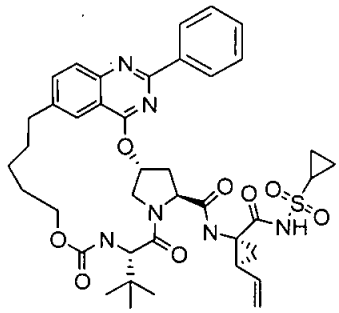
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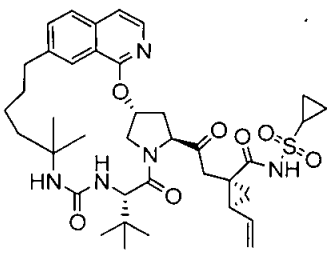
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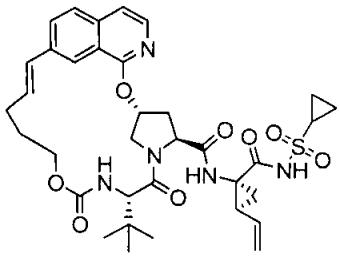
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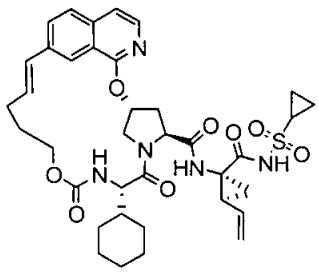
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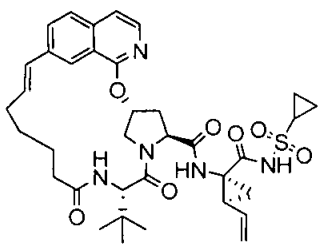
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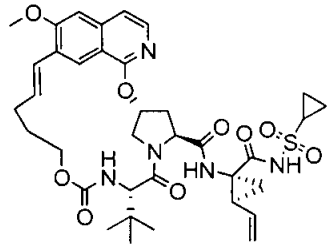
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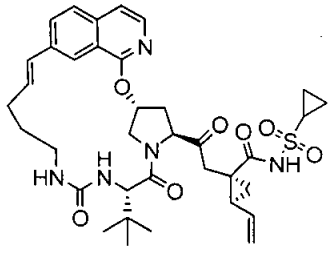
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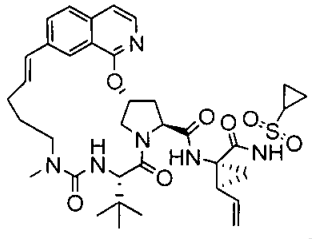
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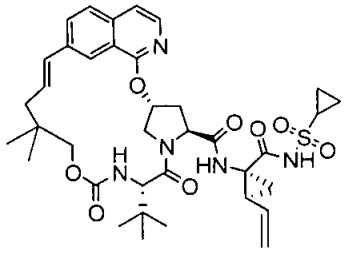


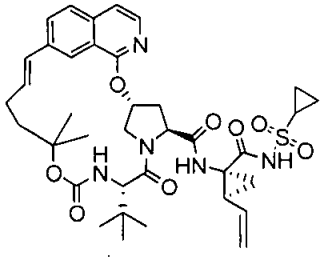
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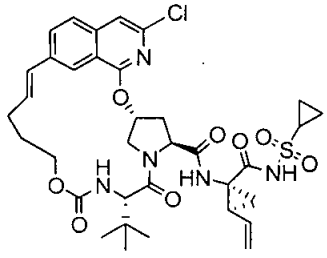
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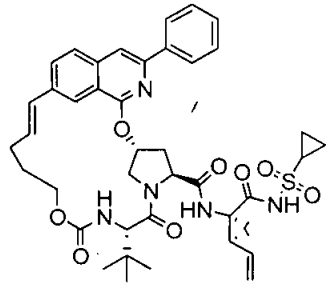




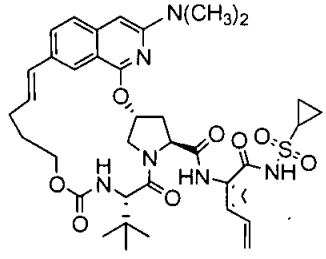
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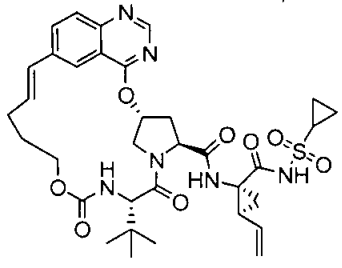
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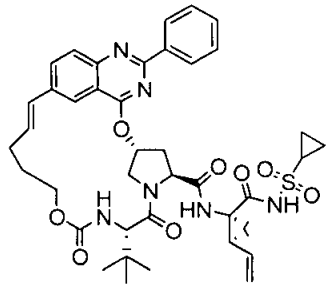
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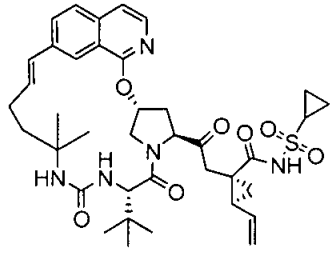
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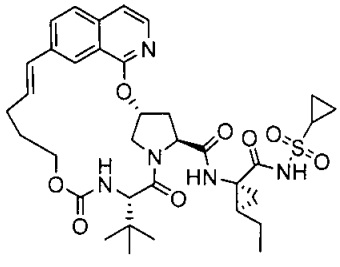
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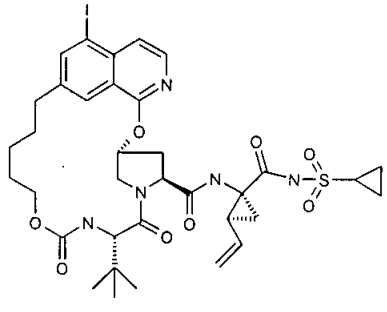
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III-34



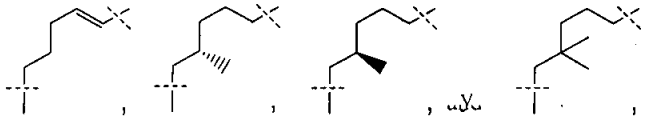
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III-36

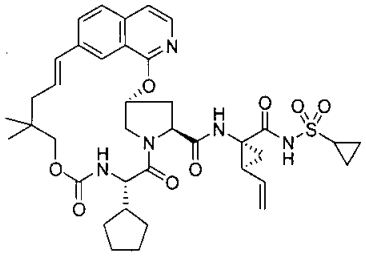
III-37 **III-38**

Una decimonovena realización de la presente invención es un compuesto de fórmula **III**, o una sal o hidrato farmacéuticamente aceptable del mismo, en el que R^1 es $CONHSO_2R^6$, R^6 es cicloalquilo C_3-C_8, alquilo C_1-C_8, arilo, o aril(C_1-C_4)alquilo, R^2 es alquilo C_1-C_4 o alquenilo C_2-C_4, R^3 es cicloalquilo C_5-C_6 o alquilo C_1-C_8 opcionalmente sustituido con 1 a 3 sustituyentes halo, R^5 es H, halo, arilo, heteroarilo o $N(R^7)_2$, y todas las otras variables son como se definen originalmente o como se definen en una cualquiera de las realizaciones precedentes. En un primer aspecto de la decimonovena realización, R^5 es H, y todas las otras variables son como se definen en la decimonovena realización o como se definen en una cualquiera de las realizaciones precedentes. En una característica del primer aspecto de la decimonovena realización, R^3 es cicloalquilo C_5-C_6 o alquilo C_3-C_5, y todas las otras variables son como se definen en la decimonovena realización o como se definen en una cualquiera de las realizaciones precedentes. En otra característica del primer aspecto de la decimonovena realización, R_6 es cicloalquilo C_3-C_5, y todas las otras variables son como se definen en la decimonovena realización o como se definen en una cualquiera de las realizaciones precedentes. En un segundo aspecto de la decimonovena realización, R^2 es alquenilo C_2-C_4, R^5 es H, R^6 es cicloalquilo C_3-C_8, W es R^7 o H, Y es C(=O), Z es O, y n es 1, y todas las otras variables son como se definen en la decimonovena realización o como se definen en una cualquiera de las realizaciones precedentes. En un tercer aspecto de la decimonovena realización, M se selecciona del grupo constituido por:

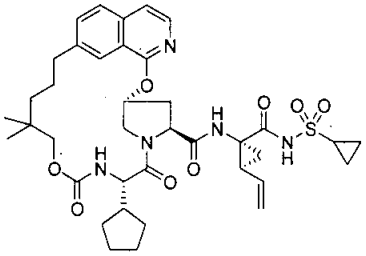


y todas las otras variables son como se definen en la decimonovena realización o como se definen en una cualquiera de las realizaciones precedentes.

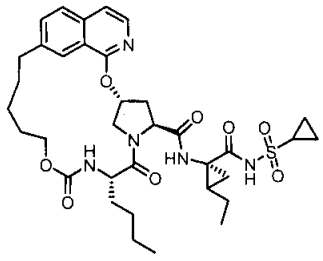
Una vigésima realización de la presente invención es un compuesto, o una sal o hidrato farmacéuticamente aceptable del mismo, seleccionado del grupo constituido por los compuestos **III-39** a **III-187**.



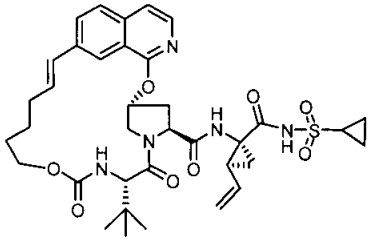
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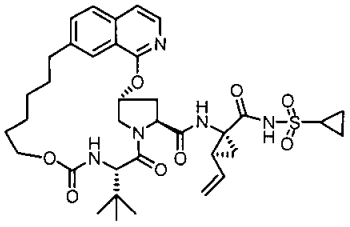
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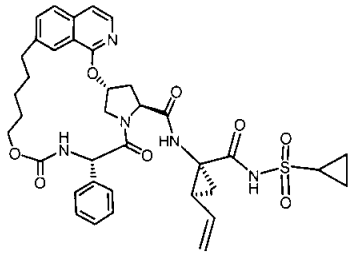
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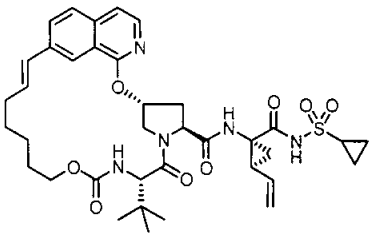
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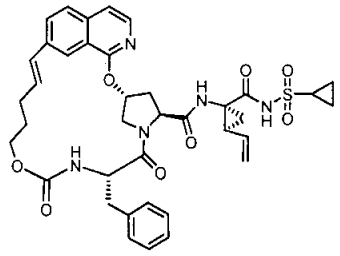
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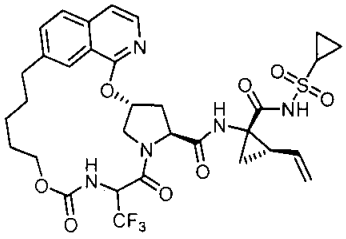
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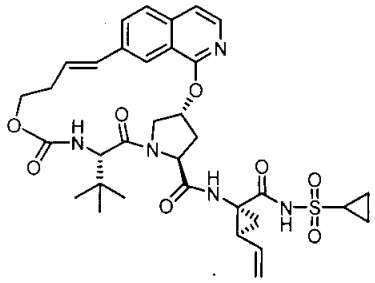
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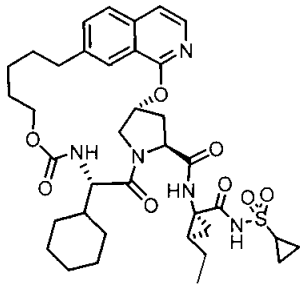
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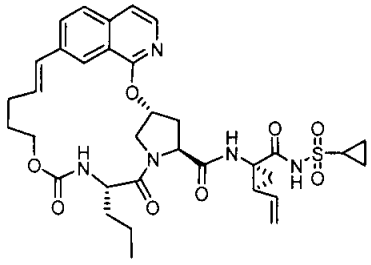
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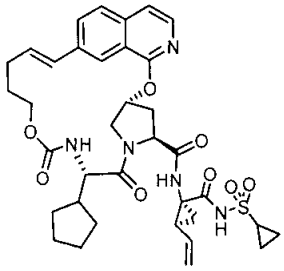
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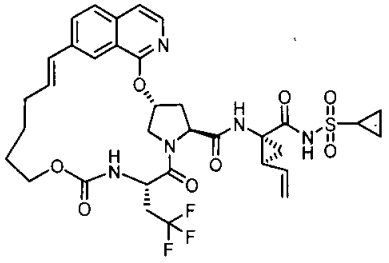
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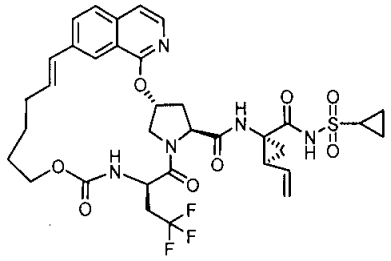
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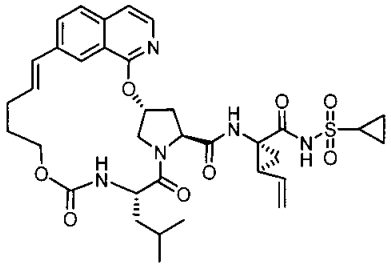
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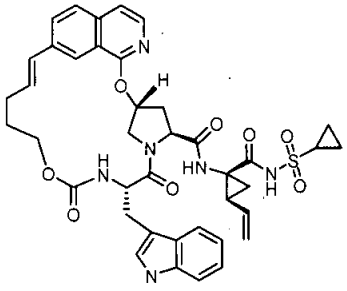
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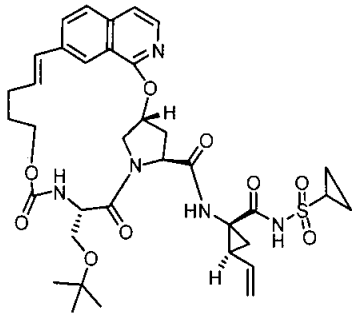
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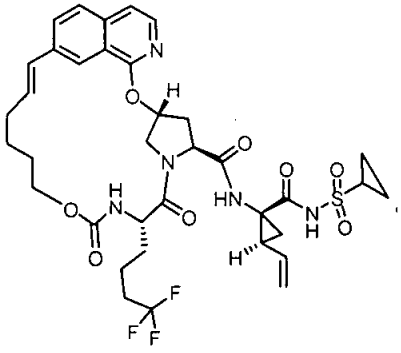
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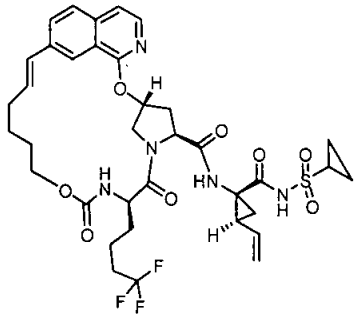
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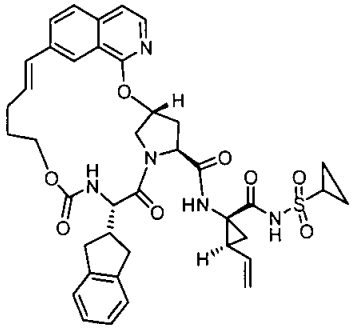
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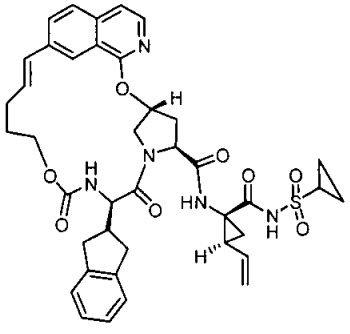
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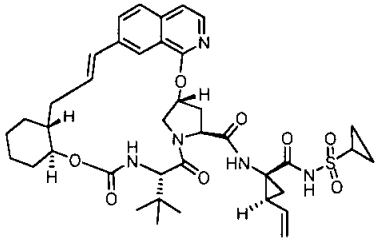
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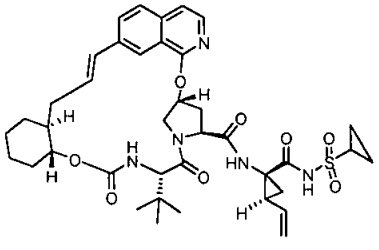
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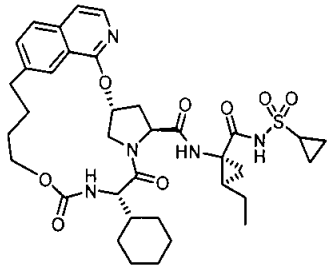
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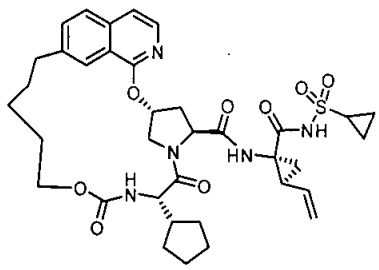
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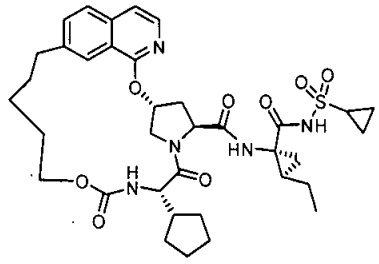
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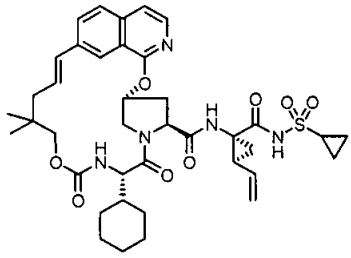
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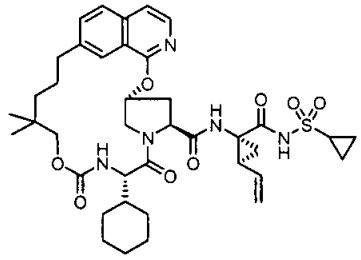
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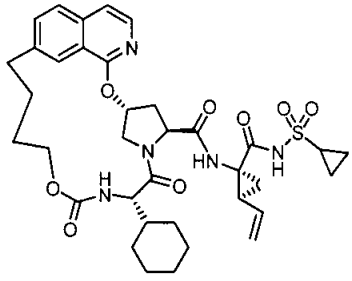
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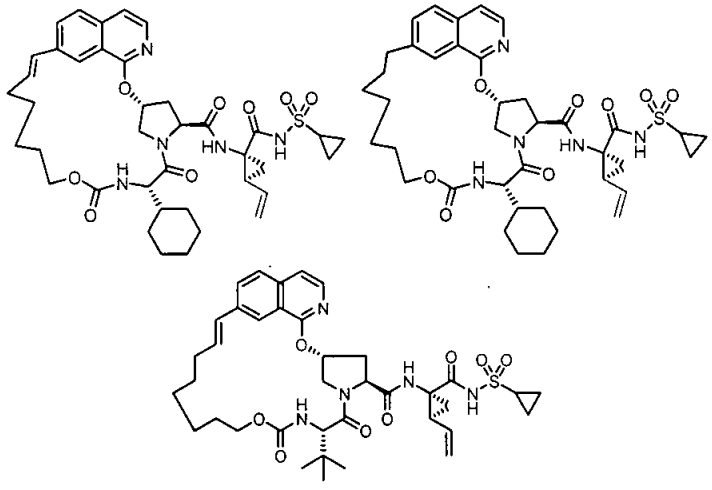
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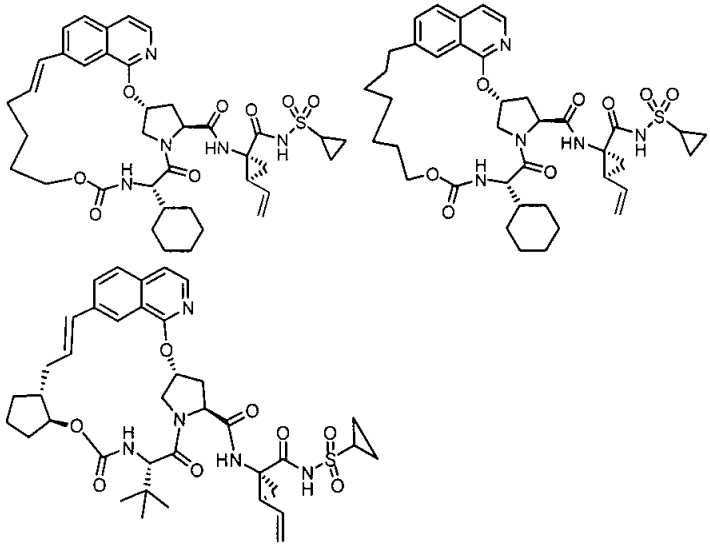
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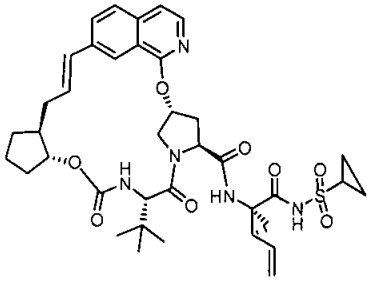
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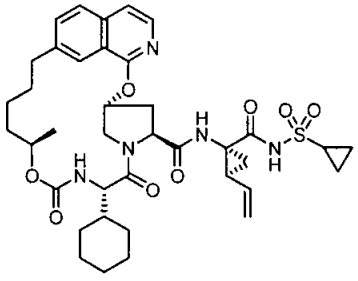
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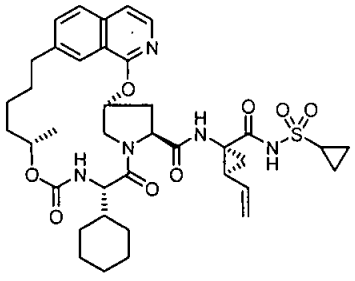
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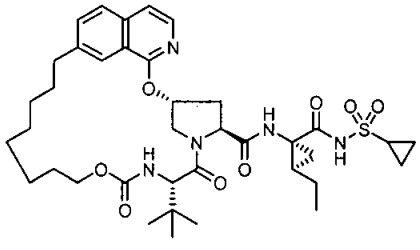
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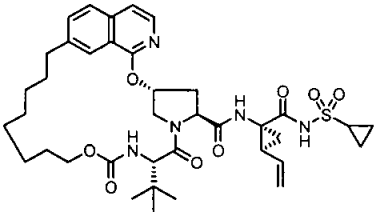
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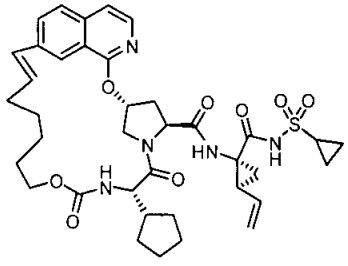
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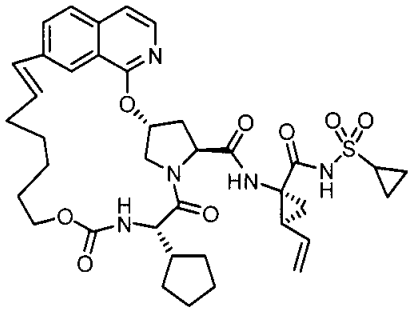
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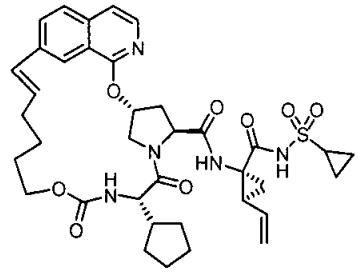
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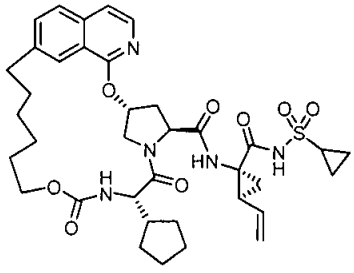
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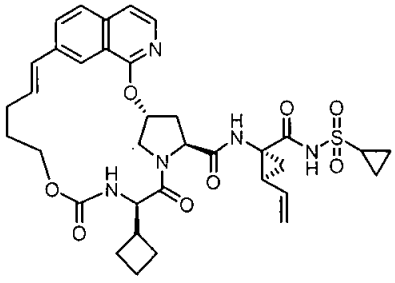
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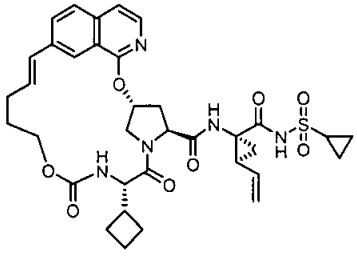
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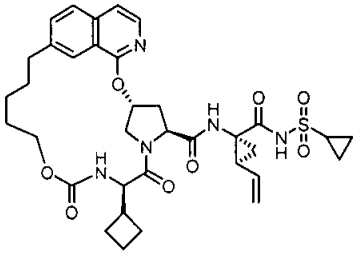
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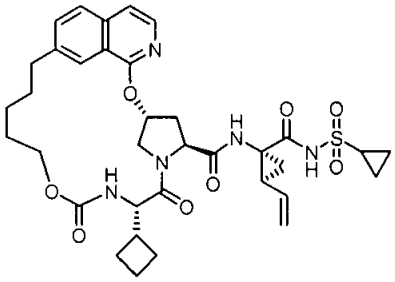
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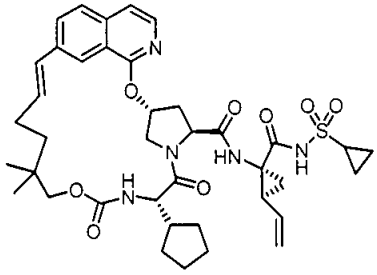
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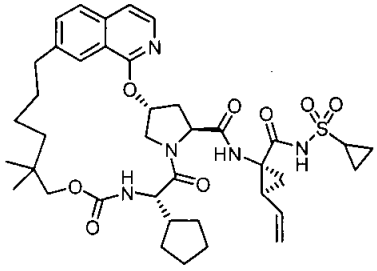
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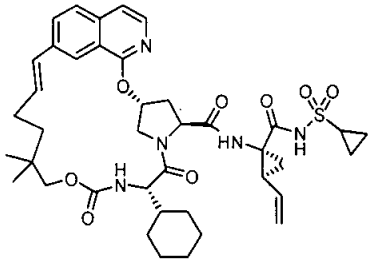
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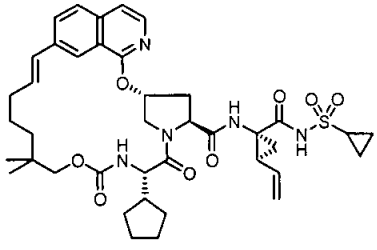
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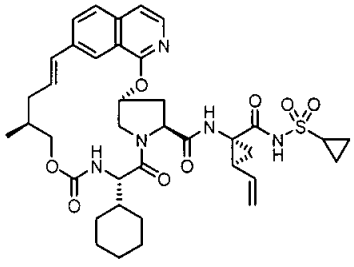
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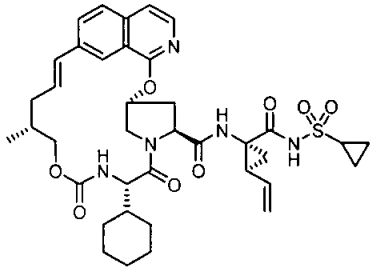
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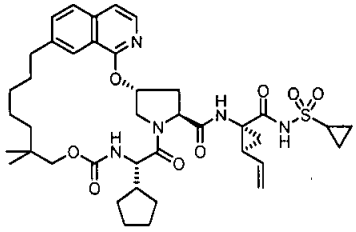
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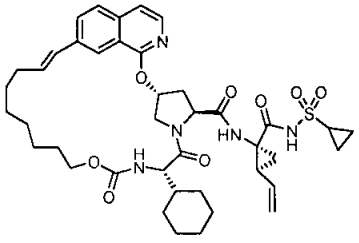
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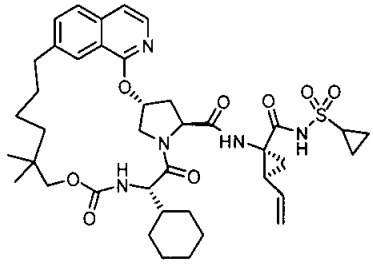
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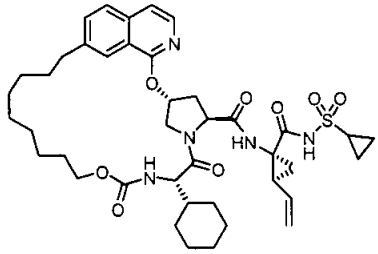
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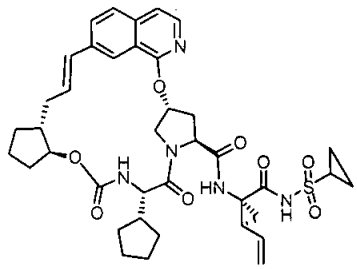
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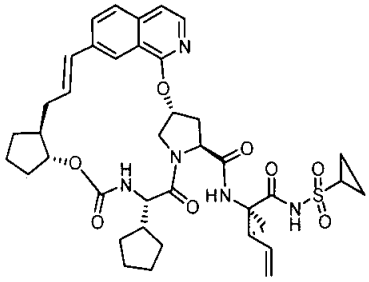
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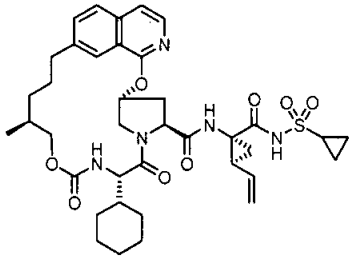
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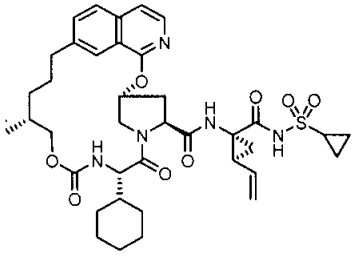
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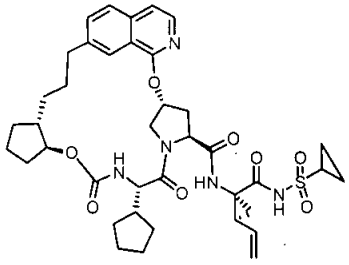
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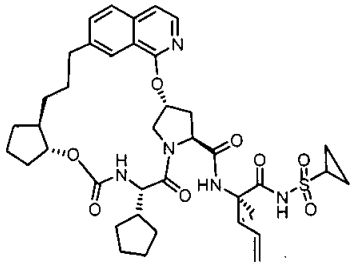
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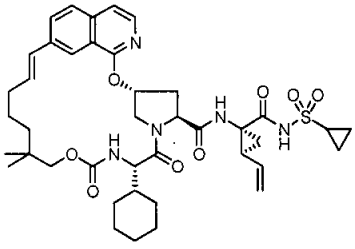
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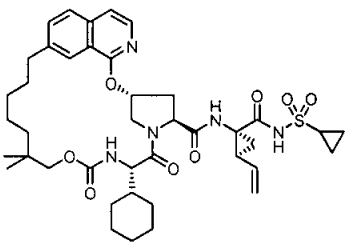
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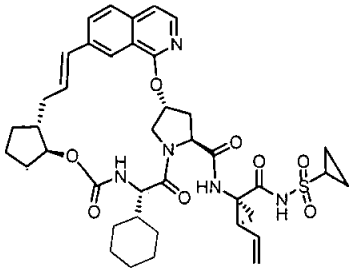
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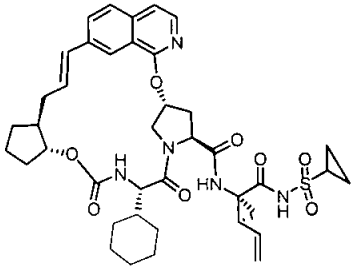
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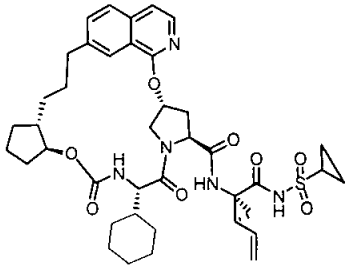
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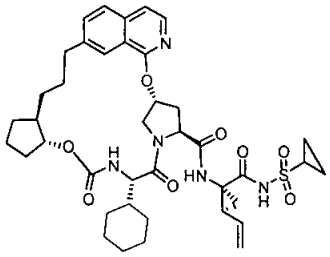
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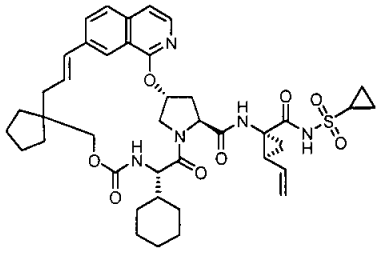
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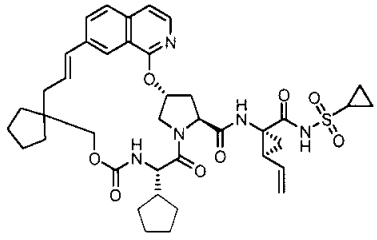
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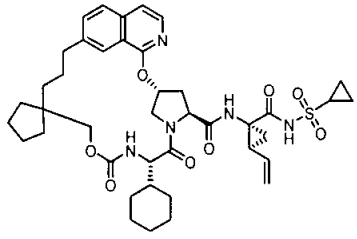
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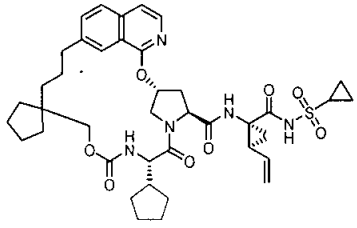
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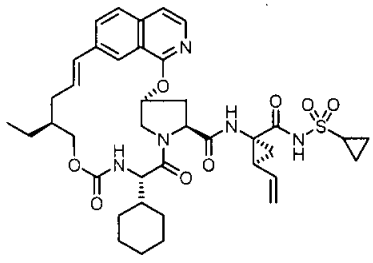
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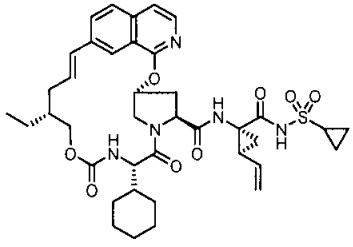
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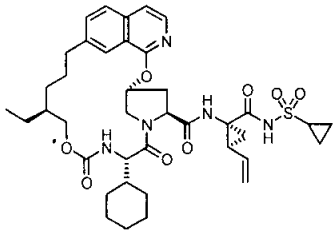
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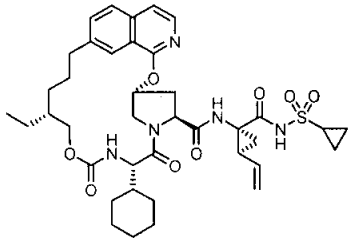
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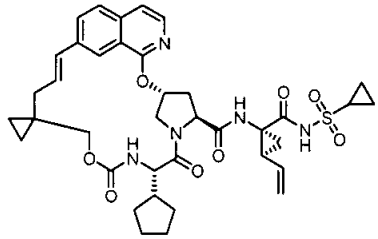


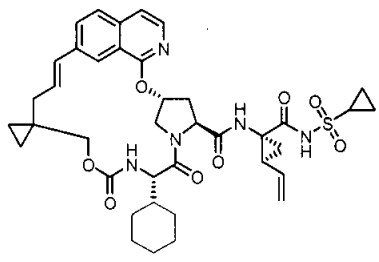
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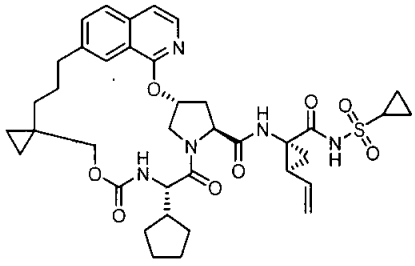
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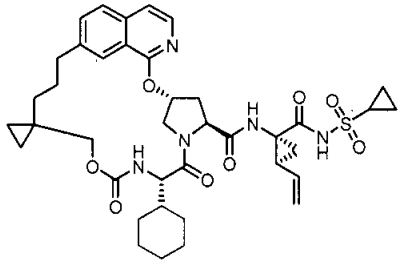




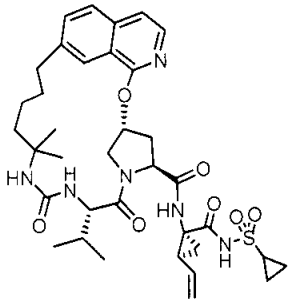
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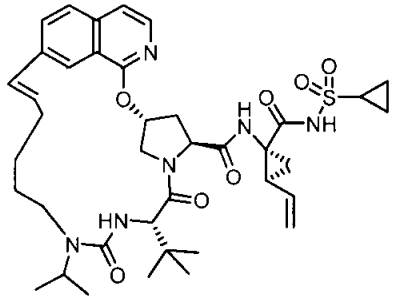
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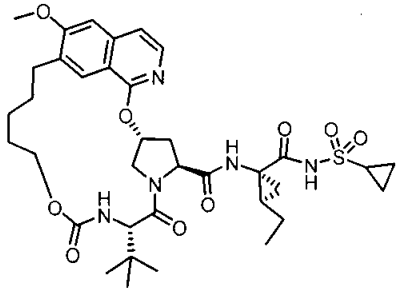
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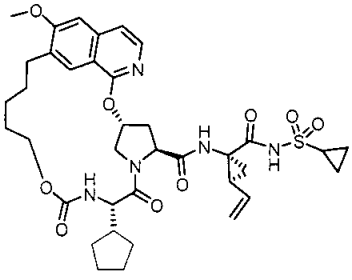
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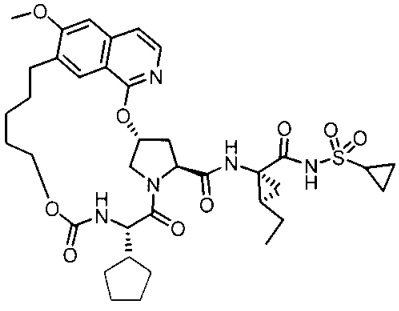
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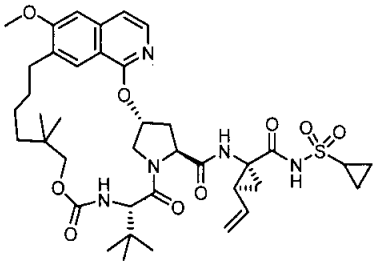
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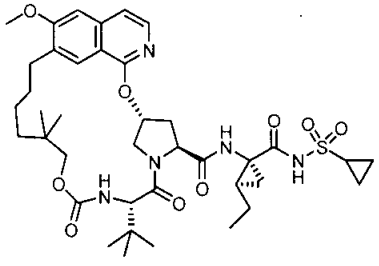
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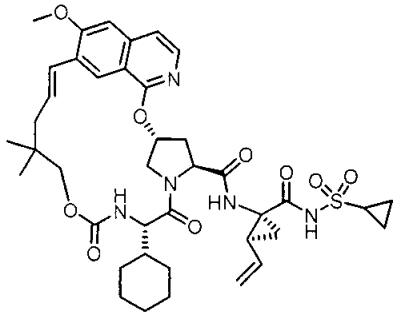
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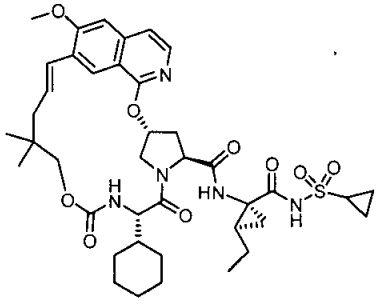
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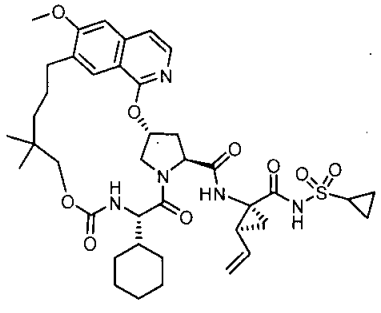
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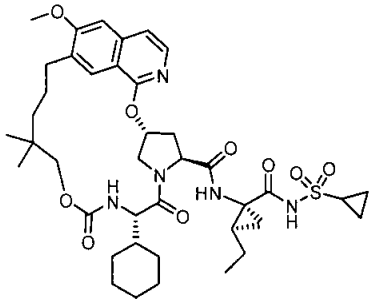
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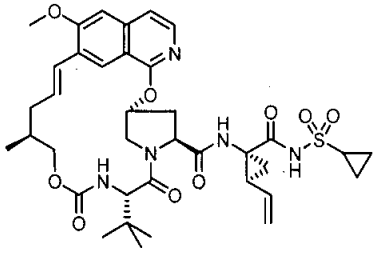


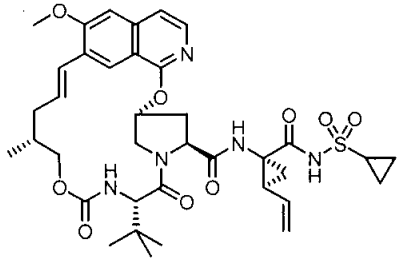
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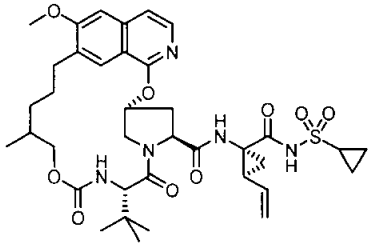
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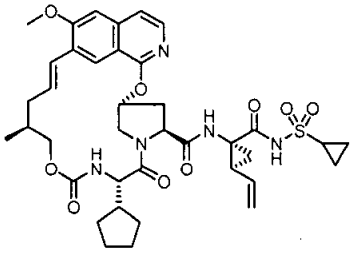


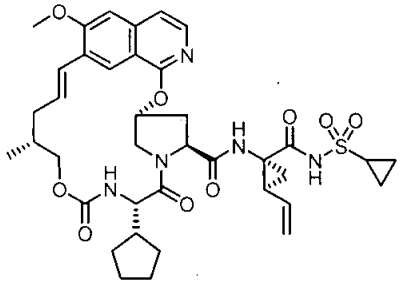




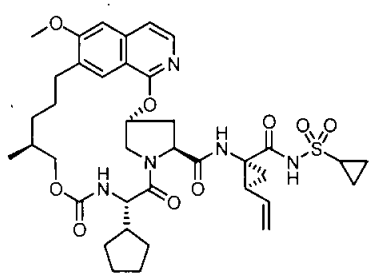
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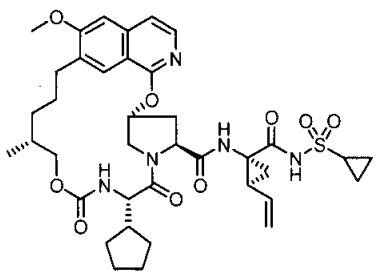




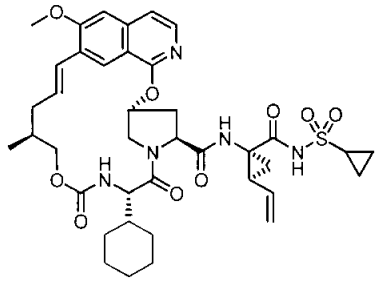
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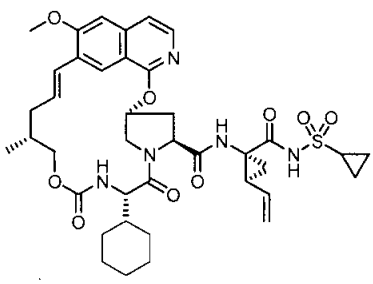
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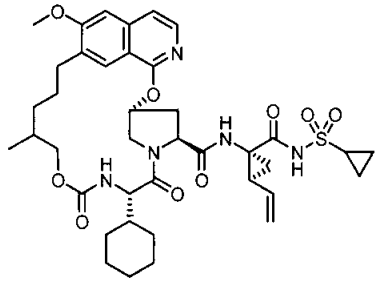
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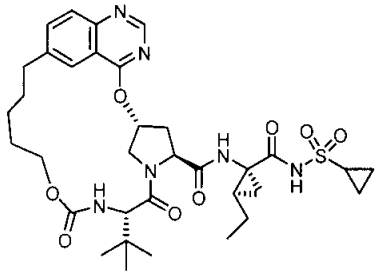
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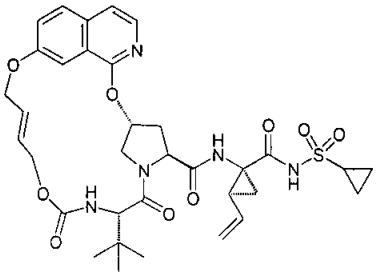
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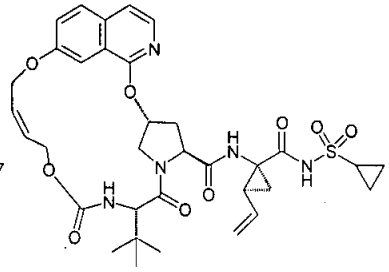
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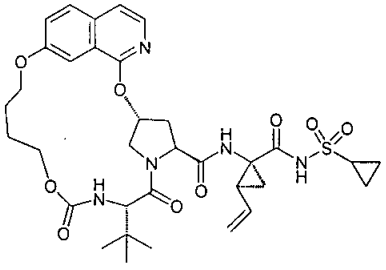
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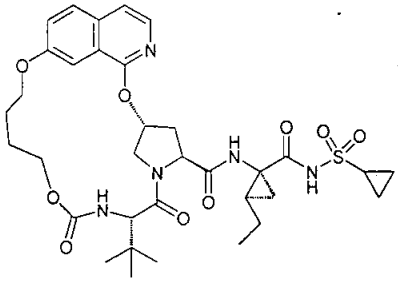
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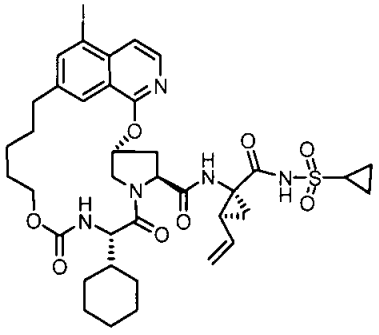
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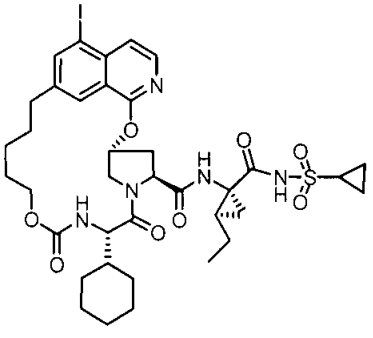
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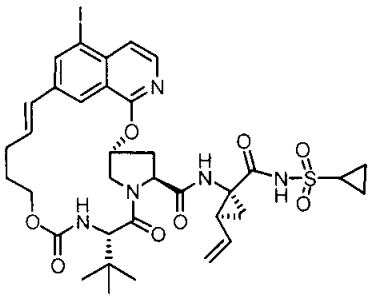
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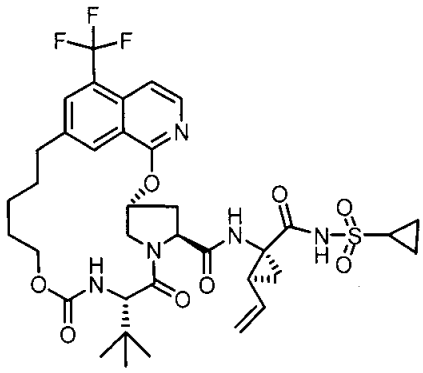
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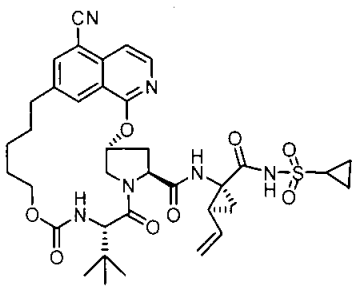
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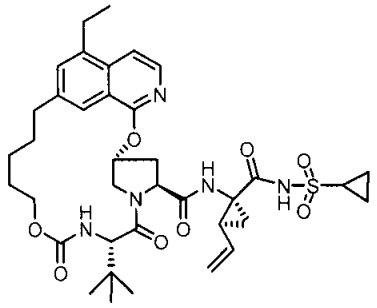
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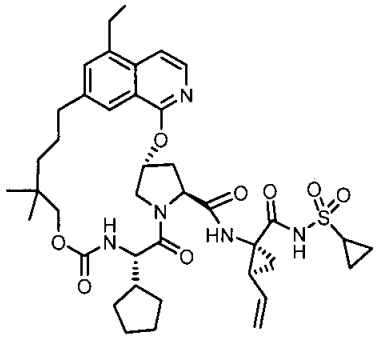
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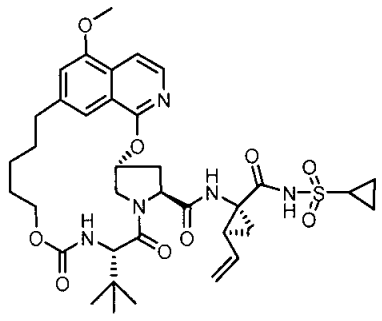
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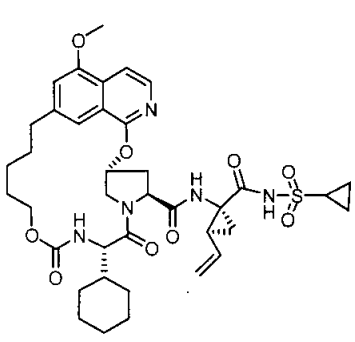
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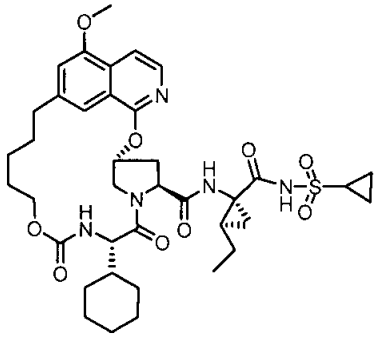
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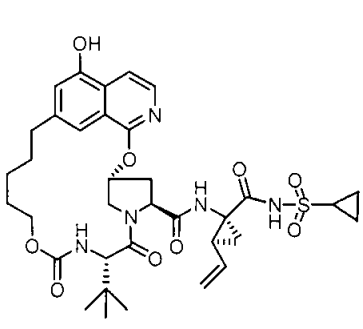


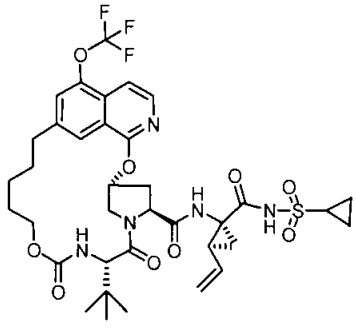
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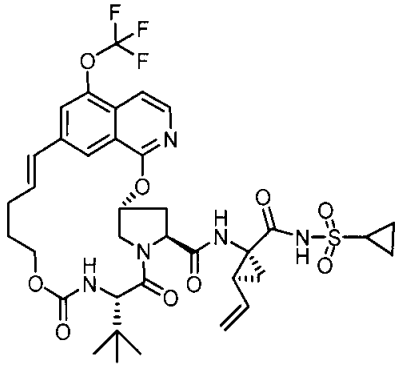


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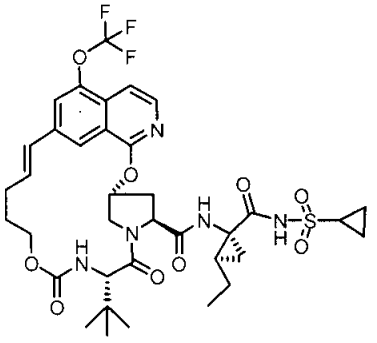




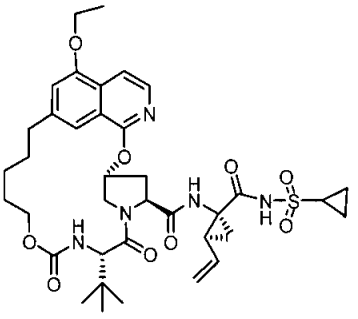
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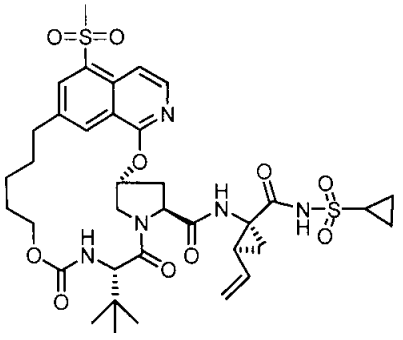
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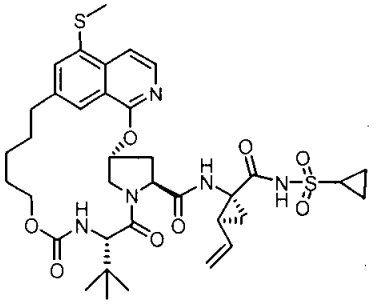
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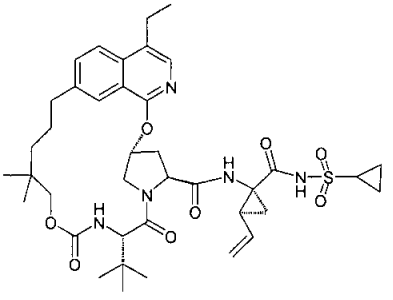
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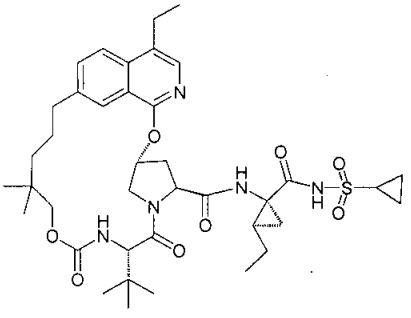
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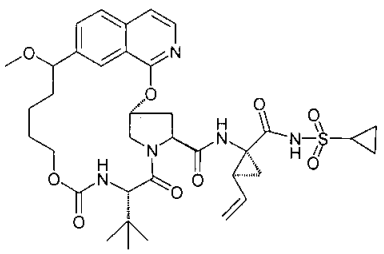
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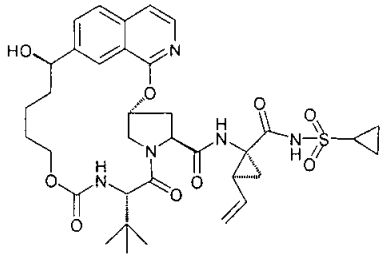
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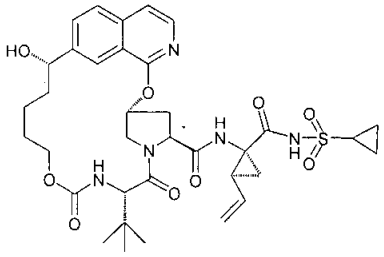
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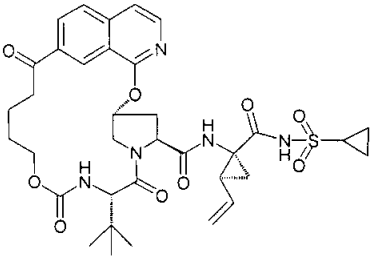
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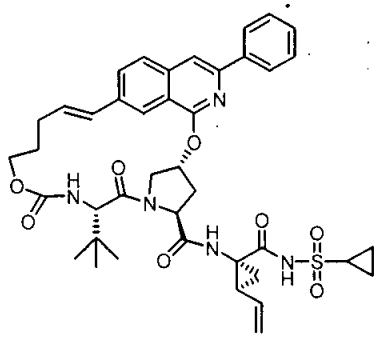
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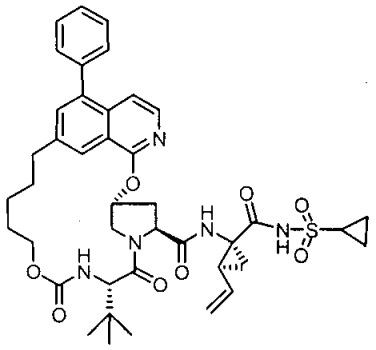
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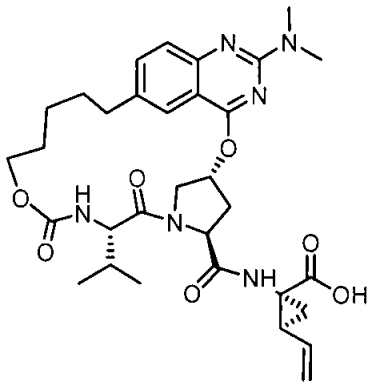
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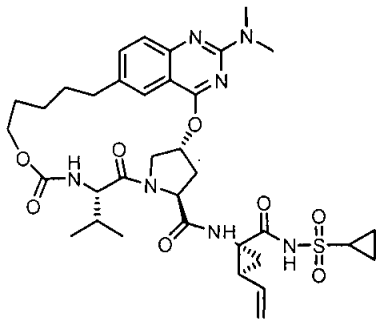
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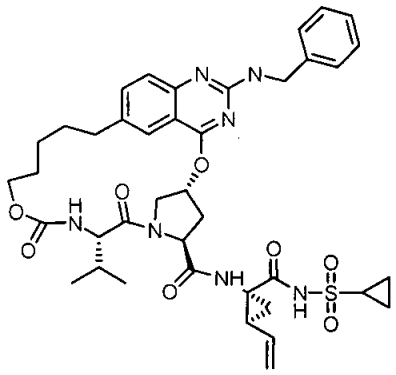
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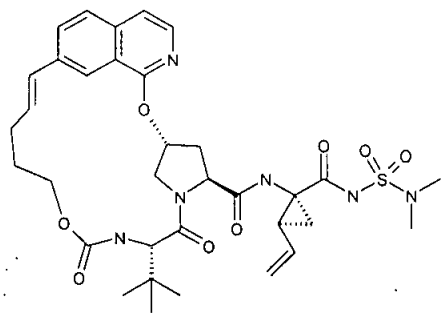
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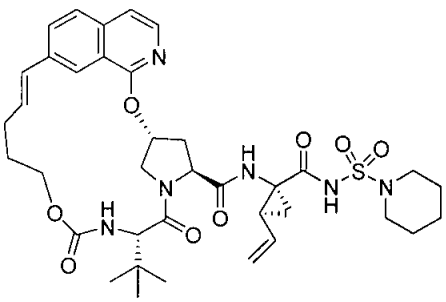
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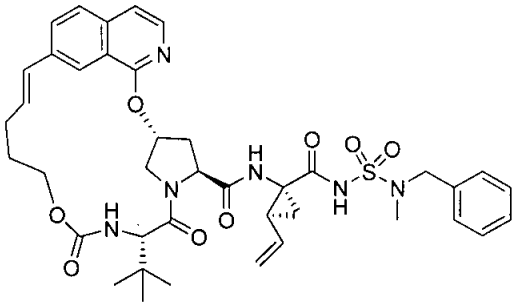
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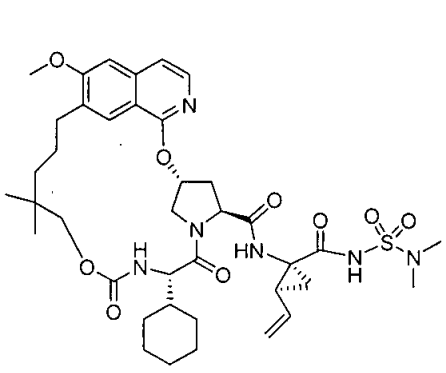
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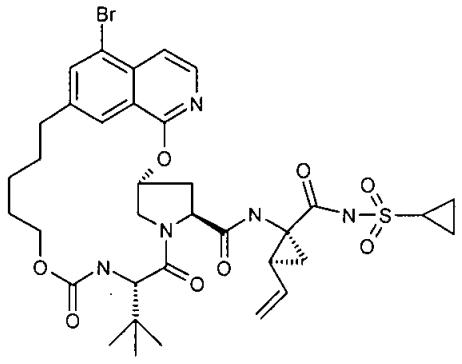
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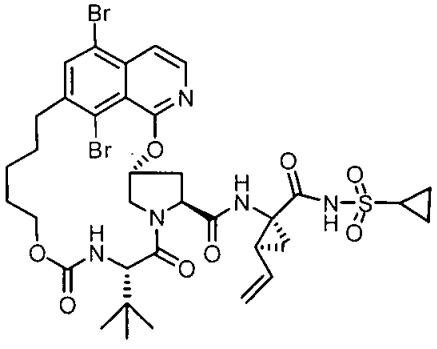
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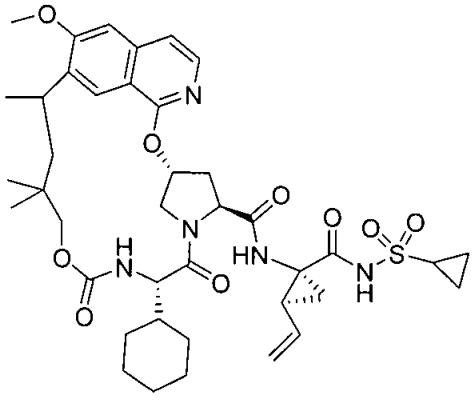
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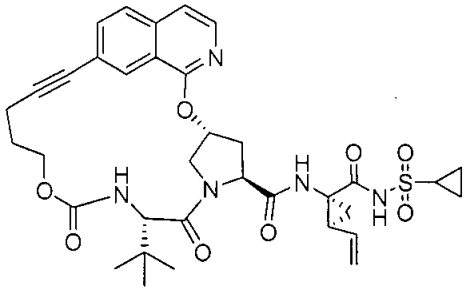
III-182



III-183



III-184



III-185

Una vigesimoprimera realización de la presente invención es un compuesto de fórmula (**I**) y/o una sal y/o hidrato farmacéuticamente aceptable del mismo:

R^1 es CO_2R^{10}, $CONR^{10}SO_2R^6$, $CONR^{10}SO_2NR^8R^9$, o tetrazolilo;

R^2 es alquilo C_1-C_6, alquenilo C_2-C_6 o cicloalquilo C_3-C_8, en los que dicho alquilo, alquenilo o cicloalquilo está opcionalmente sustituido con 1 a 3 halo;

R^3 es alquilo C_1-C_8, cicloalquilo C_3-C_8, cicloalquil C_3-C_8(alquilo C_1-C_8), aril(alquiloC_1-C_8), o Het, en los que arilo es fenilo o naftilo y dicho alquilo, cicloalquilo, o arilo está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, y $CON(R^{10})_2$;

Het es un anillo cíclico saturado de 5-6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, en el que dicho anillo está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, y $CON(R^{10})_2$;

R^4 es H, alquilo C_1-C_8, cicloalquil C_3-C_8(alquil C_1-C_8), o aril(alquiloC_1-C_8); en los que arilo es fenilo o naftilo y dicho alquilo, cicloalquilo, o arilo está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)^2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO^2R10, C(O)R10, y $CON(R^{10})_2$;

R^5 es H, halo, OH, alcoxi C_1-C_6, alquilo C_1-C_6, CN, CF_3, SR^{10}, SO_2(alquilo C_1-C_6), cicloalquilo C_3-C_8, cicloalcoxi C_3-C_8, haloalquilo C_1-C_6, $N(R^7)_2$, arilo, heteroarilo o heterociclilo; en el que arilo es fenilo o naftilo, heteroarilo es un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y heterociclilo es un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en los que dicho arilo, heteroarilo, heterociclilo, cicloalquilo, cicloalcoxi, alquilo o alcoxi está opcionalmente sustituido con 1 a 4 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^7)_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), cicloalquilo C_3-C_6, cicloalcoxi C_3-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, S(O)(alquilo C_1-C_6), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, y $CON(R^{10})_2$; en los que los 2 sustituyentes adyacentes de dicho cicloalquilo,

cicloalcoxi, arilo, heteroarilo o heterociclilo se toman opcionalmente conjuntamente para formar un anillo cíclico de 3-6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S;
R^6 es alquilo C_1-C_8, cicloalquilo C_3-C_8, cicloalquil C_3-C_8(alquilo C_1-C_5), arilo, aril(alquilo C_1-C_4), heteroarilo, heteroaril(alquilo C_1-C_4), heterociclilo, o heterociclil(alquilo C_1-C_8), en los que dicho alquilo, cicloalquilo, arilo, heteroarilo, o heterociclilo está opcionalmente sustituido con 1 a 2 sustituyentes W'; y en los que cada arilo es independientemente fenilo o naftilo, cada heteroarilo es independientemente un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y cada heterociclilo es independientemente un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un anillo de carbono o nitrógeno;

Y es C(=O), SO_2, o C(=N-CN);

Z es $C(R^{10})_2$, O, o $N(R^4)$;

M es alquileno C_1-C_{12} o alquenileno C_2-C_{12}, en el que dicho alquileno o alquenileno está opcionalmente sustituido con 1 ó 2 sustituyentes seleccionados del grupo constituido por alquilo C_1-C_8, cicloalquil C_3-C_8(alquilo C_1-C_8), y aril(alquilo C_1-C_8); y los 2 sustituyentes en átomos de carbono adyacentes de M se toman opcionalmente conjuntamente para formar un anillo cíclico de 3-6 miembros que contienen 0-3 heteroátomos seleccionados de N, O y S;

A es $C(R^{11})$ o N;

cuando R^5 es distinto de H, R^{11} es H, alquilo C_1-C_6, halo, OR^{10}, SR^{10}, o $N(R^{10})_2$;

cuando R^5 es H, halo, R^{11} es H, alquilo C_1-C_6, halo, OH, alcoxi C_1-C_6,CN, CF_3, SR^{10}, SO_2(alquilo C_1-C_6), cicloalquilo C_3-C_8, cicloalcoxi C_3-C_8, haloalquilo C_1-C_6, $N(R^7)_2$, arilo, heteroarilo o heterociclilo; en el que arilo es fenilo o naftilo, heteroarilo es un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y heterociclilo es un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en los que dicho arilo, heteroarilo, heterociclilo, cicloalquilo, cicloalcoxi, alquilo o alcoxi está opcionalmente sustituido con 1 a 4 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^7)_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), cicloalquilo C_3-C_6, cicloalcoxi C_3-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, S(O)(alquilo C_1-C_6), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, y $CON(R^{10})_2$; en los que los 2

sustituyentes adyacentes de dicho cicloalquilo, cicloalcoxi, arilo, heteroarilo o heterociclilo se toman opcionalmente conjuntamente para formar un anillo cíclico de 3-6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S;
o R^5 y R^{11} se toman opcionalmente conjuntamente parar formar un anillo cíclico saturado, no aromático insaturado, o aromático de 5 a 6 miembros, que tiene 0-2 heteroátomos seleccionados de N, O y S;

cada R^7 es independientemente H, alquilo C_1-C_6, cicloalquilo C_3-C_6, cicloalquil C_3-C_6(alquilo C_1-C_5), arilo, aril(alquilo C_1-C_4), heteroarilo, heteroaril(alquilo C_1-C_4), heterociclilo, o heterociclil(alquilo C_1-C_8), en los que dicho alquilo, cicloalquilo, arilo, heteroarilo, o heterociclilo está opcionalmente sustituido con 1 a 2 sustituyentes W'; y en los que cada arilo es independientemente fenilo o naftilo, cada heteroarilo es independientemente un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y cada heterociclilo es independientemente un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo;

cada W es independientemente halo, OR^7, alquilo C_1-C_6, CN, CF_3, NO_2, SR^7, CO_2R^7, $CON(R^7)_2$, $C(O)R^7$, $N(R^{10})C(O)R^7$, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), cicloalquilo C_3-C_8, cicloalcoxi C_3-C_8, haloalquilo C_1-C_6, $N(R^7)_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), halo(alcoxi C_1-C_6), $NR^{10}SO_2R^7$, $SO_2N(R^7)_2$, $NHCOOR^7$, $NHCONHR^7$, arilo, heteroarilo o heterociclilo; en los que arilo es fenilo o naftilo, heteroarilo es un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y heterociclilo es un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en los que 2 restos W adyacentes se toman opcionalmente conjuntamente con los átomos a los que están unidos para formar un anillo cíclico no aromático insaturado, saturado, o aromático de 5 ó 6 miembros que tiene 0-2 heteroátomos seleccionados de N, O y S;

cada W' es independientemente H, halo, OR^{10}, alquilo C_1-C_6, CN, CF_3, NO_2, SR^{10}, CO_2R^{10}, $CON(R^{10})_2$, $C(O)R^{10}$, $N(R^{10})C(O)R^{10}$, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), cicloalquilo C_3-C_8, cicloalcoxi C_3-C_8, haloalquilo C_1-C_6, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), halo(alcoxi C_1-C_6), $NR^{10}SO_2R^{10}$, $SO_2N(R^{10})_2$, $NHCOOR^{10}$, $NHCONHR^{10}$, arilo, heteroarilo o heterociclilo; en los que arilo es fenilo o naftilo, heteroarilo es un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y heterociclilo es un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en los que 2 restos W' adyacentes se toman opcionalmente

conjuntamente con los átomos a los que están unidos para formar un anillo cíclico no aromático, o aromático saturado, insaturado que tiene 0-2 heteroátomos seleccionados de N, O y S;
R^8 es alquilo C_1-C_8, cicloalquilo C_3-C_8, cicloalquil C_3-C_8 cicloalquil(alquilo C_1-C_8), arilo, aril(alquilo C_1-C_4), heteroarilo, heterociclilo, heteroaril(alquilo C_1-C_4), o heterociclil(alquilo C_1-C_8), en los que dicho alquilo, cicloalquilo, arilo, heteroarilo o heterociclilo está opcionalmente sustituido con 1 a 4 sustituyentes seleccionados del grupo constituido por arilo, cicloalquilo C_3-C_8, heteroarilo, heterociclilo, alquilo C_1-C_6, halo(alcoxi C_1-C_6), halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, $C(O)R^{10}$, haloalquilo C_1-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, y $C(O)N(R^{10})_2$; en el que cada arilo es independientemente fenilo o naftilo; cada heteroarilo es independientemente un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y cada heterociclilo es independientemente un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en el que los 2 sustituyentes adyacentes de dicho cicloalquilo, cicloalcoxi, arilo, heteroarilo o heterociclilo se toman opcionalmente conjuntamente para formar un anillo cíclico de 3 a 6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S;

R^9 es alquilo C_1-C_8, cicloalquilo C_3-C_8, cicloalquil C_3-C_8 (alquilo C_1-C_8), alcoxi C_1-C_8, cicloalcoxi C_3-C_8, arilo, aril(alquilo C_1-C_4), heteroarilo, heterociclilo, heteroaril(alquilo C_1-C_4), o heterociclil(alquilo C_1-C_8), en los que dicho alquilo, cicloalquilo, alcoxi, cicloalcoxi, arilo, heteroarilo o heterociclilo está opcionalmente sustituido con 1 a 4 sustituyentes seleccionados del grupo constituido por arilo, cicloalquilo C_3-C_8, heteroarilo, heterociclilo, alquilo C_1-C_6, halo(alcoxi C_1-C_6), halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, $C(O)R^{10}$, haloalquilo C_1-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R_{10}, y $C(O)N(R^{10})_2$; en el que cada arilo es independientemente fenilo o naftilo; cada heteroarilo es independientemente un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y cada heterociclilo es independientemente un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en la que los 2 sustituyentes adyacentes de dicho cicloalquilo, cicloalcoxi, arilo, heteroarilo o heterociclilo se toman opcionalmente conjuntamente para formar un anillo cíclico de 3 a 6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S;

o R^8 y R^9 se toman opcionalmente conjuntamente, con el átomo de nitrógeno al que están unidos, para formar un anillo monocíclico de 4-8 miembros que contienen 0-2 heteroátomos adicionales seleccionados de N, O y S; y

cada R^{10} es independientemente H o alquilo C_1-C_6.

Una vigesimosegunda realización de la presente invención es un compuesto, o una sal o hidrato farmacéuticamente aceptable del mismo, que es compuesto **III-23** ácido ((1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-terc-butil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-etanodiilideno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecin-4-il]carbonil}amino)-2-vinilciclopropanocarboxílico).

Otras realizaciones de la presente invención incluyen lo siguiente:

(a) Una composición farmacéutica que comprende una cantidad efectiva de un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B** y un vehículo farmacéuticamente aceptable.

(b) La composición farmacéutica de (a), que comprende adicionalmente un segundo agente terapéutico seleccionado del grupo constituido por un agente antiviral VHC, un inmunomodulador, y un agente antiinfeccioso.

(c) La composición farmacéutica de (b), en la que el agente antiviral de VHC es un antiviral seleccionado del grupo constituido por un inhibidor de proteasa de VHC y un inhibidor de proteasa NS5B de VHC.

(d) Una combinación farmacéutica que es (i) un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B** y (ii) un segundo agente terapéutico seleccionado del grupo constituido por un agente antiviral contra VHC, un inmunomodulador, y un agente antiinfeccioso; en el que el compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B** y el segundo agente terapéutico se emplean cada uno en una cantidad que vuelve a la combinación efectiva para inhibir proteasa NS3 de VHC, o para tratar o prevenir la infección por VHC.

(e) La combinación de (d), en la que el agente antiviral contra VHC es un antiviral seleccionado del grupo constituido por un inhibidor de proteasa de VHC y un inhibidor de polimerasa NS5B de VHC.

(f) Un procedimiento de inhibir proteasa NS3 de VHC en un sujeto en necesidad del mismo que comprende administrar al sujeto una cantidad efectiva de un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B**.

(g) Un procedimiento de prevenir o tratar infección por VHC en un sujeto en necesidad del mismo que comprende administrar al sujeto una cantidad efectiva de un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B**.

(h) El procedimiento de (g), en el que el compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B** se administró en combinación con una cantidad efectiva de al menos un

segundo agente terapéutico seleccionado del grupo constituido por un agente antiviral VHC, un inmunomodulador, y un agente antiinfeccioso.

(i) El procedimiento de (h), en la que el agente antiviral contra VHC es un antiviral seleccionado del grupo constituido por un inhibidor de proteasa de VHC y un inhibidor de polimerasa NS5B de VHC.

(j) Un procedimiento de inhibir proteasa NS3 de VHC en un sujeto en necesidad del mismo que comprende administrar al sujeto la composición farmacéutica de (a), (b), o (c) o la combinación de (d) o (e).

(k) Un procedimiento de prevenir o tratar infección por VHC en un sujeto en necesidad del mismo que comprende administrar al sujeto la composición farmacéutica de (a), (b), o (c) o la combinación de (d) o (e).

La presente invención también incluye un compuesto de la presente invención (i) para usar en, (ii) para usar como un medicamento para, o (iii) para usar en la preparación de un medicamento para: (a) inhibir proteasa NS3 de VHC, o (b) prevenir o tratar infección por VHC. En estos usos, los compuestos de la presente invención pueden emplearse opcionalmente en combinación con uno o más segundos agentes terapéuticos seleccionados de agentes antivirales contra VHC, agentes antiinfecciosos, e inmunomoduladores.

Las realizaciones adicionales de la invención incluyen las composiciones, combinaciones y procedimientos farmacéuticos expuestos en (a)-(k) anteriormente y los usos expuestos en el párrafo precedente, en los que el compuesto de la presente invención empleado en esto es un compuesto de una de las realizaciones, aspectos, clases, subclases, o características de los compuestos descritos anteriormente. En todas estas realizaciones, el compuesto puede usarse opcionalmente en la forma de una sal o hidrato farmacéuticamente aceptable según sea apropiado.

Como se usa en el presente documento, el término "alquilo" hace referencia a cualquier grupo alquilo de cadena lineal o ramificada que tiene un número de átomos de carbono en el intervalo especificado. Así, por ejemplo, "alquilo C_{1-6}" (o "alquilo C_1-C_6") se refiere a todos los isómeros de hexilalquilo y pentilalquilo así como n-, iso-, sec- y t-butilo, n- e isopropilo, etilo y metilo. Como otro ejemplo, "alquilo C_{1-4}" se refiere a n-, iso-, sec- y t-butilo, n- e isopropilo, etilo y metilo.

El término "haloalquilo" se refiere a un grupo alquilo en el que un hidrógeno se ha reemplazado por un halógeno. El término "alcoxi" se refiere a un grupo "alquil-O-".

El término "alquileno" hace referencia a cualquier grupo alquileno (o alternativamente "alcanodiílo") de cadena lineal o ramificada que tiene un número de átomos de carbono en el intervalo especificado. Así, por ejemplo, "-alquileno C_{1-6}-" se refiere a cualquiera de los alquilenos lineales o ramificados de C_1 a C_6. Una clase de alquilenos de interés particular con respecto a la invención es $-(CH_2)_{1-6}-$, y las subclases de interés particular incluyen $-(CH_2)_{1-4}-$, $-(CH_2)_{1-3}-$, $-(CH_2)_{1-2}-$, y $-CH_2-$. También de interés es el alquileno $-CH(CH_3)-$.

El término "cicloalquilo" se refiere a cualquier anillo cíclico de un alcano o alqueno que tiene un número de átomos de carbono en el intervalo especificado. Así, por ejemplo, "cicloalquilo C_{3-8}" (o "cicloalquilo C_3-C_8") hace referencia a ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, y ciclooctilo. El término "cicloalcoxi" hace referencia a un grupo "cicloalquil-O-".

El término "halógeno" (o "halo") se refiere a flúor, cloro, bromo y yodo (referido alternativamente a fluoro, cloro, bromo, y yodo).

A menos que se establezca expresamente lo contrario, todos los intervalos citados en el presente documento son inclusive. Por ejemplo, un anillo heteroarílico descrito como que contiene de "1 a 3 heteroátomos" quiere decir que el anillo puede contener 1, 2, ó 3 heteroátomos. Se entenderá también que cualquier intervalo citado en el presente documento incluye dentro de su alcance todos los subintervalos dentro de ese intervalo. Las formas oxidadas de los heteroátomos N y S están también incluidas dentro del alcance de la presente invención.

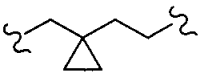
Cuando cualquier variable (por ejemplo, R^7 y R^{10}) tiene lugar más de una vez en cualquier constituyente o en fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B** o en cualquier otra fórmula que representa y que describe compuestos de la invención, su definición en cada aparición es independiente de su definición en cualquier otra aparición. Además, son permisibles combinaciones de sustituyentes y/o variables sólo si tales combinaciones dan como resultado compuestos estables.

A menos que se establezca específicamente al contrario, la sustitución con un sustituyente identificado se permite en cualquier átomo de carbono en un anillo (por ejemplo, arilo, un anillo heteroaromático, o un anillo heterocílico saturado) estipula que tal sustitución de anillo está químicamente permitida y da como resultado un compuesto estable. Un compuesto "estable" es un compuesto que se puede preparar y aislar y cuya estructura y propiedades permanecen o pueden estar causadas para permanecer esencialmente sin cambios durante un periodo de tiempo suficiente para permitir el uso del compuesto para los propósitos descritos en el presente documento (por ejemplo, administración terapéutica o preventiva a un sujeto).

Los términos que se refieren a 2 sustituyentes "en átomos de carbono adyacentes" que "se toman opcionalmente conjuntamente" forman anillos cíclicos especificados, y 2 sustituyentes "en el mismo átomo de carbono" que "se toman opcionalmente conjuntamente" forman anillos cíclicos especificados, significan que 2 sustituyentes pueden formar un anillo que incluye ambos átomos de carbono adyacentes, o pueden formar un anillo que incluye el mismo átomo de carbono. Por ejemplo, el anillo 1 mostrado más adelante está formado por dos sustituyentes de carbono individuales unidos cada uno de ellos a átomos de carbono adyacentes, y el anillo 2 mostrado más adelante está formado por dos sustituyentes de carbono individuales unidos cada uno al mismo átomo de carbono:



Anillo 1



Anillo 2

Como un resultado de la selección de sustituyentes y patrones de sustituyentes, ciertos de los compuestos de la presente invención pueden tener centros asimétricos y pueden aparecer como mezclas de estéreo isómeros, o como diastereómeros individuales, o enantiómeros. Todas las formas isómeras de estos compuestos, si están aislados o en mezclas, están dentro del alcance de la presente invención.

Como se reconocería por alguien de habilidad normal en la técnica, ciertos de los compuestos de la presente invención pueden existir como tautómeros. Para los propósitos de la presente invención una referencia a un compuesto de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B** es una referencia al compuesto per se, o a uno cualquiera de sus tautómeros per se, o a mezclas de dos o más tautómeros.

Los compuestos de las presentes invenciones son útiles en la inhibición de proteasa de VHC (por ejemplo, proteasa NS3 de VHC) y la prevención o tratamiento de infección mediante VHC. Por ejemplo, los compuestos de esta invención son útiles en tratar infección mediante VHC después de exposición pasada sospechada a VHC por medios tales como transfusión de sangre, intercambio de fluidos corporales, mordiscos, clavado de aguja accidental, o exposición a sangre de pacientes durante la cirugía.

Los compuestos de esta invención son útiles en la preparación y ejecución de ensayos de rastreo para compuestos antivirales. Por ejemplo, los compuestos de esta invención son útiles para aislar mutantes enzimáticos, que son excelentes herramientas de rastreo para los compuestos antivirales más poderosos. Además, los compuestos de esta invención son útiles en establecer o determinar el sitio de unión de otros antivirales a proteasa de VHC, por ejemplo, mediante inhibición competitiva. Así los compuestos de esta invención son productos comerciales para venderse para estos propósitos.

Los compuestos de la presente invención se pueden administrar en forma de sales farmacéuticamente aceptables. El término "sal farmacéuticamente aceptable" se refiere una sal que posee la efectividad del compuesto parental y que no es biológicamente o de otra manera indeseable (por ejemplo, no es ni tóxico ni dañino de ninguna otra manera para el receptor del mismo). Las sales adecuadas incluyen sales de adición ácida que pueden, por ejemplo, estar formadas mezclando una solución del compuesto de la presente invención con una solución de un ácido farmacéuticamente aceptable tal como ácido clorhídrico, ácido sulfúrico, ácido acético, ácido trifluoroacético, o ácido benzoico. Muchos de los compuestos de la invención llevan un resto ácido, caso en el que sales farmacéuticamente aceptables adecuadas de los mismos pueden incluir sales de metales alcalinos (por ejemplo, sales de sodio o de potasio), sales de metales alcalinotérreos (por ejemplo, sales de calcio o de magnesio), y sales

formadas con ligandos orgánicos adecuados tales como sales de amonio cuaternarias. Además, en el caso de que esté presente un grupo ácido (-COOH) o alcohol, los ésteres farmacéuticamente aceptables se pueden emplear para modificar las características de solubilidad o hidrólisis del compuesto.

El término "administración" y variantes del mismo (por ejemplo, "administrar" un compuesto) en referencia a un compuesto de la invención significan proporcionar el compuesto o un profármaco del compuesto al individuo en necesidad de tratamiento. Cuando un compuesto de la invención o un profármaco del mismo se proporciona en combinación con uno o más agentes activos diferentes (por ejemplo, agentes antivirales útiles para tratar infección por VHC), "administración" y sus variantes se entiende cada uno que incluye provisión del compuesto o sal (o hidrato) y otros agentes concurrente y secuencial.

Como se usa en el presente documento, el término "composición" se desea para abarcar un producto que comprende los ingredientes especificados, así como cualquier producto que resulte, directa o indirectamente, de combinar los ingredientes especificados.

"Farmacéuticamente aceptable" quiere decir que los ingredientes de la composición farmacéutica deben ser compatibles unos con otros y no dañinos para el receptor de los mismos.

El término "sujeto" (alternativamente referido para el presente documento como "paciente") como se usa en el presente documento se refiere a un animal, preferiblemente un mamífero, lo más preferiblemente un ser humano, quien ha sido el objeto de tratamiento, observación o experimento.

El término "cantidad efectiva" como se usa en el presente documento quiere decir la cantidad de compuesto activo o agente farmacéutico que facilita la respuesta biológica o medicinal en un tejido, sistema, animal o ser humano que se está intentando conseguir por un investigador, veterinario, doctor en medicina u otro trabajador clínico. En una realización, la cantidad efectiva es una "cantidad terapéuticamente efectiva" para el alivio de los síntomas de la enfermedad o afección que se trata. En otra realización, la cantidad efectiva es una "cantidad profilácticamente efectiva" para prevención de los síntomas de la enfermedad o afección que se está previniendo. El término incluye también en el presente documento la cantidad de compuesto activo suficiente para inhibir proteasa NS3 de VHC y por lo tanto facilitar la respuesta que se está intentando conseguir (es decir, una "cantidad efectiva de inhibición"). Cuando el compuesto activo (es decir, ingrediente activo) se administra como la sal, las referencias a la cantidad de ingrediente activo son para la forma de ácido libre o base libre del compuesto.

Para el propósito de inhibir proteasa NS3 de VHC y prevenir o tratar la infección por VHC, los compuestos de la presente invención, opcionalmente en forma de una sal o un hidrato, se pueden administrar mediante cualesquiera medios que producen contacto del agente activo con el sitio de acción del agente. Se pueden administrar mediante cualesquiera

medios convencionales disponibles para usar en conjunto con productos farmacéuticos, bien como agentes terapéuticos individuales o bien en una combinación de agentes terapéuticos. Se pueden administrar solos, pero se administran típicamente con un vehículo farmacéutico seleccionado sobre la base de la ruta de administración elegida y la práctica farmacéutica estándar. Los compuestos de la invención pueden, por ejemplo, administrarse oralmente, parenteralmente (incluyendo inyecciones subcutáneas, inyección intravenosa, intramuscular, intraesternal o técnicas de infusión), mediante pulverizador de inhalación, o rectalmente, en la forma de una dosificación unitaria de una composición farmacéutica que contiene una cantidad efectiva del compuesto y transportadores, coadyuvantes y vehículos farmacéuticamente aceptables convencionales no tóxicos. Se pueden preparar preparaciones líquidas adecuadas para administración oral (por ejemplo, suspensiones, jarabes, elixires y similares) de acuerdo con las técnicas conocidas en la técnica y se pueden emplear cualquiera de los medios usuales tales como agua, glicoles, aceites, alcoholes y similares. Las preparaciones sólidas adecuadas para administración oral (por ejemplo, polvos, píldoras, cápsulas y comprimidos) se pueden preparar de acuerdo con técnicas conocidas en la técnica y se pueden emplear excipientes sólidos tales como almidones, azúcares, caolín, lubricantes, aglutinantes, agentes disgregantes y similares. Las composiciones parenterales se pueden preparar de acuerdo con técnicas conocidas en la técnica y típicamente emplean agua estéril como un vehículo y opcionalmente otros ingredientes, tales como un coadyuvante de solubilidad. Las soluciones inyectables se pueden preparar de acuerdo con procedimientos conocidos en la técnica en los que el vehículo comprende una solución salina, una solución de glucosa o una solución que contiene una mezcla de solución salina y glucosa. Se proporciona descripción adicional de procedimientos adecuados para usar en preparar composiciones farmacéuticas de la presente invención y de ingredientes adecuados para usar en dichas composiciones en Remington's Pharmaceutical Sciences, 18ª edición, editado por A. R. Gennaro, Mack Publishing Co., 1990.

Los compuestos de esta invención se pueden administrar oralmente en un intervalo de dosificación de 0,001 a 1000 mg/kg de peso corporal de mamífero (por ejemplo, ser humano) por día en una dosis individual o en dosis divididas. Un intervalo de dosificación preferida es 0,01 a 500 mg/kg de peso corporal por día oralmente en una dosis individual o en dosis divididas. Otro intervalo de dosificación preferido es 0,1 a 100 mg/kg de peso corporal por día oralmente en dosis individual o dosis divididas. Para administración oral, las composiciones se pueden proporcionar en forma de comprimidos o cápsulas que contienen 1,0 a 500 miligramos del ingrediente activo, particularmente 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, y 500 miligramos del ingrediente activo para el ajuste sintomático de la dosificación para el paciente a ser tratado. El nivel específico y la secuencia de dosificación específica para cualquier paciente particular puede variar y dependerá de una variedad de factores que incluyen la actividad del compuesto específico que se emplee, la estabilidad metabólica y duración de la acción de ese compuesto, la edad, peso corporal, estado se salud

general, sexo, dieta, modo y tiempo de administración, tasa de excreción, combinación de fármacos, la gravedad de la afección particular, y el huésped que se somete a tratamiento.

Como se destaca anteriormente, la presente invención se refiere además a un procedimiento de inhibir proteasa NS3 de VHC, inhibir replicación de VHC, o prevenir o tratar infección por VHC con un compuesto de la presente invención en combinación con uno o más agentes terapéuticos y una composición farmacéutica que comprende un compuesto de la presente invención y uno o más agentes terapéuticos seleccionados del grupo constituido por un agente antiviral contra VHC, un inmunomodulador, y un agente antiinfeccioso. Tales agentes terapéuticos contra VHC incluyen, pero no se limitan a, ribavirina, levovirina, viramidina, alfa-1 timosina, interferón-β, interferón-α, interferón-α pegilado (peginterferón-α), una combinación de interferón-α y ribavirina, una combinación de peginterferón-α y ribavirina, una combinación de interferón-α y levovirina, y una combinación de peginterferón-α y levovirina. interferón-α incluye, pero no se limita a, interferón-α2a recombinante (tal como el interferón Roferon disponible de Hoffmann-LaRoche, Nutley, NJ), interferón-α2a pegilado (Pegasys™), interferón-α2b (tal como interferón de Intrón-A disponible de Schering Corp., Kenilworth, NJ), interferón-α2b pegilado (PegIntron™), un interferón recombinante consenso (tal como interferón alphacon-1), y un producto de interferón-α purificado. El interferón consenso recombinante de Amgen tiene el nombre de marca Infergen®. La levovirina es el enantiómero L de ribavirina que ha mostrado actividad inmunomoduladora similar a ribavirina. La viramidina representa un análogo de ribavirina descrito en el documento WO 01/60379 (cedido a ICN Pharmaceuticals). De acuerdo con el procedimiento de la presente invención, los componentes individuales de la combinación se pueden administrar por separado a tiempos diferentes durante el curso de terapia o concurrentemente en formas de combinación divididas o individuales.

Para el tratamiento de infección por VHC, los compuestos de la presente invención se pueden administrar también en combinación con un agente que es un inhibidor de serina proteasa NS3 de VHC. La serina proteasa NS3 de VHC es una enzima viral esencial y se ha descrito como que es un objetivo excelente para inhibición de replicación de HCV. Tanto inhibidores basados en sustrato como inhibidores no basados en sustrato de inhibidores de proteasa de VHC se describen en los documentos WO 98/22496, WO 98/46630, WO 99/07733, WO 99/07734, WO 99/38888, WO 99/50230, WO 99/64442, WO 00/09543, WO 00/59929, GB-2337262, WO 02/48116, WO 02/48172 y la Patente de los Estados Unidos N°.: 6.323.180.

Ribavirina, levovirina, y viramidina pueden ejercer sus efectos anti-VHC modulando reservas intracelulares de nucleótidos de guanina por medio de inhibición de la enzima intracelular inosina monofosfato deshidrogenasa (IMPDH). IMPDH es la enzima limitadora de velocidad de la vía de biosíntesis de nucleótidos de guanina *de novo*. La ribavirina se fosforila fácilmente intracelularmente y el derivado de monofosfato es un inhibidor de IMPDH. Así, la inhibición de IMPDH representa otro objetivo útil para el descubrimiento de inhibidores de replicación de VHC. Por lo tanto, los compuestos de la presente invención se

pueden administrar también en combinación con un inhibidor de IMPDH, tal como VX-497, que se describe en los documentos WO 97/41211 y WO 01/00622 (cedidos a Vertex); otro inhibidor de IMPDH, tal como aquel descrito en el documento WO 00/25780 (cedido a Bristol-Myers Squibb); o mofetil micofenolato [véase A.C. Allison y E.M. Eugui, Agents Action, 44 (Suppl.): 165 (1993)].

Para el tratamiento de infección por VHC, los compuestos de la presente invención se pueden administrar también en combinación con el agente antiviral amantadina (1-aminoadamantano) [para una descripción exhaustiva de este agente, véase J. Kirschbaum, Anal. Profiles Drug Subs. 12: 1-36 (1983)].

Los compuestos de la presente invención se pueden combinar también para el tratamiento de infección por VHC con ribonucleósidos 2'-*C*-ramificados antivirales descritos en R. E. Harry-O'kuru, y col., J. Org. Chem., 62: 1754-1759 (1997); M. S. Wolfe, y col., Tetrahedron Lett., 36: 7611-7614 (1995); Patente de los Estados Unidos N°.: 3.480.613 (25 de nov., 1969); Publicación Internacional Número WO 01/90121 (29 de noviembre de 2001); Publicación Internacional Número WO 01/92282 (6 de diciembre de 2001); y Publicación Internacional Número WO 02/32920 (25 de abril de 2002); y Publicación Internacional Número WO 04/002999 (8 de enero de 2004); y Publicación Internacional Número WO 04/003000 (8 de enero de 2004); y Publicación Internacional Número WO 04/002422 (8 de enero de 2004); el contenido de las cuales se incorpora en el presente documento mediante referencia en su totalidad. Tales ribonucleósidos 2'-*C*-ramificados incluyen, pero no se limitan a, 2'-*C*-metil-citidina, 2'-*C*-metil-uridina, 2'-*C*-metil-adenosina, 2'-*C*-metil-guanosina, y 9-(2-*C*-metil-β-D-ribofuranosil)-2,6-diaminopurina, y el éster de aminoácido correspondiente de los hidroxilos C-2', C-3', y C-5' de ribosa y los ésteres de 1,3-propanodiol cíclicos opcionalmente sustituidos correspondientes de los derivados de 5'-fosfato.

Los compuestos de la presente invención se pueden combinar también para el tratamiento de infección por VCH con otros nucleósidos que tienen propiedades anti-VHC, tales como aquellos descritos en el documento WO 02/51425 (4 de julio de 2002), cedido a Mitsubishi Pharma Corp.; los documentos WO 01/79246, WO 02/32920, y WO 02/48165 (20 de junio 2002), cedidos a Pharmasset, Ltd.; el documento WO 01/68663 (20 de septiembre de 2001), cedido a ICN Pharmaceuticals; el documento WO 99/43691 (2 de septiembre de 1999); el documento WO 02/18404 (7 de marzo de 2002), cedido a Hoffmann-LaRoche; los documentos U.S. 2002/0019363 (14 de febrero de 2002); WO 02/100415 (19 de diciembre de 2002); WO 03/026589 (3 de abril de 2003); WO 03/026675 (3 de abril de 2003); WO 03/093290 (13 de noviembre de 2003); US 2003/0236216 (25 de diciembre de 2003); US 2004/0006007 (8 de enero de 2004); WO 04/011478 (5 de febrero de 2004); WO 04/013300 (12 de febrero de 2004); US 2004/0063658 (1 de abril de 2004); y WO 04/028481 (8 de abril de 2004); el contenido de cada uno se incorpora en el presente documento mediante referencia en su totalidad.

Para el tratamiento de infección por VHC, los compuestos de la presente invención se pueden administrar también en combinación con un agente que es un inhibidor de polimerasa NS5B de VHC. Tales inhibidores de polimerasa NS5B de VHC que se pueden usar en terapia de combinación incluyen, pero no se limitan a, aquellos descritos en los documentos WO 02/057287, US 6.777.395, WO 02/057425, US 2004/0067901, WO 03/068244, WO 2004/000858, WO 04/003138 y WO 2004/007512; el contenido de cada uno se incorpora en el presente documento mediante referencia en su totalidad. Otros inhibidores de polimerasas de VHC tales incluyen, pero no se limitan a, valopicitabina (NM-283; Idenix) y 2'-F-2'-beta-metilcitidina (véase también el documento WO 2005/003147, cedido a Pharmasset, Ltd.).

En una realización, los inhibidores de polimerasa NS5B de VHC nucleosídicos que se usan en combinación con la presente proteasa NS3 de inhibidores de VHC se seleccionan de los siguientes compuestos:

4-amino-7-(2-C-metil-β-D-arabinofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-amino-7-(2-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-metilamino-7-(2-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-dimetilamino-7-(2-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-ciclopropilamino-7-(2-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-amino-7-(2-C-vinil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-amino-7-(2-C-hidroximetil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-amino-7-(2-C-fluorometil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-amino-5-metil-7-(2-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; ácido 4-amino-7-(2-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina-5-carboxílico; 4-amino-5-bromo-7-(2-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-amino-5-cloro-7-(2-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-amino-5-fluoro-7-(2-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 2,4-diamino-7-(2-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 2-amino-7-(2-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 2-amino-4-ciclopropilamino-7-(2-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 2-amino-7-(2-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidin-4(3H)-ona; 4-amino-7-(2-C-etil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-amino-7-(2-C,2-O-dimetil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 7-(2-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidin-4(3H)-ona; 2-amino-5-metil-7-(2-C, 2-O-dimetil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidin-4(3H)-ona; 4-amino-7-(3-deoxi-2-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-amino-7-(3-deoxi-2-C-metil-β-D-arabinofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-amino-2-fluoro-7-(2-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-amino-7-(3-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-amino-7-(3-C-metil-β-D-xilofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-amino-7-(2,4-di-C-metil-β-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-amino-7-(3-deoxi-3-fluoro-2-C-metil-β-D-ribofuranosil)-7H-pirrolo[2 ,3-d]pirimidina; y los 5'-trifosfatos correspondientes; o una sal farmacéuticamente aceptable de los mismos.

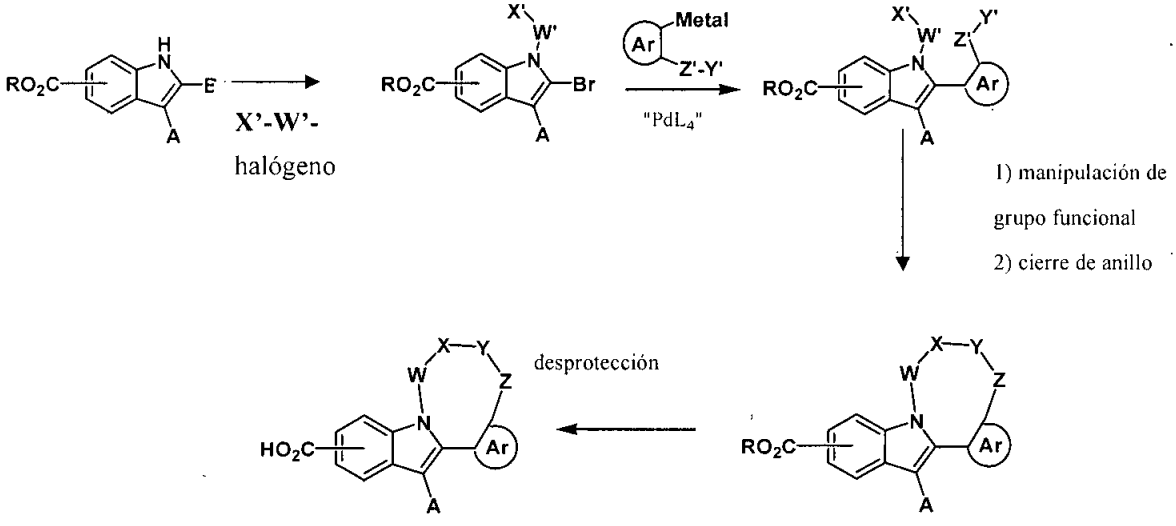
Los compuestos de la presente invención se pueden combinar también para el tratamiento de infección por VHC con inhibidores no nucleosídicos de VHC polimerasa tales como aquellos descritos en el documento WO 01/77091 (18 de oct. de 2001), cedido a Tularik, Inc.; el documento WO 01/47883 (5 de julio de 2001), cedido a Japan Tobacco, Inc.; el documento WO 02/04425 (17 de enero de 2002), cedido a Boehringer Ingelheim; el documento WO 02/06246 (24 de enero de 2002), cedido al Istituto di Ricerche di Biologia Moleculare P. Angeletti S.P.A.; el documento WO 02/20497 (3 de marzo de 2002); el documento WO 2005/016927 (en particular JTK003), cedido a Japan Tobacco, Inc.; el contenido de cada uno se incorpora mediante referencia en su totalidad; y cada una se incorpora en el presente documento en su totalidad; y VHC-796 (Viropharma Inc.).

En una realización, los inhibidores de polimerasa NS5B de VHC no nucleosídicos que se usan en combinación con la presente proteasa NS3 de inhibidores de VHC se seleccionan de los siguientes compuestos:
ácido 14-ciclohexil-6-[2-(dimetilamino)etil]-7-oxo-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-6-(2-morfolin-4-iletil)-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-6-[2-(dimetilamino)etil]-3-metoxi-5,6,7,8-tetrahidroindolo[2,1-*a*][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-3-metoxi-6-metil-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ({[(14-ciclohexil-3-metoxi-6-metil-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocin-11-il)carbonil]amino}sulfonil)acetato de metilo; ácido ({[(14-ciclohexil-3-metoxi-6-metil-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocin-11-il)carbonil]amino}sulfonil)acético; 14-ciclohexil-*N*-[(dimetilamino)sulfonil]-3-metoxi-6-metil-5,6,7,8-tetrahidroindolo[2,1-*a*][2,5]benzodiazocina-11-carboxamida; 3-cloro-14-ciclohexil-6-[2-(dimetilamino)etil]-7-oxo-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina del ácido 11-carboxílico; bis(trifluoroacetato) de *N*'-(11-carboxi-14-ciclohexil-7,8-dihidro-*6H*-indolo[1,2-e][1,5]benzoxazocin-7-il)-*N*,*N*-dimetiletano-1,2-diaminio; ácido 14-ciclohexil-7,8-dihidro-6H-indolo[1,2-e][1,5]benzoxazocina-11-carboxílico; ácido 14-ciclohexil-6-metil-7-oxo-5,6,7,8-tetrahidroindolo[2,1-*a*][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-3-metoxi-6-metil-7-oxo-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-6-[2-(dimetilamino)etil]-3-metoxi-7-oxo-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-6-[3-(dimetilamino)propil]-7-oxo-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-7-oxo-6-(2-piperidin-1-iletil)-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-6-(2-morfolin-4-iletil)-7-oxo-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-6-[2-(dietilamino)etil]-7-oxo-5,6,7,8-tetrahidroindolo[2,1-*a*][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-6-(1-metilpiperidin-4-il)-7-oxo-5,6,7,8-tetrahidroindolo[2,1-*a*][2,5]benzodiazocina-11-carboxílico; 14-ciclohexil-N-[(dimetilamino)sulfonil]-7-oxo-6-(2-piperidin-1-iletil)-5,6,7,8-tetrahidroindolo[2,1-

a][2,5]benzodiazocina-11-carboxamida; 14-ciclohexil-6-[2-(dimetilamino)etil]-*N*-[(dimetilamino)sulfonil]-7-oxo-5,6,7,8-tetrahidroindolo[2,1-*a*][2,5]benzodiazocina-11-carboxamida; ácido 14-ciclopentil-6-[2-(dimetilamino)etil]-7-oxo-5,6,7,8-tetrahidroindolo[2,1-*a*][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 6-alil-14-ciclohexil-3-metoxi-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclopentil-6-[2-(dimetilamino)etil]-5,6,7,8-tetrahidroindolo[2,1-*a*][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-6-[2-(dimetilamino)etil]-5,6,7,8-tetrahidroindolo[2,1-*a*][2,5]benzodiazocina-11-carboxílico; ácido 13-ciclohexil-5-metil-4,5,6,7-tetrahidrofuro[3',2':6,7][1,4]diazocino[1,8-*a*]indol-10-carboxílico; ácido 15-ciclohexil-6-[2-(dimetilamino)etil]-7-oxo-6,7,8,9-tetrahidro-5*H*-indolo[2,1-*a*][2,6]benzodiazonina-12-carboxílico; ácido 15-ciclohexil-8-oxo-6,7,8,9-tetrahidro-5*H*-indolo[2,1-*a*][2,5]benzodiazonina-12-carboxílico; ácido 13-ciclohexil-6-oxo-6,7-dihidro-5*H*-indolo[1,2-*d*][1,4]benzodiazepina-10-carboxílico; y sales farmacéuticamente aceptables de los mismos.

Los inhibidores de polimerasa NS5B de VHC basados en indol tetracíclico anteriores se pueden obtener siguiendo procedimientos A-E como se destaca más adelante, en los que se pueden seleccionar diferentes variables de acuerdo con el compuesto de indol tetracíclico específico a prepararse:

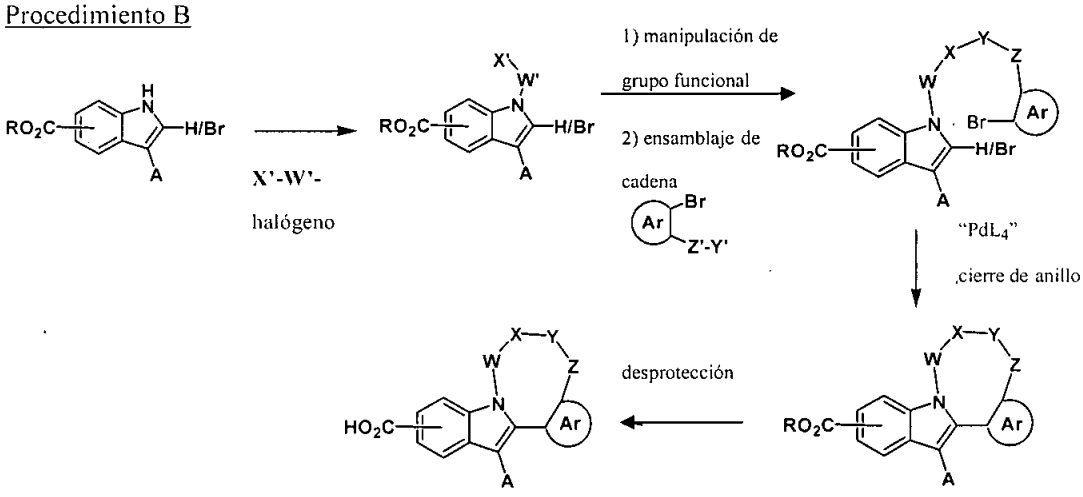
Procedimiento A



El intermedio 2-bromoindol (preparado como se describe en la Solicitud de Patente Internacional publicada WO2004087714) se funcionalizó en el nitrógeno de indol para introducir funcionalidad W'/X' de precursor a cualquiera de o a ambos elementos W/X de la cadena. La metodología de apareamiento entrecruzado mediado por Pd ((por ejemplo, Suzuki, Stille *etc.*) se trae después en la funcionalidad Z'/Y' de precursor que lleva C2 aromático a cualquiera de o a ambos elementos W/X de la cadena. La manipulación del grupo funcional seguida por cierre del anillo proporcionó el sistema tetracíclico. La desprotección de éster

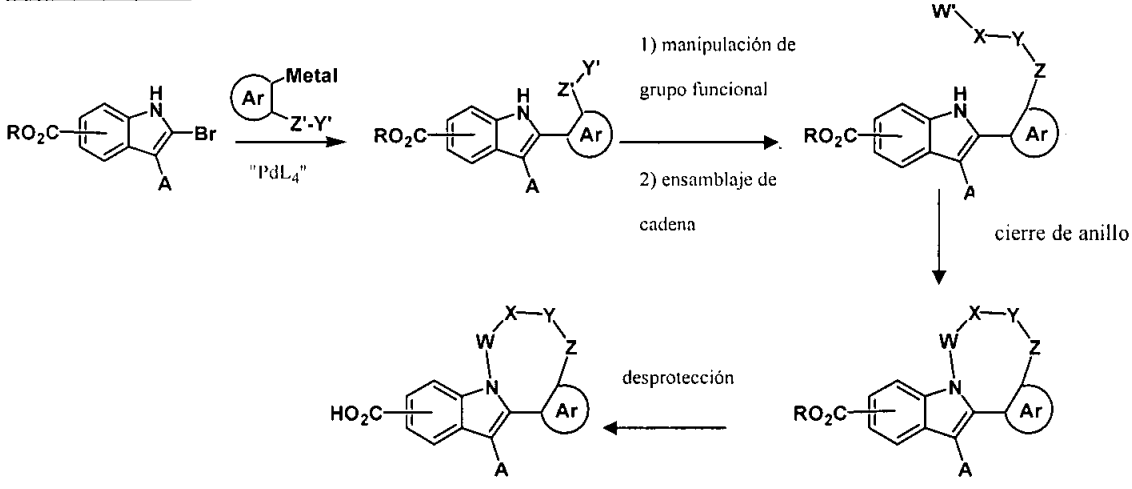
produjo después los ácidos carboxílicos de indol objetivo, con el C2 aromático unido por la cadena al nitrógeno de indol.

Procedimiento B



Tras la unión de cadena fuera del 2-haloaromático apropiado, el cierre del anillo mediado por Pd proporcionó el sistema tetracíclico condensado. La desprotección de éster produjo después los ácidos carboxílicos de indol objetivo, con el C2 aromático unido al nitrógeno de indol.

Procedimiento C



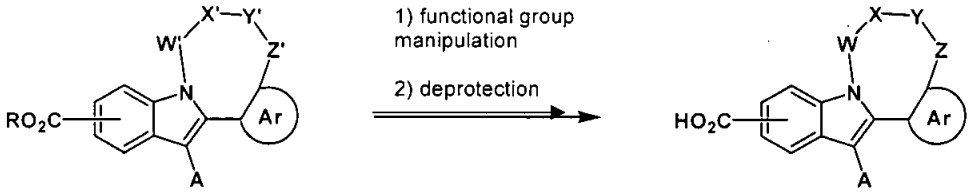
El C2 aromático se introdujo al principio por medio de metodología de acoplamiento entrecruzado mediado por Pd(Suzuki, Stille etc.). La cadena se acumula después, con ciclación sobre el nitrógeno de indol que cierra finalmente el anillo. La desprotección de éster produjo después los ácidos carboxílicos de indol objetivo, con el C2 aromático unido al nitrógeno de indol.

Procedimiento D

1) manipulación de

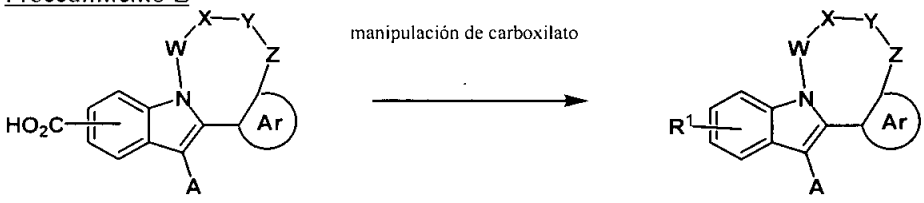
grupo funcional

2) desprotección



Los intermedios tetracíclicos que surgen de la manipulación sufrida indeseada de los procedimientos A-C de la funcionalidad en la cadena antes de la desprotección de éster para proporcionar los ácidos carboxílicos de indol unidos con cadena a C2 objetivos.

Procedimiento E



Los ácidos carboxílicos de indol unidos con cadena a C2 que surgen a partir de los procedimientos A-D se derivatizaron adicionalmente por manipulación de la funcionalidad carboxilato para dar compuestos que llevan un reemplazamiento de carboxilato o carboxamida. Durante cualquiera de las secuencias sintéticas anteriores puede ser necesario y/o deseable proteger grupos sensibles o reactivos en cualquiera de las moléculas implicadas. Esto se puede lograr por medio de grupos protectores convencionales, tales como aquellos descritos en *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; y T.W. Greene y P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3ª edición, 1999. Los grupos protectores se pueden eliminar a una fase subsiguiente conveniente usando procedimientos conocidos de la técnica.

La actividad inhibidora de proteasa NS3 de VHC de los presentes compuestos se puede probar usando los ensayos conocidos en la técnica. Un ensayo tal es ensayo de fluorescencia resuelto en el tiempo de proteasa NS3 de VHC (TRF) como se describe en el ejemplo 9. Otros ejemplos de tales ensayos se describen en por ejemplo, la Publicación de Patente Internacional WO2005/046712. Compuestos útiles como inhibidores de proteasa NS3 de VHC tendrían una Ki de menos de 50 μM, más preferiblemente menos de 10 μM, e incluso más preferiblemente menos de 100 nM.

La presente invención también incluye procedimientos para fabricar compuestos de fórmula **I**, **II**, **II-A**, **II-B**, **III**, **III-A**, o **III-B**. Los compuestos de la presente invención pueden prepararse fácilmente de acuerdo con los siguientes esquemas de reacción y ejemplos, o modificaciones de los mismos, usando materiales iniciales y reactivos fácilmente disponibles y procedimientos de síntesis convencionales. En estas reacciones, también es posible hacer uso de variantes que se conocen en sí mismas por aquellos de habilidad normal en la técnica, pero no se mencionan en mayor detalle. Además, otros procedimientos para preparar compuestos de la invención serán fácilmente patentes para la persona de habilidad ordinaria en la técnica a la luz de los siguientes esquemas y ejemplos de reacción. A menos que se indique

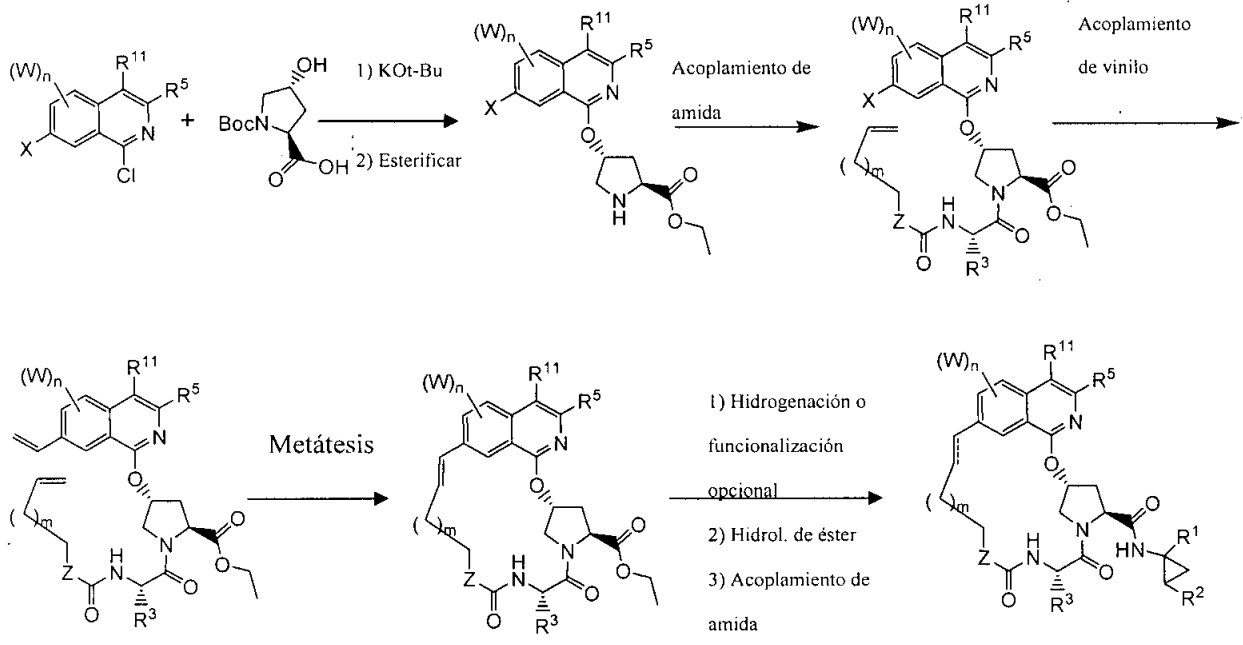
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lo contrario, todas las variables son como se definen anteriormente. Los siguientes esquemas y ejemplos de reacción sirven sólo para ilustrar la invención y su práctica. Los ejemplos no deben interpretarse como limitaciones en el alcance o espíritu de la invención.

Descripción General de Síntesis:

Los compuestos de la presente invención se pueden sintetizar como se destaca en los esquemas generales 1, 2 y 3.

ESQUEMA 1

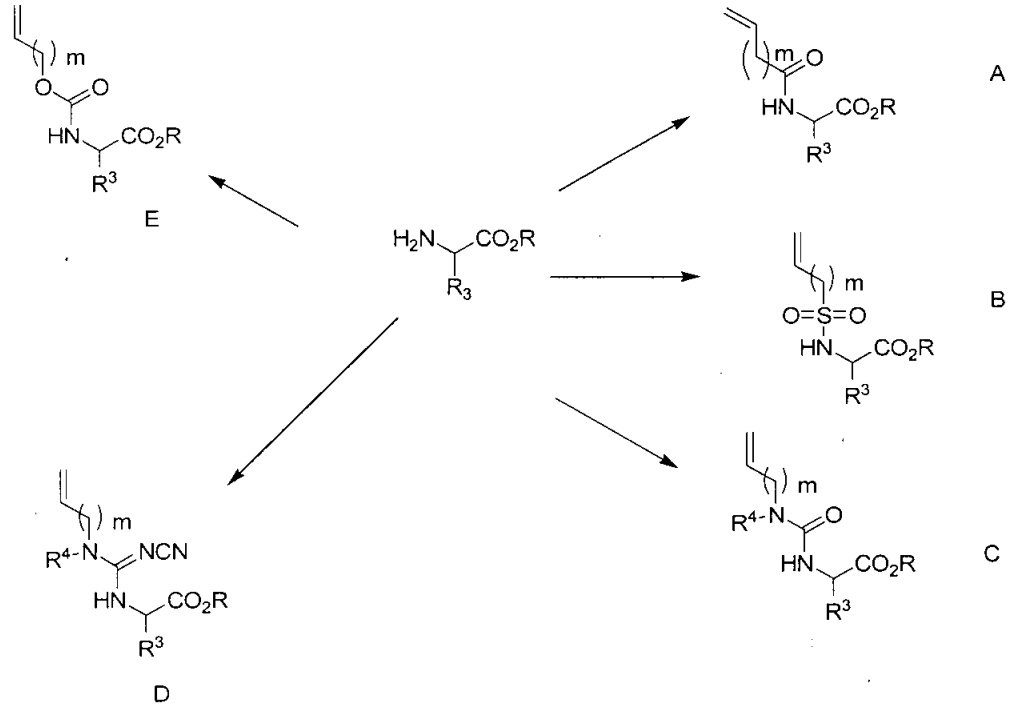


El esquema 1 (m = 0-9) destaca la síntesis de una molécula representativa. Un derivado de 4-hidroxiprolina apropiadamente protegida (por ejemplo, un nitrógeno protegido por carbamato) se puede hacer reaccionar con t-butóxido de potasio o reactivo equivalente y después se hace reaccionar con una cloro-isoquinolina apropiadamente sustituida. El ácido se puede esterificar con ácido en un disolvente de alcohol apropiado. Estas afecciones también retiran el grupo protector BOC en el nitrógeno de prolina.

El esquema 2 describe la síntesis de la olefina que contiene la parte aminoacídica. Un aminoácido (bien comercialmente disponible o bien se puede preparar fácilmente usando procedimientos conocidos en la técnica) en el que la funcionalidad ácida se protege como un éster (por ejemplo, R = metilo) se pueden convertir en amidas A acoplando un ácido carboxílico olefínico utilizando un amplio intervalo de agentes de acoplamiento peptídico conocidos por aquellos expertos en la técnica tales como DCC, EDC, BOP, TBTU, etc. La preparación de las sulfonamidas B se puede llevar a cabo mediante reacción con el cloruro de sulfonilo apropiado en un disolvente orgánico (por ejemplo, THF) con una base de amina como desoxidante. Los derivados de urea C se pueden preparar haciendo reaccionar el aminoéster con un reactivo tal como carbonildiimidazol, formando un isocianato intermedio (Catalano y col., WO 03/062192) seguido por adición de un segundo agente que contiene olefina.

Alternativamente, se pueden usar fosgeno, difosgeno o trifosgeno en lugar de carbonildiimidazol. Los derivados de cianoguanidina D se pueden preparar mediante reacción del éster aminoacídico con C-cianocarbonimidato de difenilo en un disolvente orgánico, seguido por adición de la segunda olefina que contiene amina. Los derivados de carbamato E se pueden preparar haciendo reaccionar un alcohol que contiene olefina con carbonildiimidazol (o fosgeno, trifosgeno o difosgeno) en un disolvente orgánico, seguido por adición del éster de amino.

ESQUEMA 2



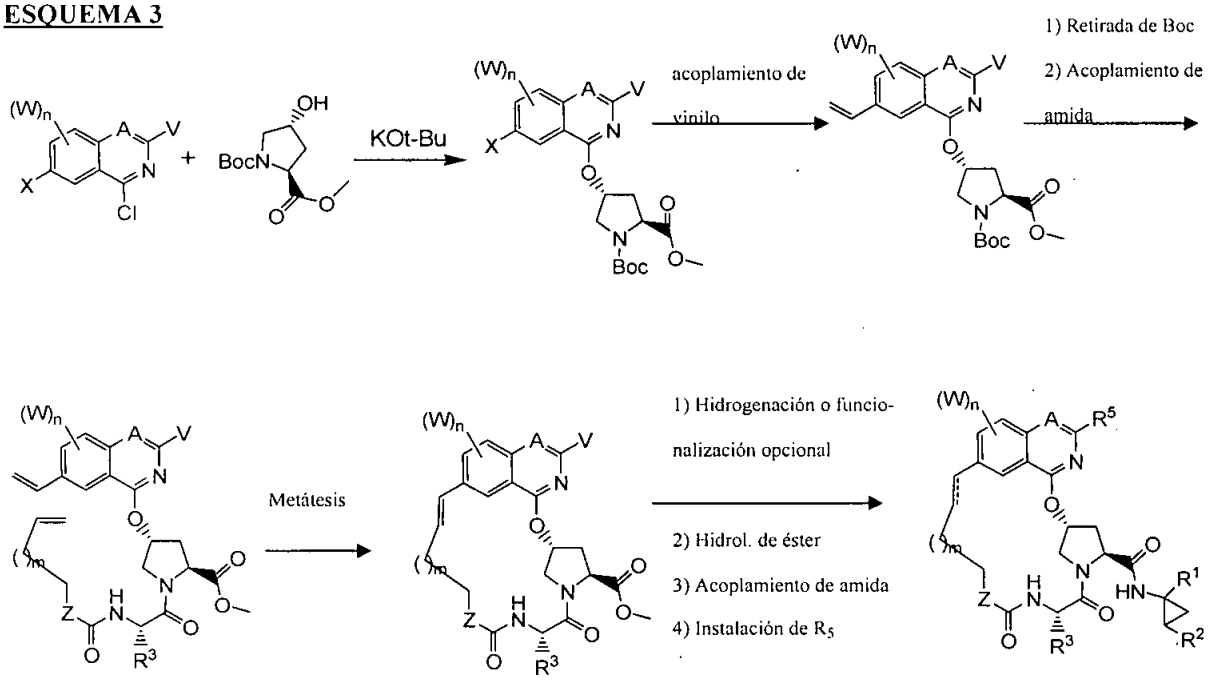
Tras la funcionalización de la amina, el éster se puede hidrolizar bajo un intervalo de condiciones básicas conocidas por aquellos expertos en la técnica (Theodora W. Greene, Protective Groups in Organic Synthesis, Tercera Edición, John Wiley and Sons, 1999).

La desprotección del grupo protector de carbamato en la parte de prolina se puede llevar a cabo mediante una diversidad de procedimientos conocidos por personas expertas en la técnica (Theodora W. Greene, Protective Groups in Organic Synthesis, Tercera Edición, John Wiley and Sons, 1999). Para completar la síntesis de los compuestos de esta invención, el derivado aminoacídico puede acoplarse al derivado de prolina por medio de un amplio intervalo de reactivos de acoplamiento peptídico tales como DCC, EDC, BOP, TBTU, etc. (véase esquema 1). La funcionalidad de alquenilo se puede introducir en esta fase mediante reacción catalizada por paladio de un sustituyente haluro tal como bromuro o yoduro, u otra funcionalidad tal como un triflato con un reactivo organometálico tal como un vinilo o aliltrialquiltina. La macrociclación se logró después mediante una metátesis de olefina usando un intervalo de catalizadores que se han descrito en la bibliografía para este propósito. En esta

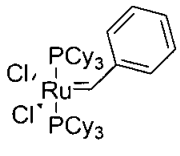
fase el puente olefínico producido en la metátesis que cierra el anillo puede estar opcionalmente hidrogenado dando un enlace saturado o funcionalizado en rutas alternativas tales como ciclopropanación. El éster de prolina se hidroliza después bajo condiciones básicas y se acopla con el éster de ácido de ciclopropilamino (la parte de alquenilo o alquilciclopropano apropiada de la molécula se puede preparar como se describe previamente (Llinas-Brunet y col., US 6.323.180)) y se somete a una etapa de hidrólisis básica adicional proporcionando los compuestos finales. El éster de prolina se puede hidrolizar y acoplar directamente a una acilsulfonamida de ácido de ciclopropilamino funcionalizada apropiadamente (que se puede preparar de acuerdo con Wang X.A. y col. WO2003/099274) proporcionando los compuestos finales.

Se pueden preparar moléculas con isoquinolinas sustituidas en 3 o quinalolinas sustituidas en 2 de acuerdo con el esquema 3 (en el que V es, por ejemplo, halo tal como cloro). Una 3-haloisoquinolina o 2-haloquinazolina apropiadamente sustituida se puede emplear en una secuencia similar a la vía mostrada en el esquema 1. En una etapa adicional final, se puede instalar un grupo R^5 por medio de reacciones de desplazamiento o reacciones de acoplamiento mediadas por metales.

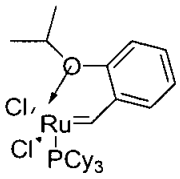
ESQUEMA 3



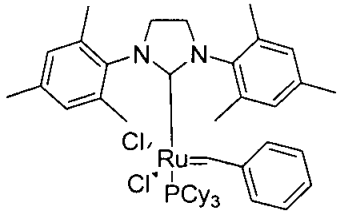
Los catalizadores de metátesis olefínica incluyen las siguientes especies químicas basadas en rutenio: F: Miller y col. *J. Am. Chem. Soc* 1996, 118, 9606; G: Kingsbury y col. *J. Am. Chem. Soc* 1999, 121, 791; H: Scholl y col. Org. Lett. 1999, 1, 953; Hoveyda y col. US2002/0107138; K: Furstner y col. J. Org. Chem 1999, 64, 8275. La utilidad de estos catalizadores en metátesis de cierre de anillo se conoce bien en la bibliografía (por ejemplo Trnka y Grubbs, *Acc. Chem. Res.* 2001, 34, 18).



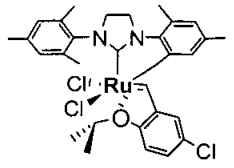
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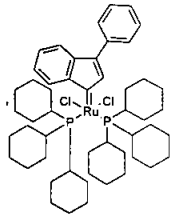
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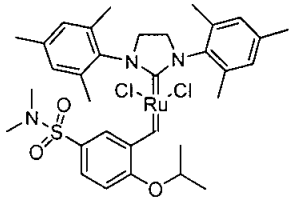
H



J



K



L

La estructura L es el catalizador de metátesis de rutenio de Zhan RC-303 (catalizador de Zhan 1B, RC-303, Zannan Pharma Ltd.)

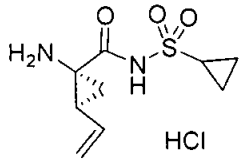
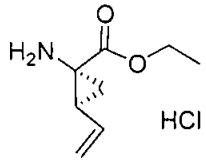
Lista de Abreviaturas

BOP	Hexafluorofoafato de benzotriazol-1-il-oxi-tris-(dimetilamino)-fosfonio
Cloruro de brosilo	Sulfonilcloruro de 4-bromofenilo
CH_3CN	Acetonitrilo
DABCO	1,4-diazabiciclo[2.2.2]octano
DBU	1,8-diazabiciclo[5.4.0]undec-7-eno
DCC	Diciclohexilcarbodiimida
DCE	Dicloroetano
DCM	Diclorometano
DMAP	4-dimetilaminopiridina
DIPEA	Diisopropiletilamina
DMF	Dimetilformamida
DMSO	Dimetilsulfóxido
EDC	*N*-(3-dimetilaminopropil)-*N'*-etilcarbodiimida
Et_3N	Trietilamina
Et_2O	Éter dietílico
EtOAc	Acetato de etilo
EtOH	Etanol
HATU	Hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio
HBr	Ácido bromhídrico
HCl	Ácido clorhídrico
HOAc	Ácido acético

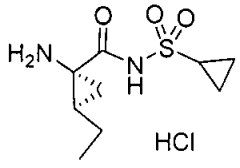
HOAt	1-hidroxi-7-azabenzotriazol
LiOH	Hidróxido de litio
MeOH	Metanol
$MgSO_4$	Sulfato de magnesio
Na_2SO_4	Sulfato de sodio
$NaHCO_3$	Bicarbonato de sodio
NaOH	Hidróxido de sodio
NH_4Cl	Cloruro de amonio
NH_4OH	Hidróxido de amonio
Nle	Norleucina
Pd/C	Paladio en carbono
PhMe	Tolueno
PPh_3	Trifenilfosfina
TA	Temperatura ambiente
TBAF	Fluoruro de tetrabutilamonio
TBTU	Tetrafluoroborato de O-benzotriazol-1-il-N,N,N',N'-tetrametiluronio
THF	Tetrahidrofurano

Síntesis de Intermedios:

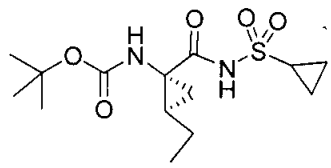
Síntesis de Intermedios A

Intermedio #	Estructura	Nombre	Referencia bibl.
A1		Clorhidrato de (1*R*,2*S*)-1-amino-*N*-(ciclopropilsulfonil)-2-vinilciclopropanocarboxamida	Wang y col., US 6.995.174
A2		Clorhidrato de (1*R*,2*S*)-1-amino-2-vinilciclopropanocarboxilato de etilo	Llinas-Brunet y col., US 6.323.180

Intermedio A3: clorhidrato de (1*R*,2*R*)-1-amino-*N*-(ciclopropilsulfonil)-2-etilciclopropanocarboxamida

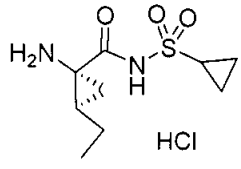


Etapa 1: (1R,2R)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)carbamato de terc-butilo



Un vaso de hidrogenación se cargó con una suspensión de metanol (1000 ml) de ((1R,2S)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)carbamato de terc-butilo (164 g, 0,50 mol) (Wang y col., US 6.995.174) y Ru al 5%/C (seco, 7,5% en peso, 12,4 g) y agitación de grupo. El recipiente se situó bajo nitrógeno (689540 pascales manométricos (20 psig)) y se descargó a presión atmosférica tres veces eliminando el oxígeno residual. El recipiente se situó después bajo hidrógeno (1723850 pascales manométricos (50 psig)). Después de 20 horas, el recipiente se descargó a presión atmosférica. La suspensión de reacción se transfirió después fuera de la reacción y se filtró a través de solka flok (34 gramos, humedecido con 100 ml de metanol) proporcionando una solución transparente, marrón claro. El solka flok se aclaró con metanol (200 ml x 2). Las soluciones de metanol combinadas se concentraron bajo presión reducida proporcionando producto en bruto como un sólido blanco (153 g). El producto en bruto se suspendió en acetato de etilo (800 ml), se calentó a 40°C y se dejo madurar 30 minutos. La solución se sembró después, se dejó madurar 30 minutos, y se añadió heptano (500 ml) por medio de embudo de adición durante 30 minutos. El sólido parcialmente cristalizado se enfrió a temperatura ambiente y se dejó madurar durante toda una noche después de lo que se añadió heptano (500 ml) adicional. Después de una hora, se añadió heptano (250 ml) adicional, y la suspensión blanca se dejó madurar durante una hora. La solución se filtró y el sólido se aclaró con heptano/EtOAc (500 ml, 4:1) y se secó bajo presión reducida dando ((1R,2R)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)carbamato de terc-butilo (125,9 g).

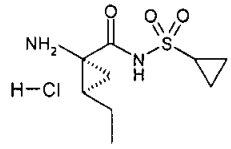
Etapa 2: clorhidrato de (1*R*,2*R*)-1-amino-*N*-(ciclopropilsulfonil)-2-etilciclopropanocarboxamida (intermedio A3)



Una solución del producto de etapa 1 anterior (92 g, 0,28 mol) en DCM (1200 ml) se enfrió a 0°C y se hizo burbujear HCla través de la solución durante 10 minutos, el baño enfriador se retiró y la mezcla de reacción se agitó durante 2 h. El nitrógeno se hizo burbujear a través de la mezcla de reacción durante 5 minutos y las sustancias volátiles se evaporaron. El residuo se azeotropó con DCM (x3) dando un polvo blanquecino (75 g). EMBR $(M+H)^+$ Calcd. = 233; hallado 233

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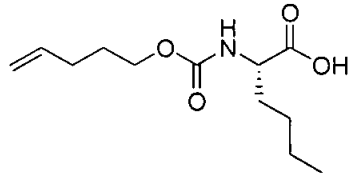
Preparación alternativa de y nombre para intermedio A3 cloruro de (1R,2R)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropanaminio:



Una mezcla de cloruro de (1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropanaminio (0,05 g, 0,187 mmol) y paladio en carbono (10% en peso, 0,01 g) en EtOAc (5 ml) se agitó vigorosamente bajo atmósfera de hidrógeno proporcionada por un balón de hidrógeno durante 1 hora. La mezcla de reacción se filtró y concentró dando cloruro de (1*R*,2*R*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropanaminio (0,045 g, rendimiento del 89%).

Preparación de Intermedios B

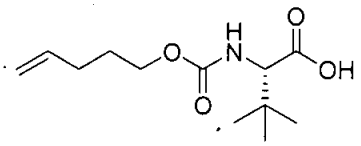
Preparación de Intermedio B1: *N*-[(pent-4-en-1-iloxi)carbonil]-L-norleucina:



A una solución de 1-penten-4-ol (0,95 g, 11,0 mmol) en DMF (15 ml) a 0°C se añadió carbonildiimidazol (1,79 g, 11,0 mmol). La mezcla de reacción se calentó a temperatura ambiente y se agitó durante 30 min. Se añadió después clorhidrato de éster metílico de L-norleucina (2,0 g, 11,0 mmol), la mezcla de reacción se calentó a 50°C y se agitó durante 15 minutos. Tras enfriar, la mezcla de reacción se diluyó con éter etílico y se lavó dos veces con agua. La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró. El producto en bruto mediante cromatografía en gel de sílice (elución de gradiente de acetato de etilo del 10 al 90% en hexanos) proporcionando 2,1 g (74%) *N*-[(pent-4-en-1-iloxi)carbonil]-L-norleucinato de metilo como un aceite transparente.

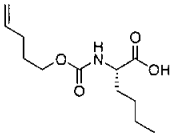
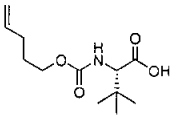
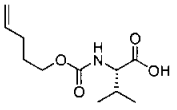
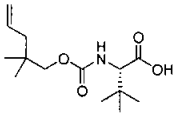
A una solución agitada de *N*-[(pent-4-eniloxi)carbonil]-L-norleucinato de metilo (8,50 g, 33,03 mmol) en THF (20 ml) se añadió NaOH 1N (20 ml). Esta solución de reacción se agitó a temperatura ambiente durante 3 horas, después se acidificó a pH 3 con HCl 1N y se extrajo con EtOAc (3 x 250 ml). La fase de EtOAc combinada se lavó con 50 ml de agua, 50 ml de salmuera, se secó sobre sulfato de sodio, se filtró y se concentró dando 7,09 g (88%) del producto del título como aceite transparente. EMBR (ESI) *m/z* 244 [$(M+H)^+$; calcd. para $C_{12}H_{22}NO_4$: 244].

Preparación de intermedio B2 ácido (2S)-3,3-dimetil-2-{[(pent-4-en-1-iloxi)carbonil]amino}butanoico

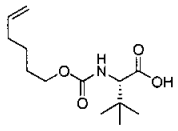
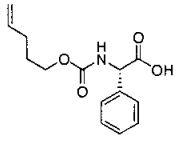
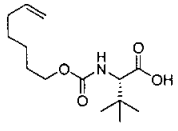
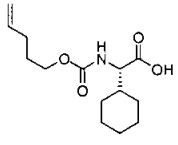
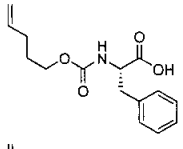
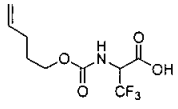
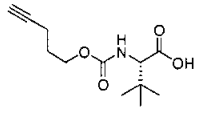
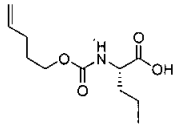
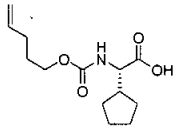
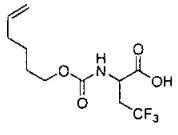


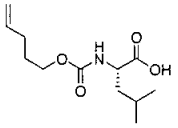
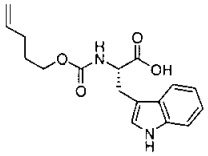
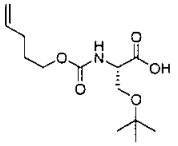
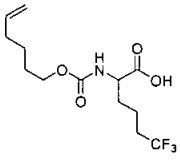
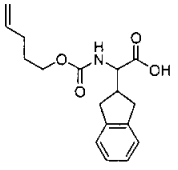
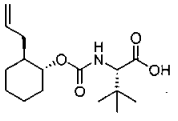
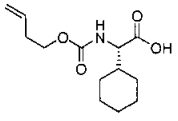
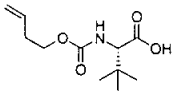
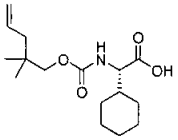
Se añadió diisopropiletilamina (9,85 g, 76,2 mmol) gota a gota a una solución a 0°C de 4-penten-1-ol (7,22 g, 83,9 mmol) y trifosgeno (11,3 g, 38,1 mmol) en 160 ml de dioxano. La suspensión blanca resultante se agitó durante 5 minutos a 0 °C, después se dejó calentar a 25°C durante 1 hora. La suspensión se enfrió a 0°C con una baño de hielo y NaOH 1 N (76,2 ml) y se añadió *L-terc*-butilglicina (10,0 g, 76,2 mmol). La mezcla de reacción se calentó a 25°C y se agitó durante 18 horas. El dioxano se retiró *a vacío* y la mezcla de reacción se basificó a pH 12 con NaOH 1 N. La fase acuosa se extrajo con diclorometano (150 ml 3x), después se acidificó a pH~1 con HCl 6 N. La fase acuosa se extrajo con diclorometano (150 ml 3x). Las fases orgánicas combinadas se secaron sobre $MgSO_4$ y se concentró dando el compuesto como un aceite canela (13,7 g, rendimiento del 73,9%). EMBR (ESI) *m/z* 244 [$(M+H)^+$; calcd. para $C_{12}H_{22}NO_4$: 244].

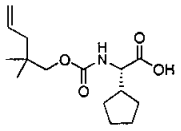
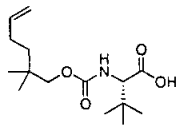
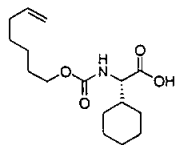
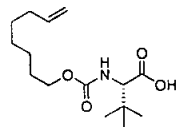
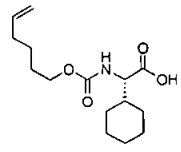
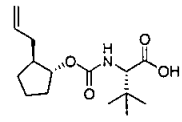
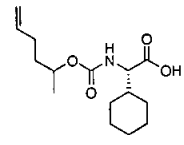
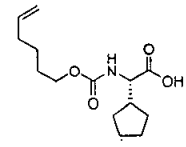
Los siguientes intermedios de carbamato (B3-B49) se prepararon usando la química descrita para la preparación de ácido (2S)-3,3-dimetil-2-{[(pent-4-en-1-iloxi)carbonil]amino}butanoico (B2), utilizando el aminoácido y el alcohol apropiados o la preparación de *N*-[(pent-4-en-1-iloxi)carbonil]-L-norleucina (B1) utilizando el alcohol y el éster de amino apropiados.

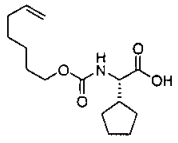
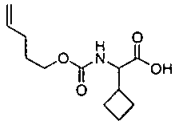
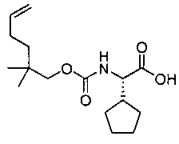
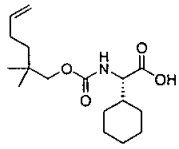
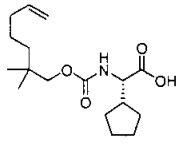
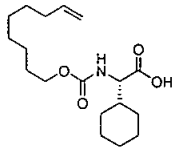
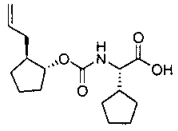
Int.	Aminoácido	Alcohol	Estructura	Nombre	EMBR $(M+H)^+$
B1	L-Norleucina	4-penten-1-ol		*N*-[(pent-4-en-1-iloxi)carbonil]-L-norleucina (intermedio 1)	244,3
B2	L-*t*-butil-glicina	4-penten-1-ol		Ácido (2S)-3,3-dimetil-2-{[(pent-4-en-1-iloxi)carbonil]amino}butanoico	244,2
B3	L-valina	4-penten-1-ol		*N*-[(pent-4-en-1-iloxi)carbonil]-L-valina	230,3
B4	L-*t*-butil-glicina	3,3-dimetil-4-penten-1-ol Ref.:		*N*-{[(2,2-dimetilpent-4-en-1-il)oxi]carbonil}-3-	272,3

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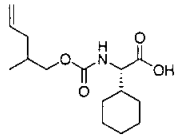
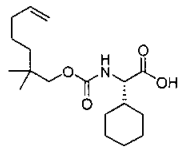
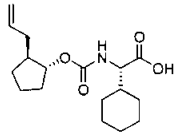
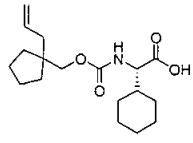
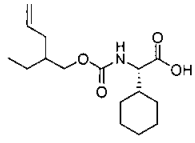
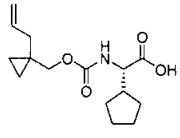
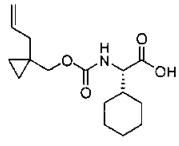
		Tetrahedron Lett. (**2004**), *45*, 2939.		metil-L-valina	
B5	L-*t*-butil-glicina	5-hexen-1-ol		*N*-[(hex-5-en-1-iloxi)carbonil]-3-metil-L-valina	258,3
B6	L-fenil-glicina	4-penten-1-ol		Ácido (2*S*)-{[(pent-4-en-1-iloxi)carbonil]amino}(fenil)acético	264,3
B7	L-*t*-butil-glicina	6-hepten-1-ol		*N*-[(hept-6-en-1-iloxi)carbonil]-3-metil-L-valina	272,3
B8	L-ciclohexil-glicina	4-penten-1-ol		Ácido (2S)-ciclohexil{[(pent-4-en-1-iloxi)carbonil]amino}acético	270,3
B9	L-fenilalanina	4-penten-1-ol		*N*-[(pent-4-en-1-iloxi)carbonil]-L-fenilalanina	278,2
B10	3,3,3-trifluoroalanina	4-penten-1-ol		3,3,3-trifluoro-*N*-[(pent-4-en-1-iloxi)carbonil]ala-nina	256,2
B11	L-*t*-butil-glicina	4-pentin-1-ol		3-metil-*N*-[(pent-4-in-1-iloxi)carbonil]-L-valina	242,2
B12	L-norvalina	4-penten-1-ol		*N*-[(pent-4-en-1-iloxi)carbonil]-L-norvalina	230,3
B13	L-ciclopentil-glicina	4-penten-1-ol		ácido (2*S*)-ciclopentil{[(pent-4-en-1-iloxi)carbonil]amino}acético	256,3
B14	Ácido 2-amino-4,4,4-trifluorobutanoico	5-hexen-1-ol		Ácido 4,4,4-trifluoro-2-{[(hex-5-en-1-iloxi)carbonil]amino}butanoico	305,2 (M+ Na)$^+$

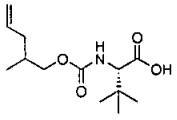
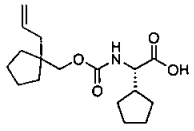
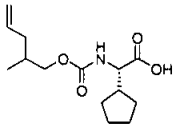
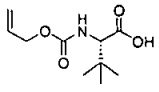
B15	L-leucina	4-penten-1-ol		*N*-[(pent-4-en-1-iloxi)carbonil]-L-leucina	244,3
B16	L-triptófano	4-penten-1-ol		*N*-[(pent-4-en-1-iloxi)carbonil]-L-triptófano	317,4
B17	*O*-(*terc*-butil)- L-serina	4-penten-1-ol		*O*-(*terc*-butil)-*N*-[(pent-4-en-1-iloxi)carbonil]-L-serina	218,3 $(M-tBu)^+$
B18	6,6,6-trifluoronor-leucina	5-hexen-1-ol		6,6,6-trifluoro-*N*-[(hex-5-en-1-iloxi)carbonil]nor-leucina	353,2 $(M+MeCN)^+$
B19	Ácido amino(2,3-dihidro-1*H*-inden-2-il)acético	4-penten-1-ol		Ácido 2,3-dihidro-1*H*-inden-2-il{[(pent-4-en-1-iloxi)carbonil]amino} acético	304,3
B20	L-*t*-butil-glicina	(trans)-2-alilciclohexanol Ref.: *Tetrahedron* (**2004**), *60*, 4837.		*N*-({[(trans)-2-alilciclohexil]oxi}carbonil)-3-metil-L-valina	298,4
B21	L-ciclohexil-glicina	3-buten-1-ol		Ácido (2*S*)-{[(but-3-en-1-iloxi)carbonil]amino} (ciclohexil)acético	256,2
B22	L-*t*-butil-glicina	3-buten-1-ol		*N*-[(but-3-en-1-iloxi)carbonil]-3-metil-L-valina	230,3
B23	L-ciclohexil-glicina	2,2-dimetil-4-penten-1-ol Ref.: *Tetrahedron Lett.* (**2004**), *45*, 2939.		Ácido (2*S*)-ciclohexil({[(2,2-dimetilpent-4-en-1-il)oxi]carbonil}amino)acético	298,3

B24	L-ciclopentil-glicina	2,2-dimetil-4-penten-1-ol Ref.: *Tetrahedron Lett.* (**2004**), *45*, 2939.		Ácido (2*S*)-ciclopentil({[(2,2-dimetilpent-4-en-1-il)oxi]carbonil}amino)acético	284,3
B25	L-*t*-butil-glicina	2,2-dimetilhex-5-en-1-ol Ref.: *J. Org. Chem.* (**1991**), *56*, 1623.		*N*-{[(2,2-dimetilhex-5-en-1-il)oxi]carbonil}-3-metil-L-valina	286,3
B26	L-ciclohexil-glicina	6-hepten-1-ol		Ácido (2*S*)-ciclohexil{[(hept-6-en-1-iloxi)carbonil]amino}acético	298,3
B27	L-*t*-butil-glicina	7-octen-1-ol		3-metil-*N*-[(oct-7-en-1-iloxi)carbonil]-L-valina	286,3
B28	L-ciclohexil-glicina	5-hexen-1-ol		Ácido (2*S*)-ciclohexil{[(hex-5-en-1-iloxi)carbonil]amino}acético	284,4
B29	L-*t*-butil-glicina	(trans)-2-alilciclopentanol Ref.: *J. Chem. Soc., Perkin Trans 1* (**1994**), *11*, 1377.		*N*-({[(trans)-2-alilciclopentil]oxi}carbonil)-3-metil-L-valina	284,2
B30	L-ciclohexil-glicina	1-metilpent-4-en-1-ol Ref.: *Tetrahedron Assym.* (**1998**), *9*, 657.		Ácido (2*S*)-ciclohexil({[(1-metilpent-4-en-1-il)oxi]carbonil}amino)acético	284,2
B31	L-ciclopentil-glicina	5-hexen-1-ol		Ácido (2*S*)-ciclopentil{[(hex-5-en-1-	270,3

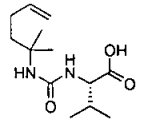
				iloxi)carbonil]amino} acético	
B32	L-ciclopentil-glicina	6-hepten-1-ol		Ácido (2*S*)-ciclopentil{[(hept-6-en-1-iloxi)carbonil]amino} acético	284,4
B33	L-ciclobutil-glicina	4-penten-1-ol		Ácido ciclobutil{[(pent-4-en-1-iloxi)carbonil]amino} acético	242,3
B34	L-ciclopentil-glicina	2,2-dimetilhex-5-en-1-ol Ref.: *J. Org. Chem.* (**1991**), *56*, 1623.		Ácido (2*S*)-ciclopentil({[(2,2-dimetilhex-5-en-1-il)oxi]carbonil}amino)acético	298,3
B35	L-ciclohexil-glicina	2,2-dimetilhex-5-en-1-ol Ref.: *J. Org. Chem.* (**1991**), *56*, 1623.		Ácido (2*S*)-ciclohexil({[(2,2-dimetilhex-5-en-1-il)oxi]carbonil}amino)acético	312,3
B36	L-ciclopentil-glicina	2,2-dimetilhept-6-en-1-ol Ref.: *J. Org. Chem.* (**1980**), *45*, 2685.		Ácido (2*S*)-ciclopentil({[(2,2-dimetilhept-6-en-1-il)oxi]carbonil}amino)acético	312,2
B37	L-ciclohexil-glicina	8-nonen-1-ol		Ácido (2*S*)-ciclohexil{[(non-8-en-1-iloxi)carbonil]amino} acético	326,3
B38	L-ciclopentil-glicina	(trans)-2-alilciclopentanol Ref.: *J. Chem. Soc., Perkin Trans 1* (**1994**), *11*, 1377.		Ácido (2*S*)-[({[(trans)-2-alilciclopentil]oxi}carbonil)amino](ciclopentil)acético	296,4

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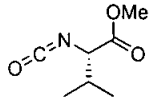
B39	L-ciclohexil-glicina	2-metilpent-4-en-1-ol Ref.: *Tetrahedron* (**1993**), *49*, 947.		Ácido (2*S*)-ciclohexil({[(2-metilpent-4-en-1-il)oxi]carbonil}amino)acético	284,4
B40	L-ciclohexil-glicina	2,2-dimetilhept-6-en-1-ol Ref.: *J. Org. Chem.* (**1980**), *45*, 2685.		Ácido (2*S*)-ciclohexil({[(2,2-dimetilhept-6-en-1-il)oxi]carbonil}amino)acético	326,4
B41	L-ciclohexil-glicina	(trans)-2-alilciclopentanol Ref.: *J. Chem. Soc., Perkin Trans 1* (**1994**), *11*, 1377.		Ácido (2*S*)-[({[(trans)-2-alilciclopentil]oxi}carbonil)amino](ciclohexil)acético	310,5
B42	L-ciclohexil-glicina	1-alil ciclopentil) metanol Ref.: *J. Org. Chem.* (**1992**), *57*, 1727.		Ácido (2*S*)-({[(1-alilciclopentil)metoxi]carbonil}amino)(ciclohexil)acético	324,3
B43	L-ciclohexil-glicina	2-etilpent-4-en-1-ol Ref.: *Tetrahedron Lett.* (**1985**), *26*, 6085.		Ácido (2*S*)-ciclohexil({[(2-etilpent-4-en-1-il)oxi]carbonil}amino)acético	298,2
B44	L-ciclopentil-glicina	1-alil ciclopropil) metanol Ref.: *Helv. Chim. Acta* (**1986**), *69*, 1655.		Ácido (2*S*)-({[(1-alilciclopropil)metoxi]carbonil}amino)(ciclopentil)acético	282,3
B45	L-ciclohexil-glicina	1-alil ciclopropil) metanol Ref.: *Helv. Chim. Acta* (**1986**), *69*,		Ácido (2*S*)-({[(1-alilciclopropil)metoxi]carbonil}amino)(ciclohexil)acético	296,3

		1655.			
B46	L-*t*-butil-glicina	2-metilpent-4-en-1-ol Ref.: *Tetrahedron* (**1993**), *49*, 947.		3-metil-*N*-{[(2-metilpent-4-en-1-il)oxi]carbonil}-L-valina	258,3
B47	L-ciclopentil-glicina	1-alil ciclopentil) metanol Ref.: *J. Org. Chem.* (**1992**), *57*, 1727.		Ácido (2*S*)-({[(1-alilciclopentil)metoxi] carbonil}amino) (ciclopentil)acético	310,3
B48	L-ciclopentil-glicina	2-metilpent-4-en-1-ol Ref.: *Tetrahedron* (**1993**), *49*, 947.		Ácido (2*S*)-ciclopentil({[(2-metilpent-4-en-1-il)oxi]carbonil}amino)acético	270,2
B49	L-*t*-butil-glicina	Alcohol alílico		*N*-[(aliloxi)carbonil]-3-metil-L-valina	215,2

Intermedio B50: *N*-{[(1,1-dimetilpent-4-en-1-il)amino]carbonil}-L-valina

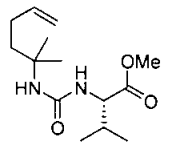


Etapa 1: *N*-(oxometileno)-L-valinato de metilo



Una mezcla de clorhidrato de éster de metil-L-valina (10,0 g, 59,9 mmol), DCM (300 ml), y piridina (19,3 ml, 240 mmol) se enfrió en un baño de hielo/sal y una solución de fosgeno al 20% en tolueno (35,6 ml, 719 mmol) se añadió gota a gota, manteniendo la temperatura de reacción por debajo de 5°C durante la adición. Resultó una suspensión blanca y después de 1,5 h, la mezcla de reacción se vertió en ácido clorhídrico 1 M enfriado en hielo y se extrajo con DCM (500 ml 2 ×). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro, y se evaporaron. La cromatografía en columna ultrarrápida en sílice (95 hexano/5 acetato de etilo) dio el compuesto del título como un aceite incoloro (6,43 g). RMN ^{1}H ($CDCl_3$ 500MHz) δ 3,94 (d, J = 4,0 Hz, 1 H), 3,82 (s, 3 H), 2,24 (m, 1 H), 1,03 (d, J = 7,0 Hz, 3 H), 0,90 (d, J = 6,5Hz, 3 H) ppm.

Etapa 2 : *N*-{[(1,1-dimetilpent-4-en-1-il)amino]carbonil}-L-valinato de metilo

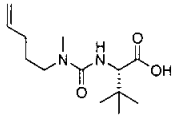
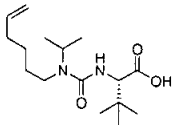


Se añadió *N*-(oxometileno)-L-valinato de metilo (2,80 g, 17,7 mmol) a 2-metilhex-5-en-2-amina [*J. Org. Chem.* (**1976**) *41*(5) 855-863.] (2,00 g, 17,7 mmol) en THF (15 ml). Después de 5 minutos, la mezcla de reacción se evaporó dando el compuesto del título como un sólido que se trituró con hexano y se aisló mediante filtración (2,71g). EMBR $(M+H)^+$ = 271,4.

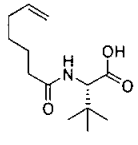
Etapa 3: *N*-{[(1,1-dimetilpent-4-en-1-il)amino]carbonil}-L-valina (intermedio B50)

Se añadió hidróxido de litio 1M (54 ml, 54 mmol) a *N*-{[(1,1-dimetilpent-4-en-1-il)amino]carbonil}-L-valina (2,94 g, 10,9 mmol) en THF (20 ml). La mezcla de reacción se agitó a TA bajo nitrógeno durante 18 horas después se trató a reflujo durante 2 horas, se enfrió a temperatura ambiente y el THF se retiró mediante evaporación. Se añadió el agua y la mezcla se extrajo con DCM (4×). La fase acuosa se hizo ácida con ácido clorhídrico 1M y se extrajo con DCM (70 ml 3 ×). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 anhidro y el disolvente se evaporó dando el compuesto del título como una espuma blanca (2,25 g). EMBR $(M+H)^+$ = 257,3.

Los siguientes intermedios de urea (B51-B52) se prepararon usando la química descrita para la preparación de *N*-{[(1,1-dimetilpent-4-en-1-il)amino]carbonil}-L-valina (como se describe en el intermedio B50), utilizando el aminoácido y la amina apropiados.

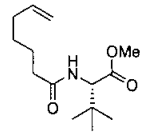
Int.	Aminoácido	Amina	Estructura	Nombre	EMBR $(M+H)^+$
B51	L-*t*-butil-glicina	*N*-metilpent-4-en-1-amina		3-metil-*N*-{[metil(pent-4-en-1-il)amino]carbonil}-L-valina	257,3
B52	L-*t*-butil-glicina	N-isopropilhex-5-en-1-amina		*N*-{[hex-5-en-1-il(isopropil)amino]carbonil}-3-metil-L-valina	299,3

Intermedio B53: N-hept-6-enoil-3-metil-L-valina



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Etapa 1: *N*-hept-6-enoil-3-metil-L-valinato de metilo



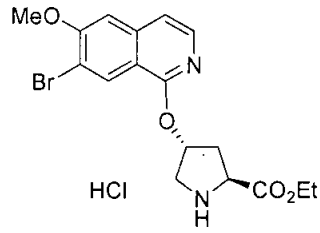
Se agitó una solución de éster metílico de L-terc-leucina (1,00 g, 6,89 mmol), ácido 6-heptenoico (1,06 g, 8,26 mmol), EDC (1,58 g, 8,26 mmol) y HOAt (1,23 g, 8,26 mmol) en DMF (10 ml) a 22°C durante 2 h. La mezcla de reacción se diluyó con $NaHCO_3$ saturado acuoso (30 ml), y extrajo con EtOAc (50 ml 3 x). Las fases orgánicas combinadas se lavaron con agua (30 ml 3 x), salmuera (20 ml), se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo se cromatografió en gel de sílice, eluyendo con EtOAc al 5-50%/hexano, dando el producto del título (1,42 g, 81%). EMBR (ESI) *m/z* 256,3 $[(M+H)^+$; calcd. para $C_{14}H_{26}NO_3$: 256,2].

Etapa 2: N-hept-6-enoil-3-metil-L-valina (intermedio B53)

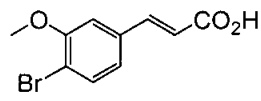
Una solución de *N*-hept-6-enoil-3-metil-L-valinato de metilo (1,40 g, 5,48 mmol) en THF (10 ml) y NaOH 1N (10 ml) se agitó a 22°C durante 2 h. La mezcla de reacción se acidificó a pH 3 con HCl 1 H y se extrajo con EtOAc (150 ml 3 x). Las fases de EtOAc se combinaron con agua (50 ml), salmuera (50 ml), se secaron sobre Na_2SO_4, se filtraron y concentraron dando el producto del título (1,12 g, 84%). EMBR (ESI) *m/z* 242,3 $[(M+H)^+$; calcd. para $C_{13}H_{24}NO_3$: 242,2].

Preparación de Intermedios C

Intermedio C1: clorhidrato de (4*R*)-4-[(7-bromo-6-metoxiisoquinolin-1-il)oxi]-L-prolinato de etilo



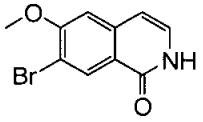
Etapa 1: ácido (2E)-3-(4-bromo-3-metoxifenil)acrílico



A una solución de 1-bromo-4-yodo-2-metoxibenzeno (L. A. Hasvold y col., US 2004/0254159, EJEMPLO 57B) (33,5 g, 107 mmol) en MeCN (100 ml) se añadió ácido acrílico (9,61 g, 133 mmol), trietilamina (37,2 ml, 267 mmol) y acetato de paladio (719 mg, 3,2 mmol).

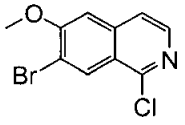
La mezcla de reacción se calentó a 90°C durante 40 min, se enfrió a TA y se vertió en 2,4 l de HCl 1M. Después de agitar durante 30 min, el sólido se filtró, se calentó a reflujo en EtOH (230 ml), se dejó enfriar a TA y se agitó durante toda una noche. El sólido se filtró y lavó con EtOH hexano 1:1 (50 ml) dando producto deseado. EMBR ESI$^+$ $(M+H)^+$ 257,0.

Etapa 2: 7-bromo-6-metoxiisoquinolin-1(2H)-ona



Una parte del producto de la etapa 1 [ácido (2E)-3-(4-bromo-3-metoxifenil)acrílico] (12,5 g, 48,6 mmol) se azeotropó con benceno y se suspendió en benceno (94 ml). Se añadieron trietilamina (9,49 ml, 68,1 mmol) y difenilfosforilazida (10,48 ml, 48,6 mmol) y la mezcla de reacción se agitó a TA durante 1 h. La mezcla se filtró a través de un lecho corto de sílice y se eluyó con ~1 L de tolueno, las sustancias volátiles se evaporaron, el residuo se resuspendió en difenilmetano (94 ml) y la mezcla se calentó a reflujo durante tres horas (250°C de temperatura interna). La mezcla de reacción se dejó enfriar a TA, se agitó durante toda una noche, se filtró y el sólido se lavó con hexanos (100 ml) dando sólido canela (7,4 g). EMBR ESI$^+$ $(M+H)^+$ 254,1.

Etapa 3: 7-bromo-1-cloro-6-metoxiisoquinolina

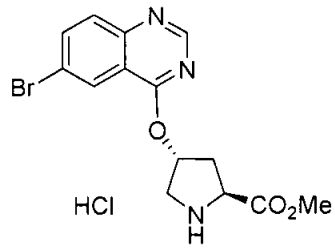


Una mezcla del producto de la etapa 2 (7-bromo-6-metoxiisoquinolin-1(2H)-ona) (4,7 g, 18,5 mmol) en oxicloruro de fósforo (30 ml) se calentó a reflujo durante 2 h, se enfrió a TA, los volátiles se evaporaron y el residuo se fraccionó entre NaOH 3M y DCM. La fase orgánica se secó sobre Na_2SO_4, el disolvente se evaporó y el sólido se trituró con Et_2O (20 ml) y se filtró dando un sólido (3,75 g). EMBR ESI$^+$ $(M+H)^+$ 274,0.

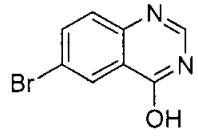
Etapa 4: clorhidrato de (4*R*)-4-[(7-bromo-6-metoxiisoquinolin-1-il)oxi]-L-prolinato de etilo (intermedio C1)

El compuesto del título se preparó a partir del producto de la etapa 3 (7-bromo-1-cloro-6-metoxiisoquinolina), utilizado el procedimiento descrito en el EJEMPLO 10, etapa 1. EMBR ESI$^+$ $(M+H)^+$ 395,0.

Intermedio C2: Clorhidrato de (4*R*)-4-[(6-bromoquinazolin-4-il)oxi]-L-prolinato de metilo

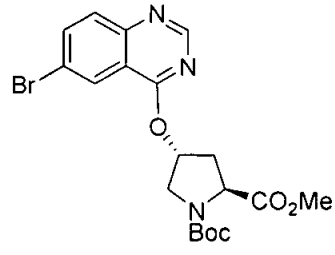


Etapa 1: 4-hidroxi-6-bromoquinazolina



Se combinaron ácido bromoantranílico (12,0 g, 55,5 mmol) y acetato de formamidina (29,2 g, 281 mmol) en ácido acético (96 ml) y se calentaron a reflujo durante 2 h. La mezcla de reacción se enfrió, se concentró eliminando ácido acético y se vertió en agua (500 ml). La mezcla de reacción se agitó durante 0,5 horas y los sólidos resultantes se filtraron. Los sólidos se secaron al aire dando un sólido canela (12,0 g). EMBR $(M+H)^+ = 225,0$.

Etapa 2: (2S,4R)-4-[(6-bromoquinazolin-4-il)oxi]pirrolidina-1,2-dicarboxilato de 1-terc-butil 2-metilo



A una solución de éster metílico de N-boc-cis-hidroxiprolina (2,0 g, 8,15 mmol), 4-hidroxi-6-bromoquinazolina (1,84 g, 8,15 mmol) y trifenilfosfina (2,57 g, 9,79 mmol) a 0°C en THF (80 ml) se añadió diisopropilazodicarboxilato (1,98 g, 9,79 mmol) gota a gota. La mezcla se agitó a 25°C durante 18 h. La reacción se diluyó con EtOAc (100 ml), se lavó con Na_2CO_3 acuoso al 10% (50 ml 2 x) y agua (2 x 50 ml). Las fases acuosas combinadas se retroextrajeron con EtOAc (50 ml) y los extractos de EtOAc combinados se secaron sobre Na_2SO_4, se filtraron y se concentraron a un aceite. El aceite se cromatografió en sílice usando EtOAc 25-60%/hexano dando el compuesto del título (3,46 g). EMBR $(M+H)^+ = 452,2$.

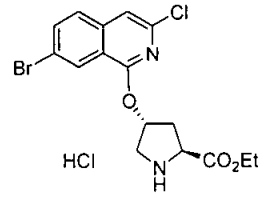
Etapa 3: clorhidrato de (4*R*)-4-[(6-bromoquinazolin-4-il)oxi]-L-prolinato de metilo (intermedio C2)

A una solución de (2S,4R)-4-[(6-bromoquinazolin-4-il)oxi]pirrolidina-1,2-dicarboxilato de 1-terc-butil-2-metilo (3,46 g, 6,65 mmol) en dioxano (80 ml) a 0 °C se

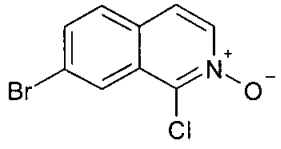
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introdujo HCl anhidro (g) durante 30 min. La reacción se completó mediante HPLC/EM. La mezcla de reacción se concentró y los sólidos resultantes se azeotroparon con éter dietílico (50 ml) dando el compuesto del título (3,0 g). EMBR $(M+H)^+ = 352,2$.

Intermedio C3: clorhidrato de (4*R*)-4-[(7-bromo-3-cloroisoquinolin-1-il)oxi]-L-prolinato de etilo

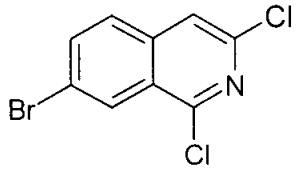


Etapa 1: 2-óxido de 7-bromo-1-cloroisoquinolina



A una solución de 7-bromo-1-cloroisoquinolina (4,0 g, 15,8 mmol) en DCM (100 ml) a 0°C se añadió mCPBA (~77%, 7,46 g, 33,3 mmol). La reacción se dejó agitar a temperatura ambiente durante 24 horas, se diluyó con DCM (100 ml) y se lavó con NaOH 1N y salmuera. Los extractos de DCM se secaron sobre Na_2SO_4, se filtraron, se concentraron y se cromatografiaron en sílice eluyendo con acetona al 5-15%/DCM dando el compuesto del título (1,43 g). EMBR $(M+H)^+ = 258,0$.

Etapa 2: 7-bromo-1,3-dicloroisoquinolina

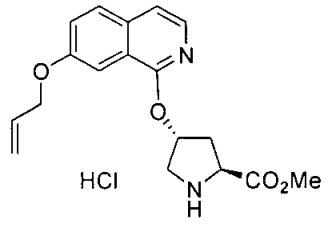


Se calentaron 2-óxido de 7-bromo-1-cloroisoquinolina (1,43 g, 5,56 mmol) y $POCl_3$ (20 ml) a reflujo durante 2 h. La mezcla de reacción se enfrió y se vertió cuidadosamente sobre una mezcla de hielo/agua (500 g), se agitó durante 1 h y el pH se ajustó a 10,0 con NaOH 10M. La mezcla se extrajo con cloroformo (100 ml 2x) y los extractos de cloroformo se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron dando el compuesto del título (1,40 g). EMBR $(M+H)^+ = 276,0$.

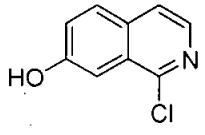
Etapa 3: clorhidrato de (4*R*)-4-[(7-bromo-3-cloroisoquinolin-1-il)oxi]-L-prolinato de etilo (intermedio C3)

Se preparó clorhidrato de (4*R*)-4-[(7-bromo-3-cloroisoquinolin-1-il)oxi]-L-prolinato de etilo a partir de 7-bromo-1,3-dicloroisoquinolina de acuerdo con el procedimiento para EJEMPLO 10, etapa 1. EMBR $(M+H)^+ = 399,1$.

Intermedio C4: (4*R*)-4-{[7-(aliloxi)isoquinolin-1-il]oxi}-L-prolinato de metilo

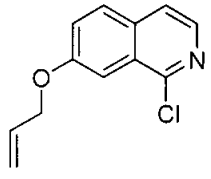


Etapa 1: 1-cloroisoquinolin-7-ol



Se combinaron 7-bromo-1-cloroisoquinolina (2,0 g, 8,25 mmol), bis(pinacolato)diboro (2,20 g, 8,66 mmol), acetato de potasio (2,43 g, 24,7 mmol) y aducto de $PdCl_2$(dppf)DCM (0,337 g, 0,412 mmol) bajo nitrógeno en dioxano (40 ml) y se calentaron en un baño de aceite a 100°C durante 24 horas. La mezcla de reacción se enfrió, se diluyó con EtOAc (100 ml) y se lavó con $KHSO_4$ acuoso al 10%. La fase orgánica se secó sobre Na_2SO_4, se filtró y se concentró a un aceite. El aceite se disolvió en acetona (100 ml) y se añadió una solución de oxona (5,07 g, 8,25 mmol) en agua (20 ml) durante 2 min. La mezcla de reacción se agitó durante 10 min, se diluyó con solución de bisulfato de sodio acuoso y se agitó durante 20 minutos adicionales y después se concentraron retirando acetona. La mezcla resultante se filtró dando el compuesto del título (1,4 g) que se usó sin purificación adicional. EMBR $(M+H)^+ = 180,1$.

Etapa 2: 7-(aliloxi)-1-cloroisoquinolina



Se combinaron 1-cloroisoquinolin-7-ol (4,87 gm, 20,34 mmol) y carbonato de cesio (6,63 g, 20,34 mmol) en acetonitrilo (100 ml) y se agitaron durante 2 min. Se añadió

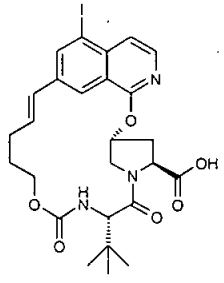
bromuro de alilo (1,76 ml, 20,34 mmol) y la mezcla de reacción se agitó durante 30 min. La mezcla de reacción se diluyó con $KHSO_4$ acuoso (40 ml) y EtOAc (100 ml) y se agitó. El extracto orgánico se retiró, se secó sobre Na_2SO_4, se concentró y se cromatografió en gel de sílice usando EtOAc al 20-50%/hexanos dando 0,85 g de un aceite que solidificó tras almacenarse en el frigorífico. EMBR $(M+H)^+ = 220,1$.

Etapa 3: (4*R*)-4-{[7-(aliloxi)isoquinolin-1-il]oxi}-L-prolinato de metilo (intermedio C4)

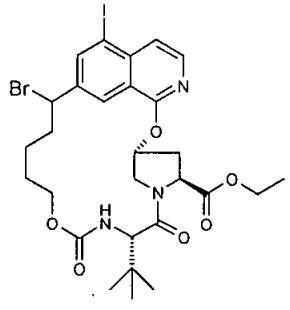
El intermedio C4 se preparó de acuerdo con el procedimiento descrito en el ejemplo 10 etapa 1, usando 7-(aliloxi)-1-cloroisoquinolina. EMBR $(M+H)^+ = 329,3$.

Preparación de Intermedios D

Intermedio D1: ácido (2R,4S,7S)-7-terc-butil-22-yodo-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxílico



Etapa 1: (2R,4S,7S)-15-bromo-7-terc-butil-22-yodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo



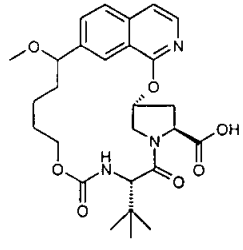
Se disolvió (2R,4S,7S)-7-terc-butil-22-yodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (EJEMPLO 13, etapa 1) (120 mg, 0,188 mmol) en tetracloruro de carbono (3 ml), seguido por la adición de N-bromosuccinimida (37 mg, 0,207 mmol) y peróxido de benzoílo catalítico (4 mg). La mezcla de reacción se calentó a reflujo bajo N_2 durante 3 h, se enfrió y se concentró y el residuo resultante se purificó

en gel de sílice (EtOAc al 10-60% en hexanos) produciendo el compuesto del título como una espuma blanca (113 mg). EMBR $(M+H)^+ = 716,4$.

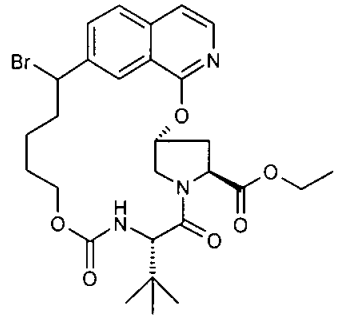
Etapa 2: ácido (2R,4S,7S)-7-terc-butil-22-yodo-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxílico (intermedio D1)

A una solución del producto de etapa 1 (43 mg, 0,06 mmol) en THF (2 ml), bajo nitrógeno, se añadió t-butóxido de potasio 1M en THF (0,09 ml, 0,09 mmol), la mezcla de reacción se agitó durante 30 min y después se añadió una segunda parte de t-butóxido de potasio (0,03 ml, 0,03 mmol). La mezcla de reacción se agitó durante 45 min, se diluyó con agua, se acidificó con HCl 1N y se extrajo con EtOAc (x2). Los productos orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron, se concentraron, y se hicieron azeótropos de Et_2O produciendo el compuesto del título en bruto como un sólido amarillo oscuro (36 mg). EMBR $(M+H)^+ = 608,4$.

Intermedio D2: ácido (2R,4S,7S)-7-terc-butil-15-metoxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxílico



Etapa 1: (2R,4S,7S)-15-bromo-7-terc-butil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo



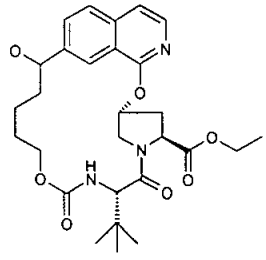
Se preparó (2R,4S,7S)-15-bromo-7-terc-butil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-

k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo de acuerdo con el procedimiento descrito para intermedio D1, etapa 1, empezando con (2R,4S,7S)-7-terc-butil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (ejemplo 11, etapa 1). EMBR $(M+H)^+ = 590,5$.

Etapa 2: ácido (2R,4S,7S)-7-terc-butil-15-metoxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxílico (intermedio D2)

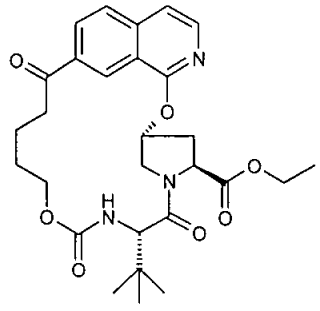
Una solución del producto de etapa 1 (78 mg, 0,132 mmol) en MeOH (4 ml) se calentó a 60°C durante 6 h. Se añadió hidróxido de sodio (1N, 0,528 ml, 0,528 mmol) y la mezcla de reacción se agitó durante 4 h. La mezcla de reacción se concentró y el residuo resultante se fraccionó entre EtOAc y HCl 1N (x2). Las fases orgánicas se combinaron, se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron, y se concentraron produciendo el compuesto del título como una espuma blanca (68 mg). EMBR $(M+H)^+ = 514,3$.

Intermedio D3: (2R,4S,7S)-7-terc-butil-15-hidroxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo



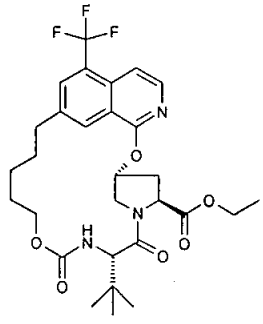
A una solución de (2R,4S,7S)-15-bromo-7-terc-butil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (intermedio D2, etapa 1) (89 mg, 0,151 mmol) en acetona (1 ml) se añadió una solución de nitrato de plata (38 mg, 0,226 mmol) en H_2O (1 ml). La mezcla de reacción se agitó en la oscuridad durante 16 horas, se filtró, se concentró, y el residuo resultante se fraccionó entre DCM y H_2O (x3). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 anhidro, y se concentraron. El producto en bruto se purificó en gel de sílice (EtOAc 15%-60% en hexanos) produciendo el compuesto del título como una espuma blanca (37 mg). EMBR $(M+H)^+ = 528,8$.

Intermedio D4: (2R,4S,7S)-7-terc-butil-6,9,15-trioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo



A una solución de (2R,4S,7S)-7-terc-butil-15-hidroxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (intermedio D3) (70 mg, 0,133 mmol) en DCM (3 ml) se añadió PCC (41 mg, 0,191 mmol) y la mezcla de reacción se agitó durante 4 h, se filtró, se concentró, y el residuo resultante se purificó en gel de sílice (acetona al 0%-5% en DCM) produciendo el compuesto del título como un sólido blanco (59 mg). EMBR $(M+H)^+ = 526,5$.

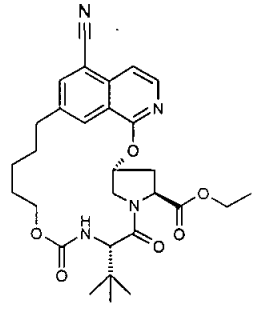
Intermedio D5: (2R,4S,7S)-7-terc-butil-6,9-dioxo-22-(trifluorometil)-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo



A una solución de (2R,4S,7S)-7-terc-butil-22-yodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (EJEMPLO 13, etapa 1) (25 mg, 0,039 mmol) en DMF (1,5 ml) se añadió fluorosulfonildifluoroacetato de metilo (0,015 ml, 0,118 mmol) y yoduro de cobre (I) (22 mg, 0,118 mmol). La mezcla se calentó a 150°C en un microondas durante 10 min, se enfrió, se filtró, se concentró, y el residuo resultante se purificó en gel de sílice (EtOAc al 10%-50% en hexanos) produciendo el compuesto del título como un sólido blanco (20 mg). EMBR $(M+H)^+ = 580,5$.

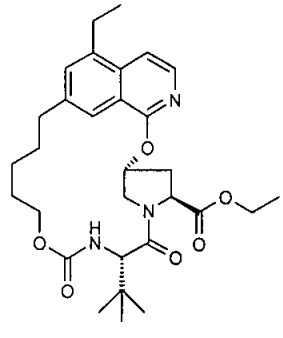
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Intermedio D6: (2R,4S,7S)-7-terc-butil-22-ciano-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo

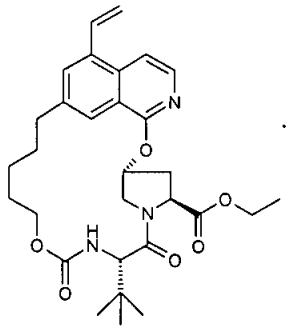


A una solución de (2R,4S,7S)-7-terc-butil-22-yodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (EJEMPLO 13, etapa 1) (75 mg, 0,118 mmol) en DMF (1,5 ml) se añadió cianuro de cobre (I) (32 mg, 0,353 mmol) y la mezcla se calentó a 150°C en un tubo sellado durante 4 h. La mezcla de reacción se fraccionó entre EtOAc y $NaHCO_3$ saturado (x3). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron, y se concentraron. El material en bruto resultante se purificó en gel de sílice (EtOAc 10%-50% en hexanos) produciendo el compuesto del título como una espuma blanca (40 mg). EMBR $(M+H)^+$ = 537,4.

Intermedio D7: (2R,4S,7S)-7-terc-butil-22-etil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo



Etapa 1: (2R,4S,7S)-7-terc-butil-6,9-dioxo-22-vinil-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo

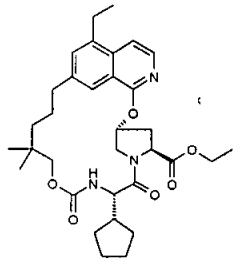


Se hizo burbujear nitrógeno a través de una solución de (2R,4S,7S)-7-terc-butil-22-yodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (EJEMPLO 13, etapa 1) (90 mg, 0,141 mmol) en tolueno (2 ml) durante 30 min. Se añadieron tributil(vinil)estaño (0,049 ml, 0,169 mmol) y tetrakis(trifenilfosfina) de paladio (0) (16 mg, 0,014 mmol) y la mezcla de reacción se calentó a reflujo durante 2 h. La mezcla de reacción enfriada se concentró y el residuo se purificó mediante cromatografía en gel de sílice (EtOAc al 10%-60% en hexanos) produciendo el compuesto del título como un aceite transparente (58 mg). EMBR $(M+H)^+$ = 538,5.

Etapa 2: (2R,4S,7S)-7-terc-butil-22-etil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (intermedio D7)

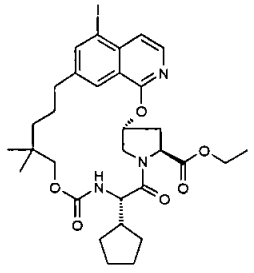
A una solución de (2R,4S,7S)-7-terc-butil-6,9-dioxo-22-vinil-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (58 mg, 0,108 mmol) en etanol (5 ml) se añadió catalizador de paladio al 10% en carbono (20 mg). La mezcla de reacción se situó bajo un balón de hidrógeno y se agitó durante 16 h. La mezcla de reacción se filtró, se concentró, y el compuesto del título se obtuvo como espuma blanca (46 mg). EMBR $(M+H)^+$ = 540,5.

Intermedio D8: (2*R*,4*S*,7*S*)-7-ciclopentil-22-etil-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo



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Etapa 1: (2*R*,4*S*,7*S*)-7-ciclopentil-22-yodo-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo

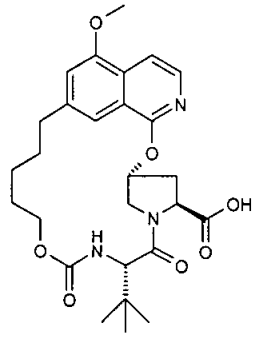


Se preparó (2*R*,4*S*,7*S*)-7-ciclopentil-22.yodo.12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de acuerdo con el procedimiento descrito para EJEMPLO 13, etapa 1 usando (2*R*,4*S*,7*S*)-7-ciclopentil-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (EJEMPLO 15, etapa 1). EMBR $(M+H)^+ = 678,3$.

Etapa 2: (2*R*,4*S*,7*S*)-7-ciclopentil-22-etil-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (intermedio D8)

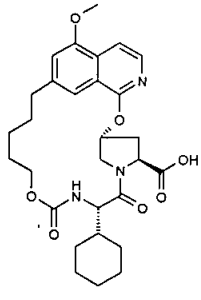
Se preparó (2*R*,4*S*,7*S*)-7-ciclopentil-22-etil-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (intermedio D8) de acuerdo con el procedimiento descrito para intermedio D7 usando (2*R*,4*S*,7*S*)-7-ciclopentil-22-yodo-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo. EMBR $(M+H)^+ = 580,3$.

Intermedio D9: ácido (2R,4S,7S)-7-terc-butil-22-metoxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxílico



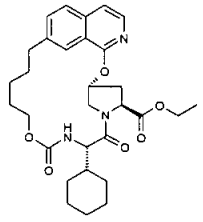
A una solución de (2R,4S,7S)-7-terc-butil-22-yodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (EJEMPLO 13, etapa 1) (195 mg, 0,306 mmol) en MeOH (4 ml) se añadió metóxido de sodio (30% en MeOH, 0,17 ml, 0,918 mmol) y yoduro de cobre (I) (9 mg, 0,046 mmol). La mezcla de reacción se calentó a 100°C en el microondas durante 20 min, se enfrió, se añadió hidróxido de sodio (1N, 1,0 ml, 1,0 mmol) y la mezcla de reacción se agitó durante 4 h. La mezcla se filtró, se concentró, y el residuo se fraccionó entre EtOAc y HCl 1N (x3). Los compuestos orgánicos combinados se lavaron en salmuera, se secaron sobre Na_2SO_4, se filtraron, y se concentraron produciendo el compuesto del título en bruto como un aceite amarillo. EMBR $(M+H)^+ = 514,4$.

Intermedio D10: ácido (2*R*,4*S*,7*S*)-7-ciclohexil-22-metoxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxílico



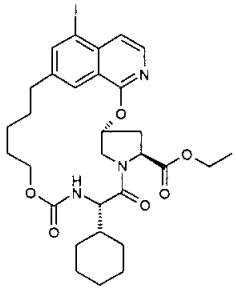
Etapa 1: (2*R*,4*S*,7*S*)-7-ciclohexil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo

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Se preparó (2*R*,4*S*,7*S*)-7-ciclohexil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo usando los procedimientos descritos en ejemplo 14, etapas 1-3 usando intermedio B8 en etapa 1, seguido por hidrogenación de acuerdo con el procedimiento dado en EJEMPLO 15, etapa 1. EMBR $(M+H)^+$ = 538,4.

Etapa 2: (2*R*,4*S*,7*S*)-7-ciclohexil-22-yodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo



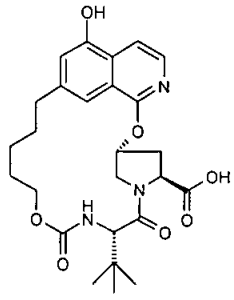
Se preparó (2*R*,4*S*,7*S*)-7-ciclohexil-22-yodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de acuerdo con el procedimiento descrito para EJEMPLO 13, etapa 1 usando (2*R*,4*S*,7*S*)-7-ciclohexil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etandiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo. EMBR $(M+H)^+$ = 664,4.

Etapa 3: ácido (2*R*,4*S*,7*S*)-7-ciclohexil-22-metoxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxílico (intermedio D10)

Se preparó intermedio D10 de acuerdo con el procedimiento descrito para intermedio D9 usando (2*R*,4*S*,7*S*)-7-ciclohexil-22-yodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo. EMBR $(M+H)^+$ = 540,4.

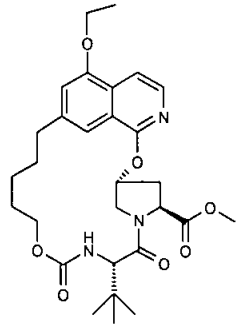
2.13

Intermedio D11: ácido (2R,4S,7S)-7-terc-butil-22-hidroxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxílico

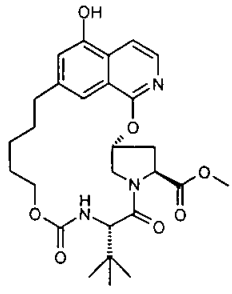


A una solución de ácido (2R,4S,7S)-7-terc-butil-22-metoxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxílico (intermedio D9) (53 mg, 0,103 mmol) en DCM (2 ml) se añadió tribromuro de boro (1M en DCM, 0,31 ml, 0,31 mmol) a -78°C y la mezcla de reacción se agitó durante 1 h, después se calentó lentamente a TA y se agitó durante 1 h. La mezcla de reacción se desactivó con varias gotas de MeOH y H_2O y después se concentró. El residuo se fraccionó entre EtOAc y HCl 1N (x3). Los compuestos orgánicos combinados se lavaron en salmuera, se secaron sobre Na_2SO_4, se filtraron, y se concentraron produciendo el compuesto del título en bruto como un sólido gris (33 mg). EMBR $(M+H)^+$ = 500,3.

Intermedio D12: (2R,4S,7S)-7-terc-butil-22-etoxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de metilo



Etapa 1: (2R,4S,7S)-7-terc-butil-22-hidroxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de metilo



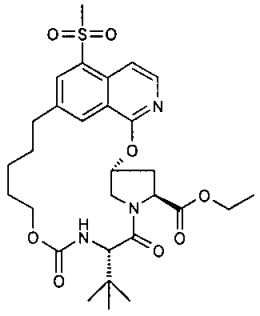
A una solución de ácido (2R,4S,7S)-7-terc-butil-22-metoxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxílico (intermedio D9) (53 mg, 0,103 mmol) en DCM (2 ml) se añadió tribromuro de boro (1M en DCM, 0,31 ml, 0,31 mmol) a -78°C y la mezcla de reacción se agitó durante 1 h. Se calentó lentamente a TA y se agitó durante 1 h. La reacción se desactivó con MeOH en exceso y después se concentró. El residuo resultante se fraccionó entre EtOAc y HCl 1N. Las fases se separaron y la fase acuosa se extrajo con EtOAc (2x). Los compuestos orgánicos combinados se lavaron en salmuera, se secaron sobre Na_2SO_4, se filtraron, y se concentraron produciendo el compuesto del título en bruto como un sólido gris (33 mg). EMBR $(M+H)^+ = 514,3$.

Etapa 2: (2R,4S,7S)-7-terc-butil-22-etoxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de metilo (intermedio D12)

A una solución de (2R,4S,7S)-7-terc-butil-22-hidroxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de metilo (254 mg, 0,495 mmol) en DMF (5 ml) se añadió yodoetano (0,079 ml, 0.989 mmol) y DBU (0,185 ml, 1,24 mmol) y la mezcla de reacción se agitó durante 16 h. La mezcla de reacción se fraccionó entre EtOAc y HCl 1N. Las fases se separaron y la fase orgánica se lavó con HCl 1N (2x), salmuera, se secó sobre Na_2SO_4, se filtró, y se concentró. El compuesto en bruto resultante se purificó en gel de sílice (elución de gradiente de EtOAc 15%-35% en hexanos) produciendo el compuesto del título como una espuma blanca (82 mg). EMBR $(M+H)^+ = 542,3$.

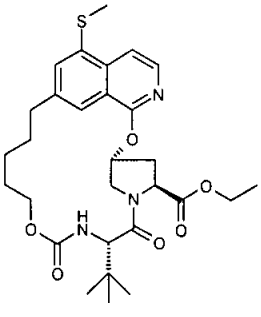
Intermedio D13: (2R,4S,7S)-7-terc-butil-22-(metilsulfonil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo

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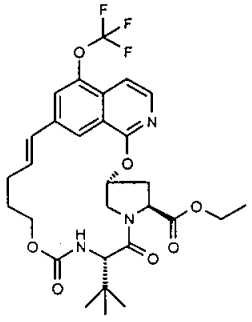
A una solución de (2R,4S,7S)-7-terc-butil-22-yodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (EJEMPLO 13, etapa 1) (50 mg, 0,078 mmol) en DMSO (1 ml) se añadió metanosulfinato de sodio (10 mg, 0,094 mmol), complejo de tolueno de trifluorometanosulfonato de cobre (I) (1 mg, 0,004 mmol) y N,N'-dimetiletilendiamina (1 mg, 0,008 mmol). La mezcla de reacción se calentó en un tubo sellado a 110°C durante 16 h, se enfrió y fraccionó entre EtOAc y H_2O. La fase orgánica se lavó con H_2O (2x), salmuera, se secó sobre Na_2SO_4, se filtró, y se concentró. El producto en bruto se purificó en gel de sílice (EtOAc al 25%-60% en hexanos) produciendo el compuesto del título como un sólido blanco (23 mg). EMBR $(M+H)^+ = 590,3$.

Intermedio D14: (2R,4S,7S)-7-terc-butil-22-(metiltio)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo



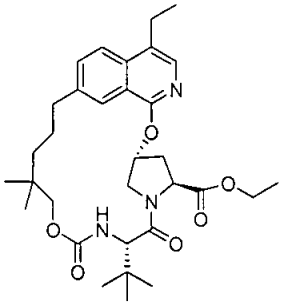
A una solución de (2R,4S,7S)-7-terc-butil-22-yodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (EJEMPLO 13, etapa 1) (50 mg, 0,078 mmol) en piridina (1 ml) se añadió dimetildisulfuro (0,004 ml, 0,039 mmol), y desecho de cobre (1 mg, 0.016 mmol) y la mezcla se calentó en un tubo sellado a 100°C durante 16 h. La mezcla de reacción enfriada se fraccionó entre EtOAc y HCl 1N y las fases se separaron. La fase orgánica se lavó con HCl 1N (2x), salmuera, se secó sobre Na_2SO_4, se filtró, y se concentró produciendo el compuesto del título en bruto como un sólido amarillo. EMBR $(M+H)^+ = 558,4$.

Intermedio D15: (2*R*,4*S*,7*S*,14*E*)-7-*terc*-butil-6,9-dioxo-22-(trifluorometoxi)-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo

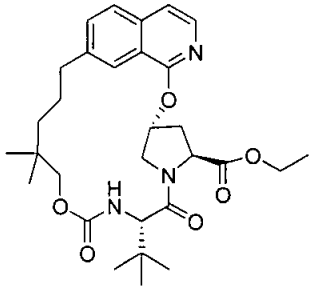


Se preparó (2*R*,4*S*,7*S*,14*E*)-7-*terc*-butil-6,9-dioxo-22-(trifluorometoxi)-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo de acuerdo con los procedimientos descritos para intermedio C1 usando 4-bromo-2-(trifluorometoxi)yodobenzeno en etapa 1, seguido por los procedimientos descritos en EJEMPLO 14, etapas 1-3 usando intermedio B2 en etapa 1. EMBR $(M+H)^+ = 596,3$.

Intermedio D16: (2R,4S,7S)-7-terc-butil-19-etil-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-(etanodiilideno)-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo



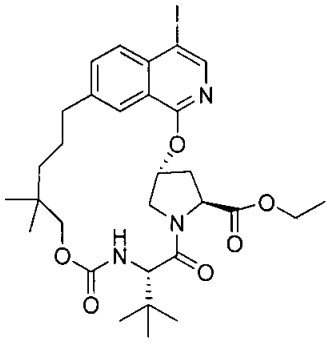
Etapa 1: (2*R*,4*S*,7*S*)-7-*terc*-butil-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo



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Se preparó (2*R*,4*S*,7*S*)-7-terc-butil-12,12-dimetilo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo usando los procedimientos descritos en EJEMPLO 14, etapas 1-3 usando intermedio B4 en etapa 1, seguido por el procedimiento de la hidrogenación de acuerdo con el procedimiento descrito en el EJEMPLO 15, etapa 1. EMBR $(M+H)^+$ = 540,3.

Etapa 2: (2R,4S,7S)-7-terc-butil-19-yodo-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-(etanodiilideno)-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo



A una solución de (2*R*,4*S*,7*S*)-7-*terc*-butil-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (0,5 g, 0,93 mmol) en DCM (5 ml) se añadió ácido tríflico (0,165 ml, 1,853 mmol) y N-yodosuccinimida (208 mg, 0,93 mmol) y la mezcla se agitó bajo N_2 durante 16 h. Se añadió una parte adicional de NIS (208 mg, 0,93 mmol) y la mezcla de reacción se agitó durante unas 24 horas adicionales. La mezcla de reacción se vertió en $NaHCO_3$ saturado y se extrajo con DCM (2x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron, y se concentraron. El material en compuesto resultante se purificó en gel de sílice (EtOAc 20%-40% en hexanos) produciendo el compuesto del título como una espuma blanca (170 mg). EMBR $(M+H)^+$ = 666,4.

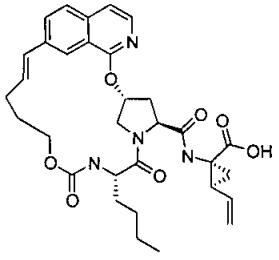
Etapa 3: (2R,4S,7S)-7-terc-butil-19-etil-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-(etanodiilideno)-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (intermedio D16)

Se preparó (2R,4S,7S)-7-terc-butil-19-etil-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-(etanodiilideno)-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo de acuerdo con el procedimiento descrito para intermedio D7, etapas 1 y 2 usando (2R,4S,7S)-7-ciclopentil-22-yodo-12,12-

dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-(etanodiilideno)-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo. EMBR $(M+H)^+ = 568,4$.

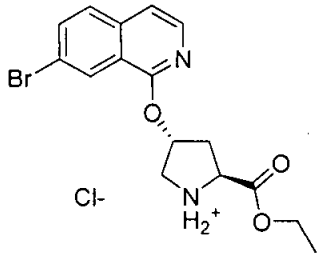
EJEMPLO 1

Ácido (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-butil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-etanodiilideno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecin-4-il]carbonil}amino)-2-vinilciclopropanocarboxílico (**III-1**)



III-1

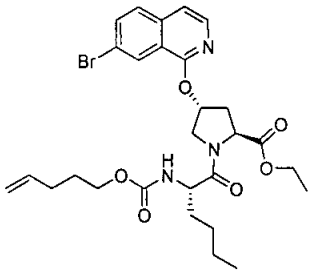
Etapa 1: clorhidrato de (4R)-4-[7-bromoisoquinolin-1-il)oxi]-L-prolinato de etilo



A una solución de trans-4-hidroxi L-BOC-prolina (4,83 g, 20,9 mmol) en 100 ml de DMSO a temperatura ambiente se añadió t-butóxido de potasio (7,03 g, 62,66 mmol) en una parte única. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, se enfrió a 17°C y se añadió 7-bromo-1-cloroisoquinolina (5,06 g, 20,9 mmol), la reacción se dejó calentar a temperatura ambiente y se agitó durante toda una noche. La mezcla de reacción se desactivó con solución de ácido cítrico al 10% enfriada en hielo y se fraccionó con acetato de etilo. La fase orgánica se lavó con solución de ácido cítrico acuosa, agua y salmuera y las fases acuosas se retroextrajeron con acetato de etilo. Las fases orgánicas combinadas se secaron sobre sulfato de sodio anhidro y el disolvente se evaporó hasta dar un sólido oscuro. El sólido se disolvió en etanol (120 ml), se enfrió a 0°C y se hizo burbujear HCl a su través hasta que la solución se saturó. La mezcla de reacción se agitó después a temperatura ambiente durante 48 h y los productos volátiles se evaporaron bajo presión reducida. El sólido restante se azeotropó con etanol (4 x 100 ml) dando 11,95 g (>100% en bruto) de un sólido gris usado directamente en la siguiente etapa. EMBR (ESI) *m/z* 365 $[(M+H)^+$; calcd. para $C_{16}H_{18}BrN_2O_3$: 365].

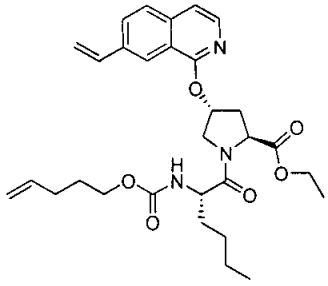
Etapa 2: *N*-[(pent-4-en-1-iloxi)carbonil]-l-norleucil-(4R)-4-[(7-bromoisoquinolin-1-il)oxi]-L-prolinato de etilo

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A una solución de clorhidrato de (4R)-4-[7-bromoisoquinolin-1-il)oxi]-L-prolinato de etilo en bruto (4 g, ~11 mmol) en DMF (30 ml) se añadió *N*-[(pent-4-en-1-iloxi)carbonil]-L-norleucina (intermedio B1) (4,0 g, 16,4 mmol), diisopropiletilamina (4,9 ml, 27 mmol) y TBTU (5,13 g, 16 mmol). La mezcla de reacción se agitó a temperatura ambiente durante toda una noche y se fraccionó entre agua y acetato de etilo. La fase orgánica se lavó con agua, solución de bicarbonato de sodio saturada, salmuera, se secó sobre sulfato de sodio anhidro y el disolvente se evaporó después. El producto en bruto se purificó mediante cromatografía en sílice (hexano EtOAc al 10-100%) dando el producto deseado (3,3 g). EMBR (ESI) *m/z* 590 [$(M+H)^+$; calcd. para $C_{28}H_{37}BrN_3O_6$: 590].

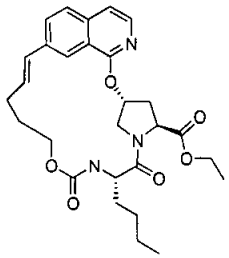
Etapa 3: N-[(pent-4-en-1-iloxi)carbonil]-L-norleucil-(4R)-4-[(7-vinilisoquinolin-1-il)oxi]-L-prolinato de etilo



El bromuro de etapa 2 (62 mg, 0,105 mmol) se disolvió en 5 ml de tolueno y se hizo burbujear nitrógeno a su través durante 15 min. Se añadieron tributilviniltina (0,037 ml, 0,126 mmol) y tetrakis(trifenilfosfina)paladio(0) (6 mg, 0,005 mmol) y la mezcla de reacción se calentó a 100°C bajo nitrógeno. Después de 5 h, la reacción se completó, los productos volátiles se evaporaron y el residuo se purificó mediante cromatografía en gel de sílice (EtOAc al 10-75%/hexano) dando un aceite transparente. EMBR (ESI) *m/z* 538 [$(M+H)^+$; calcd. para $C_{30}H_{40}N_3O_6$: 538].

Etapa 4: (2R,4S,7S)-7-butil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxodiazaciclononadecina-4-carboxilato de etilo

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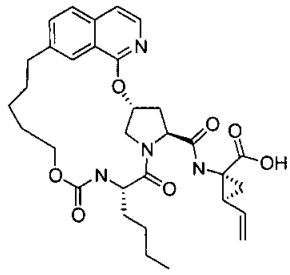
La olefina de la etapa 3 (40 mg, 0,074 mmol) se disolvió en dicloroetano (10 ml) y el nitrógeno se hizo burbujear a través de la solución durante 15 minutos. Se añadió dicloro(5-cloro-2-isopropoxibencilideno)(1,3-dimesitilimidazolidin-2-ilideno)rutenio (catalizador de metátesis de rutenio RC-301de Zhan, catalizador I de Zhan (representados igual que J en página 35), RC-301, Zannan Pharma Ltd.) (5 mg, 0,007 mmol) y la mezcla de reacción se calentó en un baño de aceite a 80°C durante 2 h, después de lo que se completó la reacción. Se evaporaron los productos volátiles y el residuo se purificó mediante cromatografía en gel de sílice (EtOAc al 10-75%/hexano) dando el compuesto del título (24 mg). EMBR (ESI) *m/z* 510 [(M+H)$^+$; calcd. para $C_{28}H_{36}N_3O_6$: 510].

Etapa 5: ácido (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-butil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-etanodiilideno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecin-4-il]carbonil}amino)-2-vinilciclopropanocarboxílico

El éster de la etapa 4 (24 mg, 0,047 mmol) se disolvió en THF (0,5 ml) y EtOH (0,5 ml) y se añadió una solución de LiOH en agua (5 mg en 0,5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 1,5 h después de lo que el análisis por HPLC indicó la reacción completa y se añadió HCl 1M (0,2 ml) y la mezcla se evaporó a un sólido. El sólido se disolvió en DMF (2 ml) y se añadió clorhidrato de éster etílico del ácido (1R,2S)-1-amino-2-vinilciclopropanocarboxílico (intermedio A2)(Llinas-Brunet y col. US6.323.180 y Wang y col. WO 03/099274) ((4 mg, 0,019 mmol), diisopropiletilamina (0,017 ml, 0,095 mmol), y TBTU (6 mg, 0,019 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante toda una noche. La mezcla de reacción se purificó directamente mediante HPLC en fase reversa proporcionando una espuma blanca que se disolvió en THF (0,25 ml) y etanol (0,25 ml) y se añadió una solución de LiOH en agua (4,5 mg en 0,25 ml). La mezcla de reacción se calentó a 40°C durante 2 h, se enfrió a temperatura ambiente, se añadieron HCl 3M (0,06 ml) y DMF (0,5 ml) y la mezcla de reacción se purificó mediante HPLC en fase reversa dando el producto deseado como sólido. EMBR (ESI) *m/z* 591 [(M+H)$^+$; calcd. para $C_{32}H_{39}N_4O_7$: 591].

EJEMPLO 2

Ácido (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-butil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-etanodiilideno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecin-4-il]carbonil}amino)-2-vinilciclopropanocarboxílico (**III-2**)

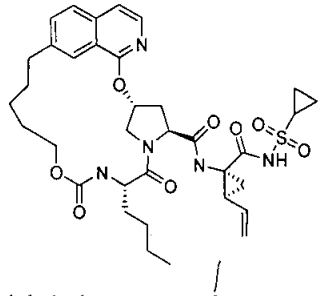


III-2

Una solución de la olefina preparada como se ha descrito en ejemplo 1, etapa 4 (180 mg, 0,353 mmol) en acetato de etilo (10 ml) se trató con Pd/C al 10% y se hidrogenó bajo un balón de hidrógeno durante 18 h. El catalizador se retiró mediante filtración y el filtrado se evaporó dando un aceite. El aceite se trató como se describe en el ejemplo 1, etapa 5 proporcionando el compuesto del título. EMBR (ESI) *m/z* 593 $[(M+H)^+$; calcd. para $C_{32}H_{40}N_4O_7$: 593].

EJEMPLO 3

(2R,4S,7S)-7-butil-N-((1R,2S)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,15,16-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-3**)

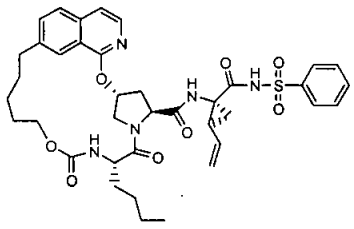


III-3

El compuesto del título se preparó como se describe para el ejemplo 2, usando clorhidrato de (1R,2S)-1-amino-N-(ciclopropilsulfonil)-2-vinilciclopropanocarboxamida (intermedio A1) (Wang y col. WO 03/099274) en lugar de clorhidrato de éster etílico del ácido (1R,2S)-1-amino-2-vinilciclopropanocarboxílico en la etapa de acoplamiento. EMBR (ESI) *m/z* 696 $[(M+H)^+$; calcd. para $C_{35}H_{45}N_5O_8S$: 696]. RMN ^1H (500 MHz, CD_3OD, ppm) δ 9,28 (s, 1 H), 7,97 (s, 1 H), 7,88 (d, *J* = 5,9 Hz, 1 H), 7,72 (d, *J* = 8,3 Hz, 1 H), 7,56 (dd, *J* = 8,3 y 1,7 Hz, 1 H), 7,28 (d, *J* = 5,9 Hz, 1 H), 6,13 (m, 1 H), 5,74 (m, 1 H), 5,27 (dd, *J* = 17,1 y 1,2 Hz, 1 H), 5,10 (dd, *J* = 10,3 y 1,5 Hz, 1 H), 4,65 (d, *J* = 11,2 Hz, 1 H), 4,53 (m, 1 H), 4,44 (t, *J* = 7,6 Hz, 1 H), 4,32 (m, 1 H), 3,99 (dd, *J* = 11,7 y 3,2 Hz, 1 H), 3,73 (m, 1 H), 2,96 (m, 1 H), 2,87 (m, 1 H), 2,71 (m, 1 H), 2,54 (m, 1 H), 2,28 (m, 1 H), 2,20 (m, 1 H), 1,60-1,90 (m, 6 H), 1,51 (m, 1 H), 1,12-1,40 (m, 10 H), 0,94 (t, *J* = 6,8 Hz, 3 H).

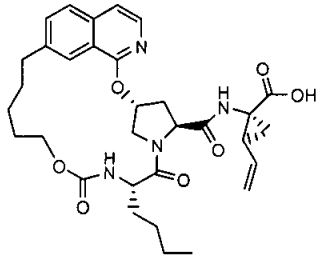
EJEMPLO 4

(2R,4S,7S)-7-butil-N-((1R,2S)-1-{[(fenilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-4**)



III-4

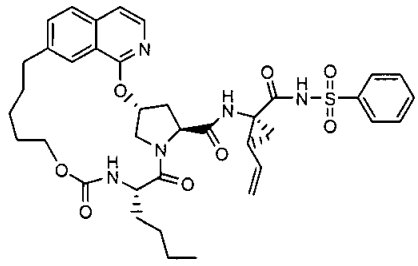
Etapa 1: ácido (1R,2S)-1-({[(2R,4S,7S)-7-butil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopiridina[2,3-k][1,10,3,6]dioxadiazaciclononadecin-4-il]carbonil}amino)-2-vinilciclopropanocarboxílico



A una solución del éster etílico (producto de hidrogenación inicial de ejemplo 2) (400 mg, 0,65 mmol) en tetrahidrofurano (10 ml), etanol (5 ml) y agua (5 ml) se añadió hidróxido de litio (155 mg, 6,45 mmol) y la mezcla se dejó agitar a 40°C durante 24 h. La reacción se enfrió, se concentró a vacío para eliminar tetrahidrofurano y etanol y se diluyó con HCl 3N (2,5 ml). La reacción se dejó agitar durante 30 min y los sólidos resultantes se filtraron y lavaron con agua (1 ml). El sólido se secó al aire dando el compuesto del título como un sólido blanco (0,44 g). EMBR (ESI) *m/z* 593 $[(M+H)^+$; calcd. para $C_{32}H_{40}N_4O_7$: 593].

Etapa 2: (2R,4S,7S)-7-butil-6,9-dioxo-N-((1R,2S)-1-{[(fenilsulfonil)amino]carbonil}-2-vinilciclopropil)-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopiridina[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida

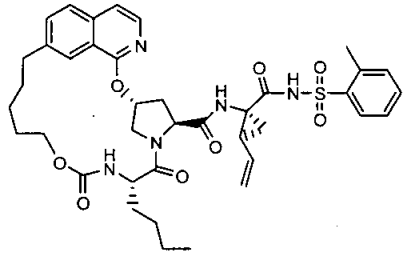
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A una solución del ácido de la etapa 1 (30 mg, 0,05 mmol) en DMF (0,34 ml), bajo nitrógeno, se añadió carbonildiimidazol (13 mg, 0,078 mmol) y la mezcla se agitó a 40 °C durante 2 horas. Se añadió bencenosulfonamida (12 mg, 0,078 mmol) y la reacción se agitó durante toda una noche a 40°C. La reacción se purificó directamente mediante cromatografía en fase reversa y el producto resultante se concentró a vacío dando el compuesto del título como un sólido blanco (18 mg). EMBR (ESI) *m/z* 732 [$(M+H)^+$; calcd. para $C_{38}H_{46}N_5O_8S$: 732].

EJEMPLO 5

(2R,4S,7S)- N-((1R,2S)-1-{[(2-metilfenilsulfonil)amino]carbonil}-2-vinilciclopropil)-7-butil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopiridina[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-5**)

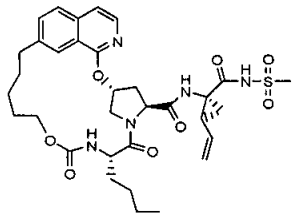


III-5

El compuesto del título se preparó en una manera similar a aquel descrito en el ejemplo 4, reemplazando bencenosulfonamida con 2-metilfenilsulfonamida. EMBR (ESI) *m/z* 746 [$(M+H)^+$; calcd. para $C_{39}H_{48}N_5O_8S$: 746].

EJEMPLO 6

(2R,4S,7S)-7-butil-N-((1R,2S)-1-{[(metilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-6**)

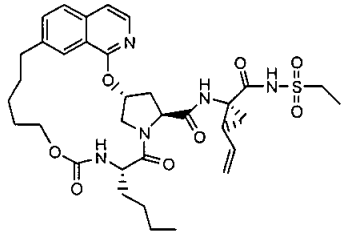


III-6

El compuesto del título se preparó en una manera similar a aquel descrito en el ejemplo 4, reemplazando bencenosulfonamida con metanosulfonamida. EMBR (ESI) *m/z* 670 [$(M+H)^+$; calcd. para $C_{33}H_{43}N_5O_8S$: 670].

EJEMPLO 7

(2R,4S,7S)-7-butil-N-((1R,2S)-1-{[(etilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-7**)

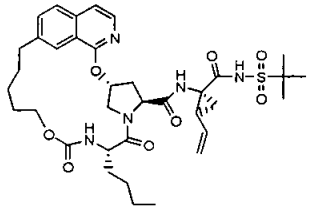


III-7

El compuesto del título se preparó en una manera similar a aquel descrito en el ejemplo 4, reemplazando bencenosulfonamida con etanosulfonamida. EMBR (ESI) *m/z* 684 [$(M+H)^+$; calcd. para $C_{34}H_{46}N_5O_8S$: 684].

EJEMPLO 8

(2R,4S,7S)-7-butil-N-((1R,2S)-1-{[(t-butilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-8**)



III-8

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El compuesto del título se preparó en una manera similar a aquel descrito en el ejemplo 4, reemplazando bencenosulfonamida con t-butilsulfonamida. EMBR (ESI) *m/z* 712 [$(M+H)^+$; calcd. para $C_{36}H_{50}N_5O_8S$: 712].

EJEMPLO 9

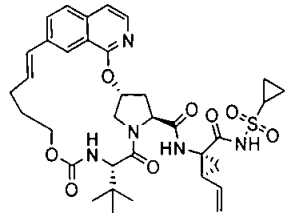
Ensayo de fluorescencia de tiempo de resolución (TRF) de proteasa NS3 de VHC

El ensayo de TRF de proteasa NS3 se llevó a cabo en un volumen final de 100 µl en tampón de ensayo que contiene HEPES 50 mM, pH 7,5, NaCl 150 mM, glicerol al 15%, Triton X-100 al 0,15%, DTT 10 mM, y PEG 8000 al 0,1%. La proteasa NS3 se preincubó con diversas concentraciones de inhibidores durante 10-30 minutos. El sustrato de péptido para el ensayo es Ac-C(Eu)-DDMEE-Abu-[COO]-XSAK(QSY7)-NH2, donde Eu es un grupo marcado con europio, Abu es ácido 1-aminobutanoico que conecta un enlace éster con ácido 2-hidroxipropanoico (X). La hidrólisis del péptido mediante la actividad de proteasa NS3 causa separación del fluoróforo del desactivador, dando como resultado un incremento en fluorescencia. La actividad de la proteasa se inició añadiendo el sustrato de péptido TRF (concentración final 50-100 nM). La reacción se desactivó después de 1 hora a temperatura ambiente con 100 µl de MES 500 mM, pH 5,5. La fluorescencia de producto se detectó usando un Victor V2 o fluorímetro de fusión (Perkin Elmer Life and Analytical Sciences) con excitación a 340 nm y emisión a 615 nm con retraso de 50-400 µs. Las concentraciones de prueba de diferentes formas de enzima se seleccionaron con una señal para razón de antecedentes de 10-30. Las constantes de inhibición se derivaron usando un ajuste de cuatro parámetros.

Los compuestos **III-1** y **III-3** a **III-9, III-10, III-12, III-14, III-15, III-20, III-23, III-24, III-25, III-28, III-29, III-31, III-32, III-34, III-37, III-38, III-39 a III-46 y III-48 a III-185** se probaron dando un valor de Ki de menos de 100 nM en el ensayo TRF de la proteasa NS3 como se describe anteriormente.

EJEMPLO 10

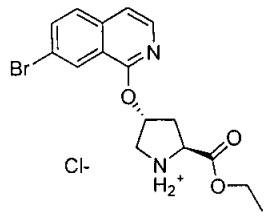
Ácido (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-terc-butil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-etanodiilideno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecin-4-il]carbonil}amino)-2-vinilciclopropanocarboxílico (**III-23**)



III-23

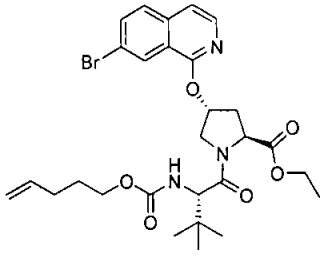
Etapa 1: clorhidrato de (4R)-4-[7-bromoisoquinolin-1-il)oxi]-L-prolinato de etilo

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A una solución de trans-4-hidroxi L-BOC-prolina (4,83 g, 20,9 mmol) en 100 ml de DMSO a temperatura ambiente se añadió t-butóxido de potasio (7,03 g, 62,66 mmol) en una parte única. La mezcla de reacción se agitó a temperatura ambiente durante 30 min, se enfrió a 17°C y se añadió 7-bromo-1-cloroisoquinolina (5,06 g, 20,9 mmol), la reacción se dejó calentar a temperatura ambiente y se agitó durante toda una noche. La mezcla de reacción se desactivó con solución de ácido cítrico al 10% enfriada en hielo y se fraccionó con acetato de etilo. La fase orgánica se lavó con solución de ácido cítrico acuosa, agua y salmuera y las fases acuosas se retroextrajeron con acetato de etilo. Las fases orgánicas combinadas se secaron sobre sulfato de sodio anhidro y el disolvente se evaporó hasta dar un sólido oscuro. El sólido se disolvió en etanol (120 ml), se enfrió a 0°C y se hizo burbujear HCl a su través hasta que la solución se saturó. La mezcla de reacción se agitó después a temperatura ambiente durante 48 h y los productos volátiles se evaporaron bajo presión reducida. El sólido restante se azeotropó con etanol (4 x 100 ml) dando 11,95 g (>100% en bruto) de un sólido gris usado directamente en la siguiente etapa. EMBR (ESI) *m/z* 365 [$(M+H)^+$; calcd. para $C_{16}H_{18}BrN_2O_3$: 365].

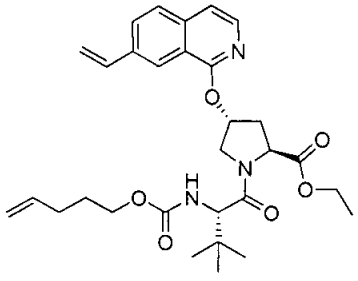
Etapa 2: *N*-[(pent-4-en-1-iloxi)carbonil]-l-terc-butil-(4R)-4-[(7-bromoisoquinolin-1-il)oxi]-L-prolinato de etilo



A una solución de clorhidrato de (4R)-4-[7-bromoisoquinolin-1-il)oxi]-L-prolinato de etilo (1,03 g, ~2,6 mmol) en DMF (10 ml) se añadió *N*-[(pent-4-en-1-iloxi)carbonil]-L-terc-butilglicina (intermedio B2) (0,44 g, 1,81 mmol), diisopropiletilamina (1,8 ml, 10,4 mmol) y TBTU (1,25 g, 3,9 mmol). La mezcla de reacción se agitó a temperatura ambiente durante toda una noche y se fraccionó entre agua y acetato de etilo. La fase orgánica se lavó con agua, solución de bicarbonato de sodio saturada, salmuera, se secó sobre sulfato de sodio anhidro y el disolvente se evaporó después. El producto en bruto se purificó mediante cromatografía en sílice (hexano EtOAc al 20-60%) dando el producto deseado (0,9 g). EMBR (ESI) *m/z* 590 [$(M+H)^+$; calcd. para $C_{28}H_{37}BrN_3O_6$: 590].

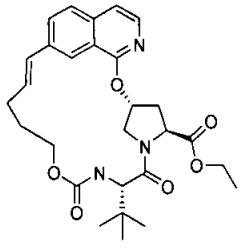
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Etapa 3: N-[(pent-4-en-1-iloxi)carbonil]-L-terc-butilglicina-(4R)-4-[(7-vinilisoquinolin-1-il)oxi]-L-prolinato de etilo



El bromuro de etapa 2 (0,90 mg, 1,53 mmol) se disolvió en 20 ml de tolueno y se hizo burbujear nitrógeno a su través durante 15 min. Se añadieron tributilviniltina (54 ml, 1,83 mmol) y tetrakis(trifenilfosfina)paladio(0) (178,0 mg, 0,153 mmol) y la mezcla de reacción se calentó a 100°C bajo nitrógeno. Después de 3 h, la reacción se completó, los productos volátiles se evaporaron y el residuo se purificó mediante cromatografía en gel de sílice (EtOAc al 20-50%/hexano) dando un aceite transparente. EMBR (ESI) *m/z* 538 [(M+H)$^+$; calcd. para $C_{30}H_{40}N_3O_6$: 538].

Etapa 4: (2R,4S,7S)-7-terc-butil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxodiazaciclononadecina-4-carboxilato de etilo



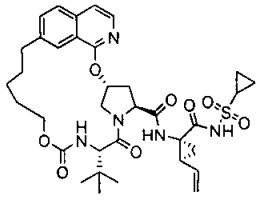
La olefina de la etapa 3 (1,0 mg, 1,86 mmol) se disolvió en dicloroetano (200 ml) y el nitrógeno se hizo burbujear a través de la solución durante 30 minutos. El dicloruro de bis(triciclohexilfosfina)-3-fenil-1H-indeno-1ilidenorutenio (catalizador Neolyst M1, Strem Chemicals, CAS#250220-36-1) (300 mg, 0,30 mmol) se disolvió en diclorometano desgasificado durante 30 minutos y la reacción se dejó agitar 24 horas o hasta completarse. Se evaporaron los productos volátiles y el residuo se purificó mediante cromatografía en gel de sílice (EtOAc al 20-60%/hexano) dando el compuesto del título (0,73 gm). EMBR (ESI) *m/z* 510 [(M+H)$^+$; calcd. para $C_{28}H_{36}N_3O_6$: 510].

Etapa 5: ácido (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-terc-butil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-etanodiilideno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecin-4-il]carbonil}amino)-2-vinilciclopropanocarboxílico

Se disolvió el éster de la etapa 4 (0,73 mg, 0,143 mmol) en THF (0,5 ml) y EtOH (10 ml) y se añadió una solución de LiOH en agua (257 mg en 10 ml). La mezcla de reacción se agitó a temperatura ambiente durante 1,5 h después de lo que el análisis por HPLC indicó la reacción completa y se añadió HCl 3M (0,2 ml) y la mezcla se evaporó a un sólido. El sólido se disolvió en acetato de etilo (20 ml) y agua (20 ml) (pH~2,0) y la fase de acetato de etilo se separó, se secó sobre sulfato de sodio, se filtró y se concentró a una espuma. La espuma se disolvió en diclorometano (40 ml) y se añadió sal clorhidrato de (1-(R)-amino-2-(S)-vinil-ciclopropanocarbonil)-amida del ácido ciclopropanosulfónico (A1) (0,419 mg, 1,58 mmol) (Llinas-Brunet y col., US03/15755 y Wang y col., WO 03/099274), diisopropiletilamina (0,75 ml, 4,30 mmol), dimetilaminopiridina (0,087 gm, 0,72 mmol) y HATU (0,65 gm, 1,72 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante toda una noche. La mezcla de reacción se purificó directamente mediante HPLC en fase reversa produciendo el producto deseado como un sólido. EMBR (ESI) *m/z* 694 [$(M+H)^+$; calcd. para $C_{35}H_{44}N_5O_8S$: 694]. RMN ^1H (500 MHz, ppm) (d_6-DMSO) δ 10,40 (s, 1 H), 8,70 (s, 1 H), 8,45 (s, 1 H), 7,95 (d, *J* = 5,9 Hz, 1 H), 7,81 (d, *J* = 8,3 Hz, 1 H), 7,61 (dd, *J* = 8,6 y 1,7 Hz, 1 H), 7,35 (d, J = 5,9 Hz, 1 H), 7,25 (d, *J* = 7,32 Hz, 1 H), 6,62 (d, *J* = 15,9 Hz, 1 H), 6,39 (m, 1 H), 5,68 (s, 1 H), 5,56 (m, 1 H), 5,17 (d, *J* = 18,1 Hz, 1 H), 5,06 (d, *J* = 11,5 Hz, 1 H), 4,52 (d, *J* = 11,2 Hz, 1 H), 4,31 (m, 3 H), 3,95 (m, 1 H), 3,86 (dd, 1 H, J = 11,5 y 2,9 Hz), 2,92 (m, 1 H), 2,61 (m, 1 H), 2,95 (m, 2 H), 2,10 (m, 2 H), 1,85 (m, 1 H), 1,75 (m, 1 H), 1,66 (m, 1 H), 1,28 (m, 1 H), 1,00-1,15 (m, 4 H), 1,04 (s, 9 H).

EJEMPLO 11

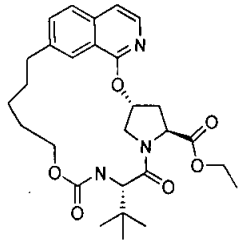
(2R,4S,7S)-7-terc-butil-N-((1R,2S)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-9**)



III-9

Etapa 1: (2R,4S,7S)-7-terc-butil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo

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El éster de ejemplo 10, etapa 4 (512 mg, 1,00 mmol) se disolvió en acetato de etilo (40 ml) se desgasificó con nitrógeno y paladio al 10% en carbono añadido (50 mg). La mezcla se purgó después con hidrógeno 3 veces y se agitó bajo un balón de hidrógeno durante 24 h. La reacción se filtró, se concentró a vacío dando el compuesto (493 mg) como una espuma. EMBR (ESI) *m/z* 512 [$(M+H)^+$; calcd. para $C_{28}H_{38}N_3O_6$: 512].

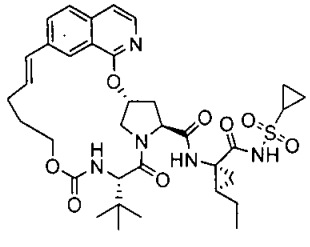
Etapa 2: (2R,4S,7S)-7-terc-butil-N-((1R,2S)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida

El compuesto del título se preparó en una manera similar a la que se describe para la preparación de la etapa 5 del ejemplo 10 utilizando el éster de la etapa 1. EMBR (ESI) *m/z* 696 [$(M+H)^+$; calcd. para $C_{35}H_{45}N_5O_8S$: 696].

RMN ^{1}H (500 MHz, ppm, $CDCl_3$) δ 9,88 (s, 1 H), 7,92 (d, *J* = 7,1 Hz, 1 H), 7,78 (s, 1 H), 7,65 (d, *J* = 10,6 Hz, 1 H), 7,49 (dd, *J* = 10,7 y 1,6 Hz, 1 H), 7,30 (d, *J* = 7,1 Hz, 1 H), 7,19 (s, 1 H), 6,22 (m, 1 H), 5,76 (m, 1 H), 5,65 (d, *J* = 11,7, 1 H), 5,26 (d, *J* = 18,8 Hz, 1 H), 5,15 (d, *J* = 11,2 Hz, 1 H), 4,62 (m, 1 H), 4,46 (m, 3 H), 3,92 (dd, 1 H, J = 11,2 y 2,9 Hz), 3,73 (m, 1 H), 2,90 (m, 2 H), 2,70 (m, 1 H), 2,62 (m, 1 H), 2,51 (m, 1 H), 2,10 (m, 1 H), 1,96 (m, 1 H), 1,72 (m, 3 H), 1,48 (m, 2 H), 1,20-1,35 (m, 4 H), 1,07 (s, 9 H), 1,01 (m, 2 H).

EJEMPLO 12

(2R,4S,7S)-7-terc-butil-N-((1R,2R)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-37**)



III-37

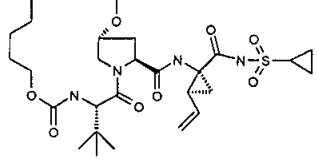
Se preparó el compuesto del título en una manera simultánea como se describe para la preparación de ejemplo 10 etapa 5 utilizando cloruro de (1R,2R)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropanaminio (intermedio A3). EMBR (ESI)

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m/z 696 [(M+H)$^+$; calcd. para $C_{35}H_{45}N_5O_8S$: 696]. RMN ^{1}H (500 MHz, ppm) (d_6-DMSO) δ 10,28 (s, 1 H), 8,66 (s, 1 H), 8,45 (s, 1 H), 7,94 (d, *J* = 5,9 Hz, 1 H), 7,81 (d, *J* = 8,3 Hz, 1 H), 7,62 (dd, *J* = 8,3 y 1,7 Hz, 1 H), 7,35 (d, *J* = 5,9 Hz, 1 H), 7,23 (d, *J* = 7,32 Hz, 1 H), 6,62 (d, *J* = 15,6 Hz, 1 H), 6,39 (m, 1 H), 5,68 (m, 1 H), 4,52 (d, *J* = 11,0 Hz, 1 H), 4,31 (m, 3 H), 3,95 (m, 1 H), 3,86 (dd, *J* = 11,7 y 3,2 Hz, 1 H), 2,93 (m, 1 H), 2,55 (m, 1 H), 2,28 (m, 2 H), 2,08 (m, 1 H), 1,84 (m, 1 H), 1,75 (m, 1 H), 1,46 (m, 1 H), 1,24-1,38 (m, 3 H), 1,00-1,15 (m, 5 H), 1,04 (s, 9 H), 0,85 (t, *J* = 7,3 Hz, 3 H).

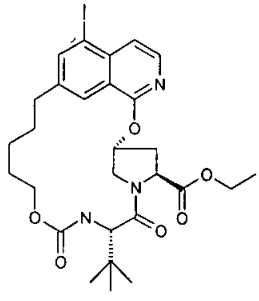
EJEMPLO 13

(2R,4S,7S)-7-terc-butil-N-((1R,2R)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-38**)



III-38

Etapa 1: (2R,4S,7S)-7-terc-butil-22-yodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo



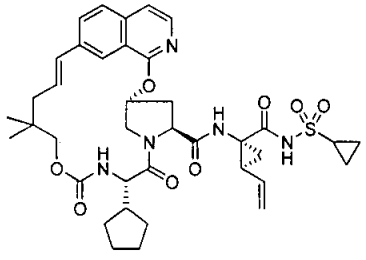
El éster de ejemplo 11, etapa 1 (0,79 gm, 1,55 mmol) se disolvió en ácido tríflico (5 ml) y se añadió N-yodosuccinimida (0,90 gm, 4,0 mmol) en 4 partes durante 4 h. La reacción se vertió en una mezcla fría de acetato de etilo y solución de bicarbonato de sodio saturada. Las fases se separaron y la fase orgánica se lavó con bicarbonato de sodio saturado y salmuera. Los productos orgánicos se secaron sobre sulfato de sodio anhidro y el disolvente se evaporó después proporcionando un aceite incoloro. El producto en bruto se purificó mediante cromatografía en sílice (EtOAc hexano 10-50%) dando el compuesto del título (0,76 gm). EMBR (ESI) *m/z* 638 [(M+H)$^+$; calcd. para $C_{28}H_{37}IN_3O_6$: 638].

Etapa 2: (2R,4S,7S)-7-terc-butil-N-((1R,2R)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida

El compuesto del título se preparó en una manera similar a la que se describe para la preparación de la etapa 5 del ejemplo 10 utilizando el éster de la etapa 1. EMBR (ESI) *m/z* 822 [(M+H)$^+$; calcd. para $C_{35}H_{45}IN_5O_8S$: 822]: RMN ^{1}H (400 MHz, ppm) (CD_3OD) δ 9,17 (s, 1 H), 8,17 (s, 1 H), 8,01 (d, *J* = 6,1 Hz, 1 H), 7,95 (s, 1 H), 7,43 (d, *J* = 6,04 Hz, 1 H), 6,2 (s, 1 H), 5,73 (m, 1 H), 5,28 (d, *J* = 18,7 Hz, 1 H), 5,12 (dd, *J*= 10,2 y 1,6 Hz, 1 H), 4,57 (m, 1 H), 4,41 (m, 3 H), 3,99 (dd, *J* = 11,7 y 3,1 Hz, 1 H), 3,74 (m, 1 H), 2,93 (m, 2 H), 2,64 (m, 1 H), 2,55 (m, 1 H), 2,24 (m, 2 H), 1,88 (m, 1 H), 1,73 (m, 3 H), 1,49 (m, 1 H), 1,43 (m, 1 H), 1,25 (m, 4 H), 1,09 (m, 2 H), y 1,06 (s, 9 H).

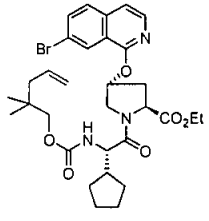
EJEMPLO 14

(2*R*,4*S*,7*S*,14*E*)-7-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-39**)



III-39

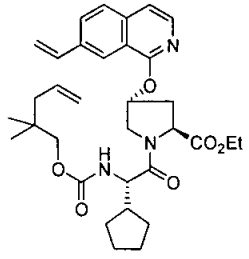
Etapa 1: (4*R*)-4-[(7-bromoisoquinolin-1-il)oxi]-1-[(2*S*)-2-ciclopentil-2-({[(2,2-dimetilpent-4-en-1-il)oxi]carbonil}amino)acetil]-L-prolinato de etilo



A una solución de clorhidrato de (4R)-4-[7-bromoisoquinolin-1-il)oxi]-L-prolinato de etilo (ejemplo 1, etapa 1) (500 mg, 1,25 mmol) y ácido (2*S*)-ciclopentil({[(2,2-dimetilpent-4-en-1-il)oxi]carbonil}amino)acético (intermedio B24) (353 mg, 1,25 mmol) en DMF (7 ml) a TA se añadió HATU (710 mg, 1,87 mmol) y DIPEA (0,87 ml, 5,00 mmol). Después de 2 h, la mezcla de reacción se vertió en EtOAc, y se extrajo con HCl 1 N. La fase orgánica se lavó con agua y salmuera, se secó sobre Na_2SO_4 y el disolvente se eliminó a vacío. El producto en bruto se purificó en sílice (elución de gradiente, EtOAc 5%-75% en hexanos) produciendo 526 mg (67%) del compuesto del título. EMBR (ESI) *m/z* 630,3 [(M+H)$^+$; calcd. para $C_{31}H_{41}BrN_3O_6$: 630,2].

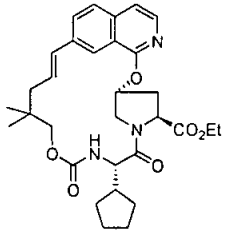
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Etapa 2: (4*R*)-1-[(2*S*)-2-ciclopentil-2-({[(2,2-dimetilpent-4-en-1-il)oxi]carbonil}amino)acetil]-4-[(7-vinilisoquinolin-1-il)oxi]-L-prolinato de etilo



Se disolvió (4*R*)-4-[(7-bromoisoquinolin-1-il)oxi]-1-[(2*S*)-2-ciclopentil-2-({[(2,2-dimetilpent-4-en-1-il)oxi]carbonil}amino)acetil]-L-prolinato de etilo (526 mg, 0,83 mmol) en etanol (10 ml) y se hizo burbujear nitrógeno a su través durante 15 min. Se añadieron viniltrifluoroborato de potasio (168 mg, 1,25 mmol) y aducto de DCM de dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio (II) (34 mg, 0,04 mmol) y se calentó a reflujo la mezcla de reacción bajo nitrógeno. Después de 15 h, la reacción se completó y los volátiles se evaporaron y el residuo se purificó mediante cromatografía en gel de sílice (elución de gradiente, EtOAc al 10-75%/hexano) dando un aceite transparente. EMBR (ESI) *m/z* 578,4 [$(M+H)^+$; calcd. para $C_{33}H_{44}N_3O_6$: 578,3].

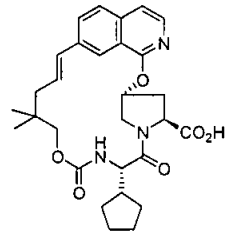
Etapa 3: (2*R*,4*S*,7*S*,14*E*)-7-ciclopentil-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo



A una solución del producto de etapa 2 (413 mg, 0,72 mmol) en DCE desgasificado (sometido a burbujeo de nitrógeno durante 30 min) (250 ml) se añadió catalizador 1B de Zhan (catalizador 1B de Zhan, RC-303, Zannan Pharma Ltd.) (52 mg, 0,07 mmol). La mezcla se agitó después a 70°C bajo una atmósfera de N_2. Después de 3 h, la reacción se completó y se concentró a vacío. El producto en bruto se purificó después directamente en sílice (elución de gradiente, EtOAc 5%-75% en hexanos) proporcionando 325 mg (83%) del compuesto del título. EMBR (ESI) *m/z* 550,4 [$(M+H)^+$; calcd. para $C_{31}H_{40}N_3O_6$: 550,3].

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Etapa 4: ácido (2*R*,4*S*,7*S*,14*E*)-7-ciclopentil-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxílico



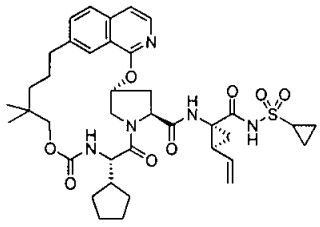
A una solución del producto de etapa 3 (160 mg, 0,29 mmol) en THF (5 ml) y EtOH (0,5 ml) a TA se añadió LiOH (1 M, 2,9 ml, 2,9 mmol). Después de 1 h, la mezcla de reacción se fraccionó entre EtOAc y HCl 1 N (x4). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 y el disolvente se eliminó a vacío produciendo 144 mg (95%) del compuesto del título que se usó sin purificación adicional. EMBR (ESI) *m/z* 522,3 [$(M+H)^+$; calcd. para $C_{29}H_{36}N_3O_6$: 522,3].

Etapa 5: (2*R*,4*S*,7*S*,14*E*)-7-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-39**)

A una solución del producto de etapa 4 (147 mg, 0,28 mmol) y clorhidrato de (1*R*,2*S*)-1-amino-*N*-(ciclopropilsulfonil)-2-vinilciclopropanocarboxamida (intermedio A1) (90 mg, 0,34 mmol) en DMF (2 ml) se añadió DIPEA (0,25 ml, 1,41 mmol), DMAP (3 mg, 0,03 mmol) y HATU (107 mg, 0,28 mmol). Después de la conversión total (15 h), la mezcla de reacción se purificó mediante HPLC en fase reversa (elución de gradiente, CH_3CN 30%-100% en TFA al 0,15%/agua) dando 122 mg (59%) del compuesto del título como un polvo blanco. RMN ^1H (500 MHz, CD_3OD) δ 9,16 (s, 1 H), 8,44 (s, 1 H), 7,87 (d, *J* = 5,9 Hz, 1 H), 7,72 (d, *J* = 8,3 Hz, 1 H), 7,56 (d, *J* = 8,3 Hz, 1 H), 7,27 (d, *J* = 6,1 Hz, 1 H), 6,47 (s, 2 H), 5,77 (s, 1 H), 5,70 (m, 1 H), 5,24 (d, *J* = 17,1 Hz, 1 H), 5,07 (d, *J* = 10,3 Hz, 1 H), 4,79 (d, *J* = 11,7 Hz, 1 H), 4,43 (d, *J* = 11,0 Hz, 1 H), 4,34 (m, 2 H), 4,03 (dd, *J* = 11,5 y 2,7 Hz, 1 H), 2,95 (m, 1 H), 2,65 (m, 1 H), 2,42 (m, 2 H), 2,22 (m, 1 H), 2,13 (c, *J* = 8,8 Hz, 1 H), 2,01 (m, 1 H), 1,92 (m, 1 H), 1,86 (m, 1 H), 1,80-1,60 (m, 5 H), 1,43-1,20 (m, 5 H), 1,15 (s, 3 H), 1,10 (m, 2 H), 0,89 (s, 3 H) ppm. EMBR (ESI) *m/z* 734,4 [$(M+H)^+$; calcd. para $C_{38}H_{48}N_5O_8S$: 734,3].

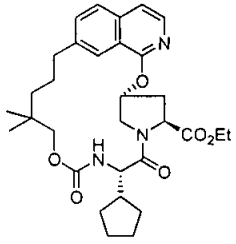
EJEMPLO 15

(2*R*,4*S*,7*S*)-7-ciclopentil-*N*-((1*R*,2*R*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-40**)



III-40

Etapa 1: (2*R*,4*S*,7*S*)-7-ciclopentil-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo



A una solución de (2*R*,4*S*,7*S*,14*E*)-7-ciclopentil-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (EJEMPLO 14, etapa 3) (160 mg, 0,29 mmol) en EtOAc (7 ml) a temperatura ambiente se añadió Pd/C (100 mg). Una balón de H_2 se situó después en el matraz de reacción, el matraz se evacuó rápidamente y se cargó con H_2. Después de 7 h, la mezcla de reacción se filtró a través de celite y se lavó con EtOAc. La concentración del filtrado dio 147 mg (92%) del compuesto del título que se usó sin purificación adicional. EMBR (ESI) *m/z* 552,4 $[(M+H)^+$; calcd. para $C_{31}H_{42}N_3O_6S$: 552,3].

(2*R*,4*S*,7*S*)-7-ciclopentil-*N*-((1R,2R)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-40**)

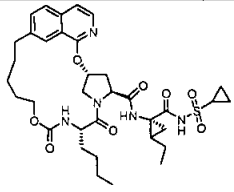
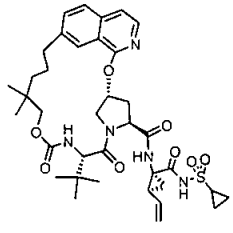
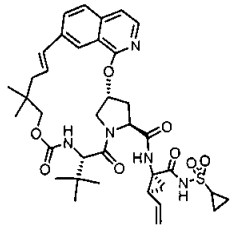
El compuesto del título se preparó a partir de (2*R*,4*S*,7*S*)-7-ciclopentil-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo usando los procedimientos descritos en EJEMPLO 14, etapas 4 y 5. RMN ^{1}H (500 MHz, CD_3OD) δ 9,26 (s, 1 H), 7,89 (s, 1 H), 7,87 (d, *J* = 5,9 Hz, 1 H), 7,71 (d, *J* = 8,3 Hz, 1 H), 7,55 (d, *J* = 8,3 Hz, 1 H), 7,29 (d, *J* = 5,9 Hz, 1 H), 6,03 (s, 1 H), 5,76 (m, 1 H), 5,28 (d, *J* = 15,6 Hz, 1 H), 5,10 (d, *J* = 8,5 Hz, 1 H), 4,58 (d, *J* = 11,5 Hz, 1 H), 4,46 (m, 1 H), 4,33 (d, *J* = 10,7 Hz, 2 H), 4,01 (dd, *J* = 11,5 y 2,7 Hz, 1 H), 3,28 (d, *J* = 10,7 Hz, 1 H), 2,97 (sep, *J* = 4,6 Hz, 1 H), 2,81 (m, 1 H), 2,64 (m, 1 H), 2,55 (c, *J* = 6,7 Hz, 1 H), 2,44 (m, 1 H), 2,26 (m, 1 H), 2,18 (c, *J* = 9,0 Hz, 1 H), 1,88 (m, 2 H), 1,70 (m, 4 H), 1,56 (m, 3 H), 1,40 (m, 3 H), 1,27 (m, 4 H), 1,07 (m, 4 H), 0,77 (s, 3 H) ppm. EMBR (ESI) *m/z* 736.4 $[(M+H)^+$; calcd. para $C_{38}H_{50}N_5O_8S$: 736,3].

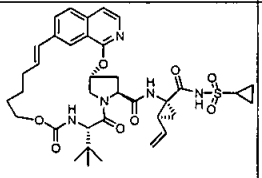
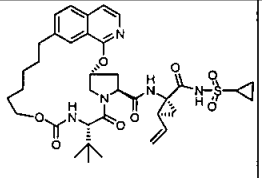
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Usando los procedimientos apropiados y los intermedios A y B apropiados en lugar de clorhidrato de (1*R*,2*S*)-1-amino-*N*-(ciclopropilsulfonil)-2-vinilciclopropanocarboxamida (intermedio A1) y ácido (2*S*)-ciclopentil({[(2,2-dimetilpent-4-en-1-il)oxi]carbonil}amino)acético (intermedio B24), se prepararon los siguientes compuestos.

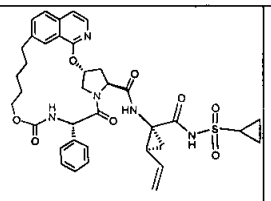
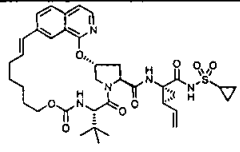
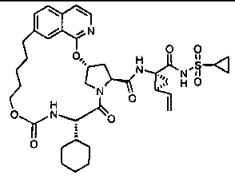
Ej.	Estructura	Nombre	EMBR (M+H)$^+$	Preparados usando los intermedios apropiados de acuerdo con el procedimiento siguiente.	Int.

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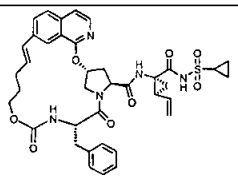
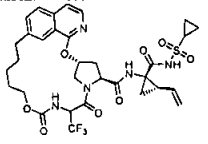
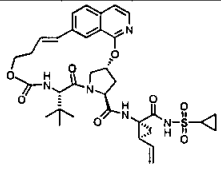
16, **III-41**		(2*R*,4*S*,7*S*)-7-butil-*N*-((1*R*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-etanodiilideno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	698,5	Véase ejemplo 15	A3, B1
17, **III-15**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-etanodiilideno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	724,4	Véase ejemplo 15	A1, B4
18, **III-29**		(2*R*,4*S*,7*S*-14*E*)-7-*terc*-butil-*N*-((1*S*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-octahidro-2*H*,11*H*-16,18-etanodiilideno-2,5-metanopirido[2,3-	722,3	Véase ejemplo 14	A1, B4

		k][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida			
19, **III-42**		(2*R*,4*S*,7*S*,15*E*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahidro-2*H*-17,19-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-cicloicosina-4-carboxamida	708,6	Véase ejemplo 14	A1, B5
20, **III-43**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14,15,16-dodecahidro-2*H*-17,19-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-cicloicosina-4-carboxamida	710,6	Véase ejemplo 15	A1, B5

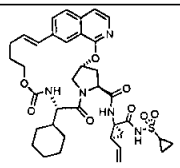
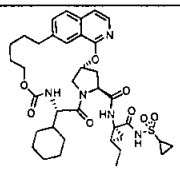
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21, **III-44**		(2*R*,4*S*,7*S*)-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-7-fenil-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	716,3	Véase ejemplo 15	A1, B6
22, **III-45**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-18,20-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclohenicosina-4-carboxamida	722,5	Véase ejemplo 14	A1, B7
23, **III-10**		(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-7-fenil-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-	708,3	Véase ejemplo 15	A1, B8

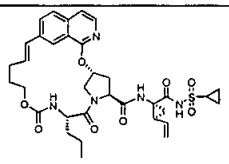
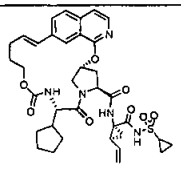
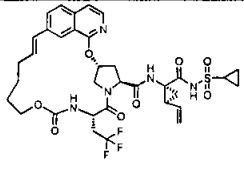
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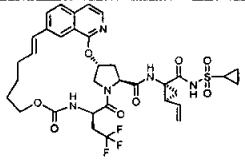
		metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida			
24, **III-46**		(2*R*,4*S*,7*S*-14*E*)-7-bencil-*N*-((1*R*,2*S*)1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)--6,9-dioxo-3,4,6,7,8,9,12,13,14,15-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	728,4	Véase ejemplo 14	A1, B9
25, **III-47**		(2*R*,4*S*)-*N*-((1*S*-1-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-7-fenil-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(enanodiilideno)2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	708,2	Véase ejemplo 15	A1, B10
26, **III-48**		(2*R*,4*S*,7*S*,13*E*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-	680,6	Véase ejemplo 14	A1, B22

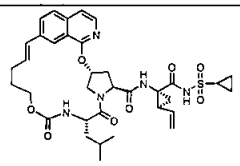
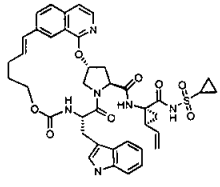
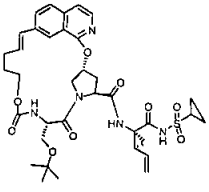
240

		3,4,6,7,8,9,11,12-octahidro-2*H*-15,17-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclooctadecina-4-carboxamida			
27, **III-24**		(2*R*,4*S*,7*S*-14*E*)-7-ciclohexil-*N*-((1*R*,2*S*)1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)--6,9-dioxo-3,4,6,7,8,9,12,13,14,15-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	720,6	Véase ejemplo 14	A1, B8
28, **III-49**		(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*R*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	724,5	Véase ejemplo 15	A3, B8

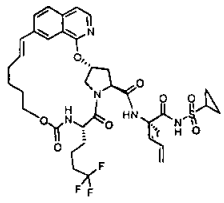
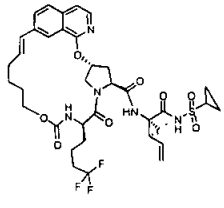
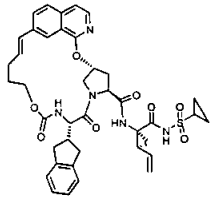
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29, **III-50**		(2*R*,4*S*,7*S*-14*E*)-*N*-((1*R*,2*S*)1-{[(ciclopropilsulfonil) amino]carbonil}-2-vinilciclopropil)--6,9-dioxo-7-dioxo-3,4,6,7,8,9,12,13,14,15-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	680,5	Véase ejemplo 14	A1, B12
30, **III-51**		(2*R*,4*S*,7*S*-14*E*)-7-ciclopentil-*N*-((1*R*,2*S*)1-{[(ciclopropilsulfonil) amino]carbonil}-2-vinilciclopropil)--6,9-dioxo-3,4,6,7,8,9,12,13,14,15-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	706,5	Véase ejemplo 14	A1, B13
31, **III-52**		(2*R*,4*S*,7*S*,15*E*)-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil) amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-7-(2,2,2-trifluoroetil)-3,4,6,7,8,9,11,12,13,14-decahidro-2*H*-	734,4	Véase ejemplo 14, diastereómeros separados	A1, B14

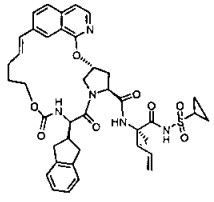
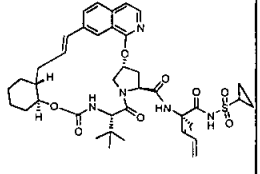
		17,19-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-cicloicosina-4-carboxamida			
32, **III-53**		(2*R*,4*S*,7*R*,15*E*)-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-7-(2,2,2-trifluoroetil)-3,4,6,7,8,9,11,12,13,14-decahidro-2*H*-17,19-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-cicloicosina-4-carboxamida	734,4	Véase ejemplo 14, diastereómeros separados	A1, B14

33, **III-54**		(2*R*,4*S*,7*S*-14*E*)-*N*-((1*R*,2*S*)1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-7-isobutil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	694,5	Véase ejemplo 14	A1, B15
34, **III-55**		(2*R*,4*S*,7*S*-14*E*)-*N*-((1*R*,2*S*)1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-7-(1*H*-indol-3-ilmetil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	767,3	Véase ejemplo 14	A1, B16
35, **III-56**		(2*R*,4*S*,7*S*-14*E*)-7-*terc*-butilmetil)-*N*-((1*S*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-octahidro-2*H*,11*H*-	724,4	Véase ejemplo 14	A1, B17

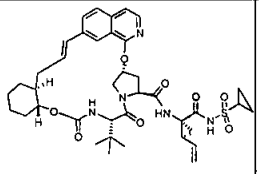
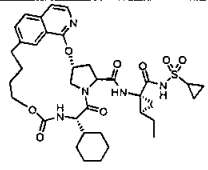
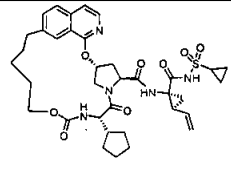
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		16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida			
36, **III-57**		(2*R*,4*S*,7*S*,15*E*)-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-7-(4,4,4-trifluorobutil)-3,4,6,7,8,9,11,12,13,14-decahidro-2*H*-17,19-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-cicloicosina-4-carboxamida	762,3	Véase ejemplo 14, diastereómeros separados	A1, B18
37, **III-58**		(2*R*,4*S*,7*R*,15*E*)-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-7-(4,4,4-trifluorobutil)-3,4,6,7,8,9,11,12,13,14-decahidro-2*H*-17,19-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-cicloicosina-4-carboxamida	762,3	Véase ejemplo 14, diastereómeros separados	A1, B18
38, **III-59**		(2*R*,4*S*,7*S*,14*E*)-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-7-	754,3	Véase ejemplo 14, diastereómeros separados	A1, B19

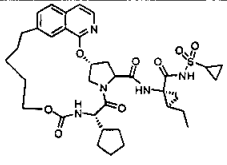
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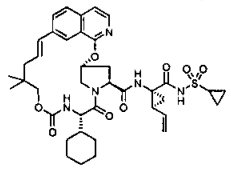
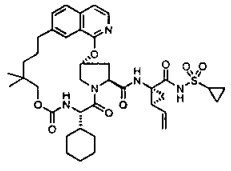
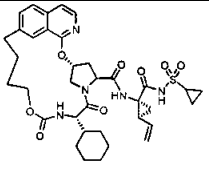
		(2,3-dihidro-1*H*-inden-2-il)-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida			
39, **III-60**		(2*R*,4*S*,7*R*,14*E*)-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-7-(2,3-dihidro-1*H*-inden-2-il)-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza ciclononadecina-4-carboxamida	754,3	Véase ejemplo 14, diastereómeros separados	A1, B19
40, **III-61**		(6*R*,8*S*,11*S*,14a*S*,18a*R*,20*E*)-11-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-10,13-dioxo-7,8,10,11,12,13,15,16,17,18,18a,19-dodecahidro-6*H*,14a*H*-1,22-eteno-6,9-metanopirido[2,3-*k*][1,10,3,6]benzodioxa-diazaciclononadecina-	748,3	Véase ejemplo 14, diastereómeros separados	A1, B20

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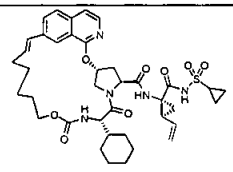
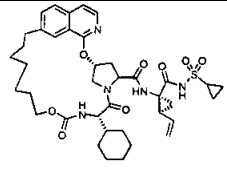
		8-carboxamida			
41, **III-62**		(6*R*,8*S*,11*S*,14a*R*,18a*S*,20*E*)-11-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-10,13-dioxo-7,8,10,11,12,13,15,16,17,18,18a,19-dodecahidro-6*H*,14a*H*-1,22-eteno-6,9-metanopirido[2,3-*k*][1,10,3,6]benzodioxa-diazaciclononadecina-8-carboxamida	748,3	Véase ejemplo 14, diastereómeros separados	A1, B20
42, **III-63**		(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1R,2R)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*-15,17-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-zaciclononadecina-4-carboxamida	710,5	Véase ejemplo 15	A3, B21
43, **III-64**		(2*R*,4*S*,7*S*)-7-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)	708,4	Véase ejemplo 15	A1, B13

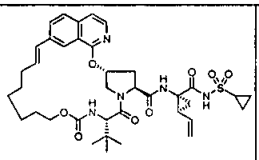
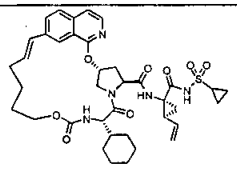
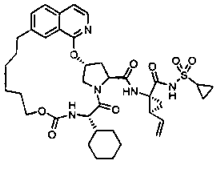
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		amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-7-fenil-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida			
44, **III-65**		(2*R*,4*S*,7*S*)-7-ciclopentil-*N*-((1*R*,2*R*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	710,5	Véase ejemplo 15	A3, B13

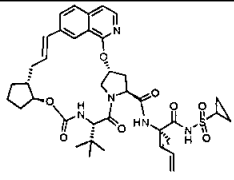
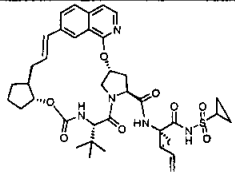
45, **III-66**		(2*R*,4*S*,7*S*-14*E*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-octahidro-2*H*,11*H*-16,18-etanodiilideno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	748,5	Véase ejemplo 14	A1, B23
46, **III-67**		(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-etanodiilideno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	750,5	Véase ejemplo 15	A1, B23
47, **III-68**		(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,1	708,3	Véase ejemplo 15	A1, B21

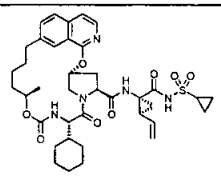
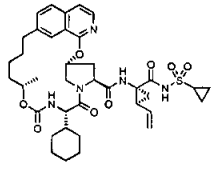
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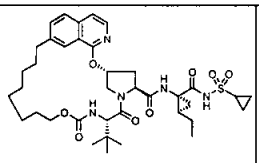
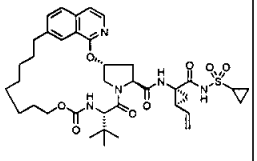
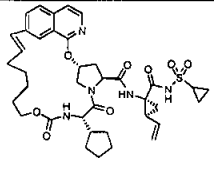
		5-decahidro-2*H*-15,17-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida			
48, **III-69**		(2*R*,4*S*,7*S*,16*E*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-18,20-etanodiilideno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclohenicosina-4-carboxamida	748,3	Véase ejemplo 14	A1, B26
49, **III-70**		(2*R*,4*S*,7*S*)-7-ciclohexil-N-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-18,20-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclohenicosina-4-carboxamida	750,5	Véase ejemplo 15	A1, B26

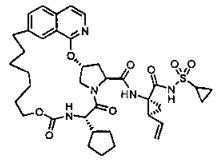
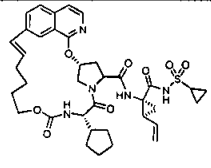
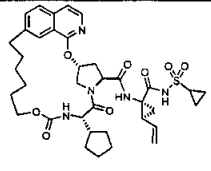
50, **III-71**		(2*R*,4*S*,7*S*,17*E*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*-19,21-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclodocosina-4-carboxamida	736,5	Véase ejemplo 14	A1, B27
51, **III-72**		(2*R*,4*S*,7*S*,*15E*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*-17,19-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	734,4	Véase ejemplo 14	A1, B28
52, **III-73**		(2R,4S,7S)-7-ciclohexil-N-((1R,2S)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-dodecahidro-2H-	736,5	Véase ejemplo 15	A1, B28

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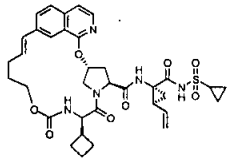
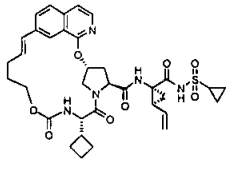
		17,19-(etanodiilideno)-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida			
53, **III-74**		(6*R*,8*S*,11*S*,14a*S*,17a*R*,19*E*)-11-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahidro-6*H*-1,21-eteno-6,9-metanociclopenta[*r*]pi-rido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-8-carboxamida	734,3	Véase ejemplo 14, diastereómeros separados	A1, B29
54, **III-75**		(6*R*,8*S*,11*S*,14a*R*,17a*S*,19*E*)-11-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahidro-6*H*-1,21-eteno-6,9-metanociclopenta[*r*]pi-rido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-8-carboxamida	734,3	Véase ejemplo 14, diastereómeros separados	A1, B29

55, **III-76**		(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-11-metil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	736,5	Véase ejemplo 15, diastereómeros separados	A1, B30
56, **III-77**		(2*R*,4*S*,7*S*,11*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-11-metil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	736,4	Véase ejemplo 15, diastereómeros separados	A1, B30

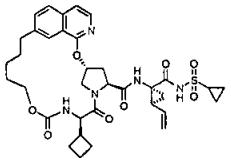
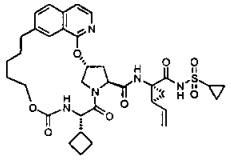
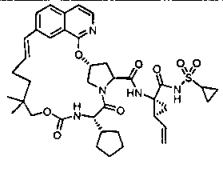
57, **III-78**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*R*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17,18-tetradecahidro-2*H*-19,21-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclodocosina-4-carboxamida	740,6	Véase ejemplo 15	A3,, B27
58, **III-79**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*R*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17,18-tetradecahidro-2*H*-19,21-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclodocosina-4-carboxamida	738,5	Véase ejemplo 15	A1, B27
59, **III-80**		(2*R*,4*S*,7*S*,*15E*)-7-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*-17,19-	720,4	Véase ejemplo 14	A1, B32

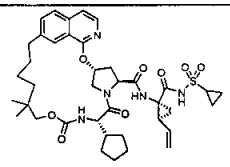
		(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida			
60, **III-81**		(2R,4S,7S)-7-ciclopentil-N-((1R,2S)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-18,20-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiaza-ciclohenicosina-4-carboxamida	722,4	Véase ejemplo 15	A1, B32
61, **III-82**		(2*R*,4*S*,7*S*)-7-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-18,20-etanodiilideno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclohenicosina-4-carboxamida	734,4	Véase ejemplo 14	A1, B31
62, **III-83**		(2*R*,4*S*,7*S*)-7-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-	736,4	Véase ejemplo 15	A1, B31

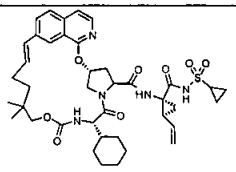
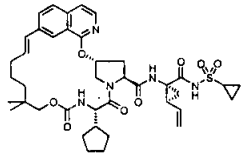
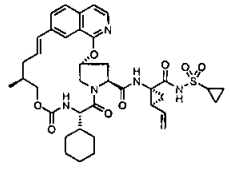
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		vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-dodecahidro-2*H*,11*H*-18,20-etanodiilideno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclohenicosina-4-carboxamida			
63, **III-84**		(2*R*,4*S*,7*R*-14*E*)-7-ciclobutil-*N*-((1*R*,2*S*)1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-octahidro-2*H*,11*H*-16,18-(eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	692,3	Véase ejemplo 14, diastereómeros separados	A1, B33
64, **III-85**		(2*R*,4*S*,7*R*-14*E*)-7-ciclobutil-*N*-((1*R*,2*S*)1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	692,4	Véase ejemplo 14, diastereómeros separados	A1, B33

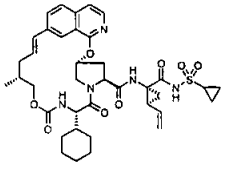
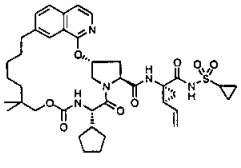
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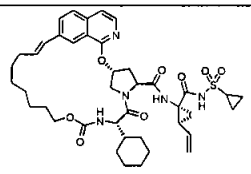
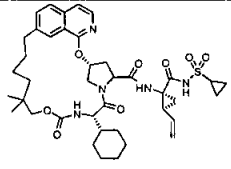
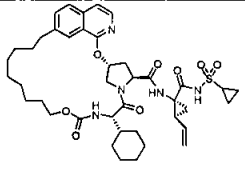
65, **III-86**		(2*R*,4*S*,7*S*)-7-ciclobutil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-7-fenil-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	694,3	Véase ejemplo 15, diastereómeros separados	A1, B33
66, **III-87**		(2*R*,4*S*,7*S*)-7-ciclobutil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-7-fenil-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	694,3	Véase ejemplo 15, diastereómeros separados	A1, B33
67, **III-88**		(2*R*,4*S*,7*S*,*15E*)-7-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,1	748,4	Véase ejemplo 14	A1, B34

		5-decahidro-2*H*-17,19-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida			
68, **III-89**		(2*R*,4*S*,7*S*)-7-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-dodecahidro-2*H*-17,19-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	750,4	Véase ejemplo 15	A1, B34

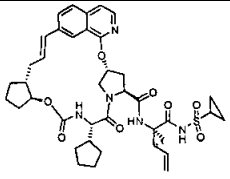
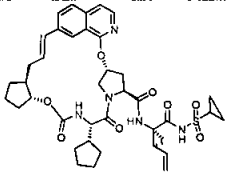
69, **III-90**		(2*R*,4*S*,7*S*,15*E*)-7-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*-17,19-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	762,4	Véase ejemplo 14	A1, B35
70, **III-91**		(2*R*,4*S*,7*S*,16*E*)-7-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-18,20-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclohenicosina-4-carboxamida	762,5	Véase ejemplo 14	A1, B36
71, **III-92**		(2*R*,4*S*,7*S*-14*E*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12-metil-6,9-dioxo-	734,4	Véase ejemplo 14, diastereómeros separados	A1, B39

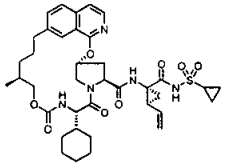
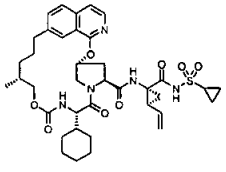
259

		3,4,6,7,8,9,12,13,-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida			
72, **III-93**		(2*R*,4*S*,7*S*,12*R*,14*E*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12-metil-6,9-dioxo-3,4,6,7,8,9,12,13,-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	734,4	Véase ejemplo 14, diastereómeros separados	A1, B39
73, **III-94**		(2*R*,4*S*,7*S*)-7-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-dodecahidro-2*H*,11*H*-18,20-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclohenicosina-4-carboxamida	764,6	Véase ejemplo 15	A1, B36

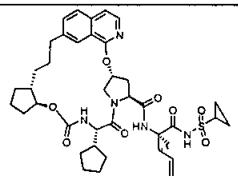
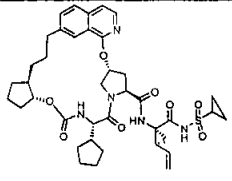
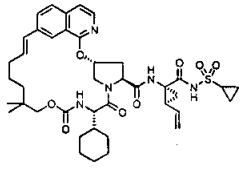
74, **III-95**		(2*R*,4*S*,7*S*,18*E*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17-dodecahidro-2*H*,11*H*-20,22-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclotricosina-4-carboxamida	776,5	Véase ejemplo 14	A1, B37
75, **III-96**		(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16-dodecahidro-2*H*-17,19-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-cicloicosina-4-carboxamida	764,4	Véase ejemplo 15	A1, B35
76, **III-97**		(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-	778,5	Véase ejemplo 15	A1, B37

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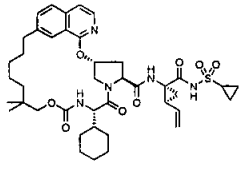
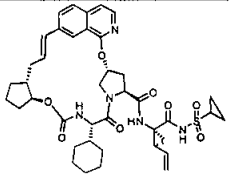
		3,4,6,7,8,9,12,13,14,15,16,17-tetradecahidro-2*H*,11*H*-20,22-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclotricosina-4-carboxamida			
77, **III-98**		(6*R*,8*S*,11*S*,14a*S*,17a*R*,19*E*)-11-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahidro-6*H*-1,21-eteno-6,9-metanociclopenta[*r*]pi-rido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-8-carboxamida	746,4	Véase ejemplo 14, diastereómeros separados	A1, B38
78, **III-99**		(6*R*,8*S*,11*S*,14a*S*,17a*R*,19*E*)-11-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahidro-6*H*-1,21-eteno-6,9-metanociclopenta[*r*]pi-rido[2,3-	746,4	Véase ejemplo 14, diastereómeros separados	A1, B38

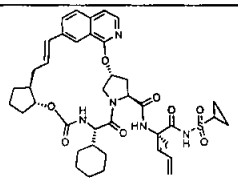
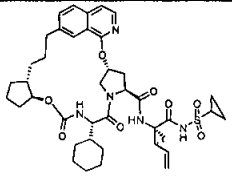
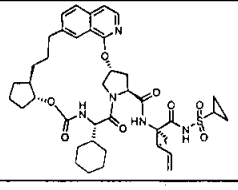
		k][1,10,3,6]dioxadiaza-ciclononadecina-8-carboxamida			
79, **III-100**		(2*R*,4*S*,7*S*,12*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12-metil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	736,3	Véase ejemplo 15, diastereómeros separados	A1, B39
80, **III-101**		(2*R*,4*S*,7*S*,12*R*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12-metil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	736,3	Véase ejemplo 15, diastereómeros separados	A1, B39

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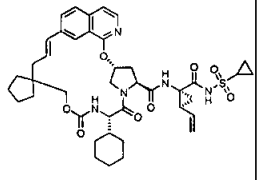
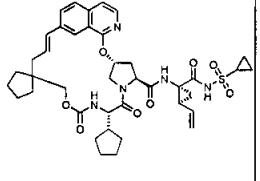
81, **III-102**		(6*R*,8*S*,11*S*,14a*S*,17a*S*)-11-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18,19,20-tetradecahidro-6*H*-1,21-eteno-6,9-metanociclopenta[*r*]pi-rido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-8-carboxamida	748,3	Véase ejemplo 15, diastereómeros separados	A1, B38
82, **III-103**		(6*R*,8*S*,11*S*,14a*S*,17a*R*)-11-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18,19,20-tetradecahidro-6*H*-1,21-eteno-6,9-metanociclopenta[*r*]pi-rido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-8-carboxamida	748,3	Véase ejemplo 15, diastereómeros separados	A1, B38
83, **III-104**		(2*R*,4*S*,7*S*,16*E*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-	776,3	Véase ejemplo 14	A1, B40

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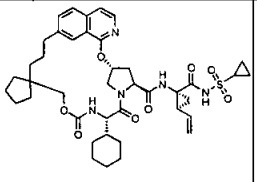
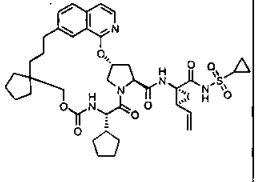
		12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-18,20-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclohenicosina-4-carboxamida			
84, **III-105**		(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16,17-dodecahidro-2*H*,11*H*-18,20-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclohenicosina-4-carboxamida	778,4	Véase ejemplo 15	A1, B40
85, **III-106**		(6*R*,8*S*,11*S*,14a*S*,17a*R*,19*E*)-11-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahidro-6*H*-1,21-eteno-6,9-metanociclopenta[*r*]pi-rido[2,3-*k*][1,10,3,6]dioxadiaz	760,5	Véase ejemplo 14, diastereómeros separados	A1, B41

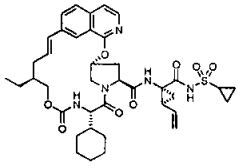
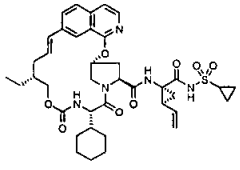
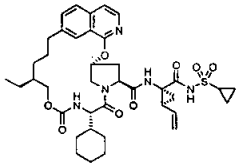
		a-ciclononadecina-8-carboxamida			
86, **III-107**		(6*R*,8*S*,11*S*,14a*S*,17a*R*,19*E*)-11-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18-dodecahidro-6*H*-1,21-eteno-6,9-metanociclopenta[*r*]pi-rido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-8-carboxamida	760,5	Véase ejemplo 14, diastereómeros separados	A1, B41
87, **III-108**		(6*R*,8*S*,11*S*,14a*S*,17a*S*)-11-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18,19,20-tetradecahidro-6*H*-1,21-eteno-6,9-metanociclopenta[*r*]pi-rido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-8-carboxamida	762,6	Véase ejemplo 15, diastereómeros separados	A1, B41
88, **III-109**		(6*R*,8*S*,11*S*,14a*S*,17a*R*)-11-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)	762,6	Véase ejemplo 15, diastereómeros separados	A1, B41

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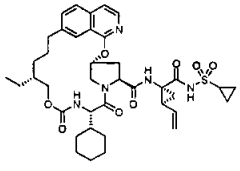
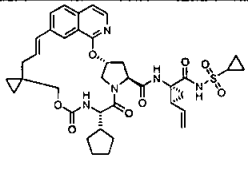
		amino]carbonil}-2-vinilciclopropil)-10,13-dioxo-7,8,10,11,12,13,14a,15,16,17,17a,18,19,20-tetradecahidro-6*H*-1,21-eteno-6,9-metanociclopenta[*r*]pi-rido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-8-carboxamida			
89, **III-110**		(2'*R*,4'*S*,7'*S*,14'*E*)-7'-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6',9'-dioxo-3',4',6',7',8',9'-hexahidro-2'*H*,13'*H*-espiro[ciclopentano-1,12'-[1,10]dioxa[5,8,21]triaza-za[16,18]eteno[2,5]metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina]-4'-carboxamida	774,2	Véase ejemplo 14	A1, B42
90, **III-111**		(2'*R*,4'*S*,7'*S*,14'*E*)-7'-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6',9'-dioxo-3',4',6',7',8',9'-hexahidro-2'*H*,13'*H*-espiro[ciclopentano-	760,3	Véase ejemplo 14	A1, B47

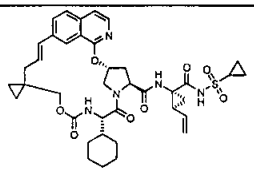
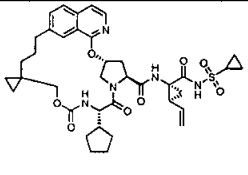
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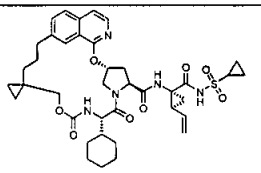
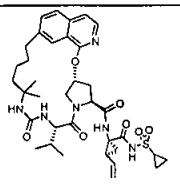
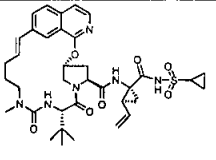
		1,12'-[1,10]dioxa[5,8,21]tria-za[16,18]eteno[2,5]metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina]-4'-carboxamida			
91, **III-112**		(2'*R*,4'*S*,7'*S*)-7'-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6',9'-dioxo-3',4',6',7',8',9',14',15'-octahidro-2'*H*,13'*H*-espiro[ciclopentano-1,12'-[1,10]dioxa[5,8,21]tria-za[16,18]eteno[2,5]metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina]-4'-carboxamida	776,4	Véase ejemplo 15	A1, B42
92, **III-113**		(2'*R*,4'*S*,7'*S*)-7'-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6',9'-dioxo-3',4',6',7',8',9',14',15'-octahidro-2'*H*,13'*H*-espiro[ciclopentano-1,12'-[1,10]dioxa[5,8,21]tri	762,3	Véase ejemplo 15	A1, B47

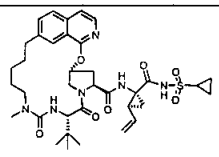
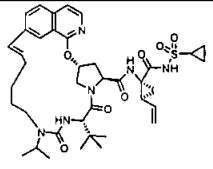
		a-za[16,18] eteno[2,5]metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina]-4'-carboxamida			
93, **III-114**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12-etil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	748,4	Véase ejemplo 14, diastereómeros separados	A1, B43
94, **III-115**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12-etil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	748,4	Véase ejemplo 14, diastereómeros separados	A1, B43
95, **III-116**		(2*R*,4*S*,7*S*,*12S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)	750,4	Véase ejemplo 15, diastereómeros separados	A1, B43

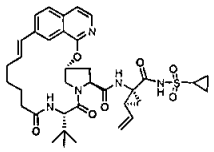
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		amino]carbonil}-2-vinilciclopropil)-12-etil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida			
96, **III-117**		(2*R*,4*S*,7*S*,12*R*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12-etil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiaza-ciclononadecina-4-carboxamida	750,5	Véase ejemplo 15, diastereómeros separados	A1, B43
97, **III-118**		(2'*R*,4'*S*,7'*S*,14'*E*)-7'-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6',9'-dioxo-3',4',6',7',8',9'-hexahidro-2'*H*,13'*H*-espiro[ciclopropano-1,12'-[1,10]dioxa[5,8,21]tria-za[16,18](etanodiilideno)[2,5]me-tanopirido[2,3-	732,3	Véase ejemplo 14	A1, B44

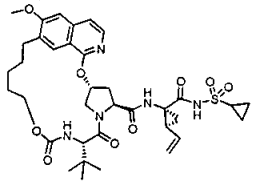
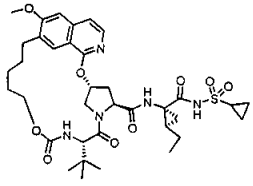
98, **III-119**		(2'*R*,4'*S*,7'*S*,14'*E*)-7'-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil) amino]carbonil}-2-vinilciclopropil)-6',9'-dioxo-3',4',6',7',8',9'-hexahidro-2'*H*,13'*H*-espiro[ciclopropano-1,12'-[1,10]dioxa[5,8,21]triaza[16,18] (etanodiilideno)[2,5]metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina]-4'-carboxamida	746,3	Véase ejemplo 14	A1, B45
99, **III-120**		(2'*R*,4'*S*,7'*S*)-7'-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil) amino]carbonil}-2-vinilciclopropil)-6',9'-dioxo-3',4',6',7',8',9'-hexahidro-2'*H*,13'*H*-espiro[ciclopropano-1,12'-[1,10]dioxa[5,8,21]triaza[16,18] (etanodiilideno)[2,5]metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina]-4'-carboxamida	734,3	Véase ejemplo 15	A1, B44

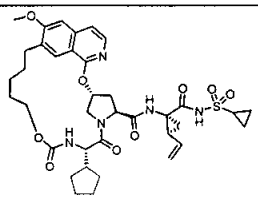
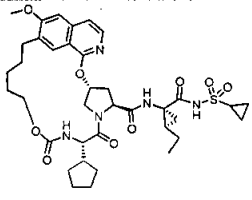
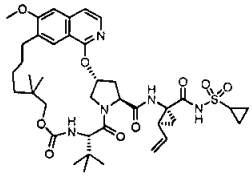
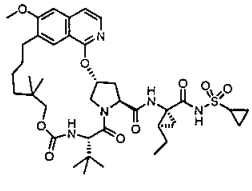
100, **III-121**		(2'*R*,4'*S*,7'*S*)-7'-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil) amino]carbonil}-2-vinilciclopropil)-6',9'-dioxo-3',4',6',7',8',9',14',15'-octahidro-2'*H*,13'*H*-espiro[ciclopropano-1,12'-[1,10]dioxa[5,8,21]triaza[16,18](etanodiilideno)[2,5]metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina]-4'-carboxamida	748,3	Véase ejemplo 15	A1, B45
101, **III-122**		(2*R*,4*S*,7*S*)-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil) amino]carbonil}-2-vinilciclopropil)-7-isopropil-11,11-dimetil-6,9-dioxo-3,4,6,7,8,9,10,11,12,13,14,15-dodecahidro-2*H*-16,18-eteno-2,5-metanopirido[3,2-*r*][1,5,8,10]oxatriazaciclononadecina-4-carboxamida	709,4	Véase ejemplo 15	A1, B50
102, **III-28**		(2*R*,4*S*,7*S*,14*E*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil) amino]carbonil}-2-vinilciclopropil)-10-	707,6	Véase ejemplo 14	A1, B51

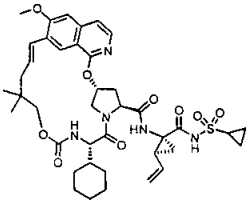
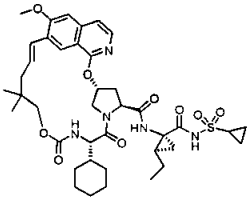
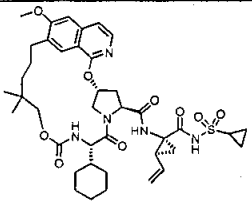
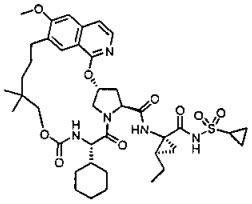
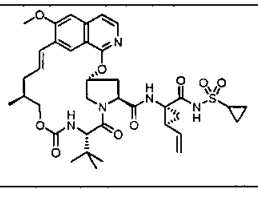
		metil-6,9-dioxo-3,4,6,7,8,9,10,11,12,13-decahidro-2*H*-16,18-(etanodiilideno)-2,5-metanopirido[3,2-*r*][1,5,8,10]oxatriazaci-clononadecina-4-carboxamida			
103, **III-14**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil) amino]carbonil}-2-vinilciclopropil)-10-metil-6,9-dioxo-3,4,6,7,8,9,10,11,12,13,14,15-dodecahidro-2*H*-16,18-(etanodiilideno)-2,5-metanopirido[3,2-*r*][1,5,8,10]oxatriazaci-clononadecina-4-carboxamida	709,7	Véase ejemplo 15	A1, B51
104, **III-123**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil) amino]carbonil}-2-vinilciclopropil)-10-isopropil-6,9-dioxo-3,4,7,8,9,10,11,12,13,14-decahidro-2*H*,6*H*-17,19-eteno-2,5-metanopirido[3,2-*s*][1,5,8,10]oxatriazaci-cloicosina-4-carboxamida	749,4	Véase ejemplo 14	A1, B52

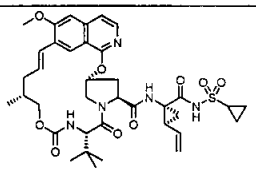
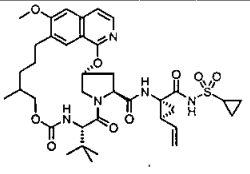
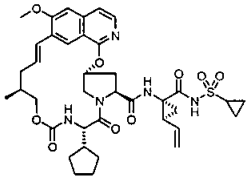
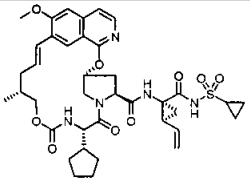
105, **III-25**		(2R,4S,7S)-7-terc-butil-N-((1R,2S)-1-{[(ciclopropilsulfonil) amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,10,11,12,13-decahidro-2H-16,18-etanodiilideno-2,5-metanopirido[3,2-r][1,5,8]oxadiazaciclononadecina-4-carboxamida	692,6	Véase ejemplo 14	A1, B53

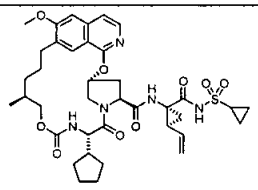
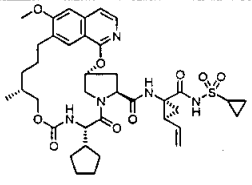
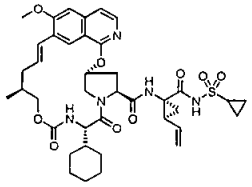
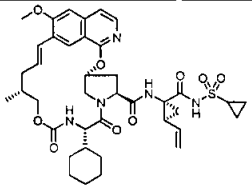
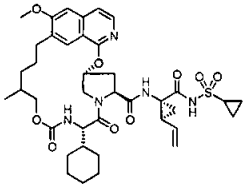
Usando los procedimientos apropiados y los intermedios A, B y C apropiados se prepararon los siguientes compuestos.

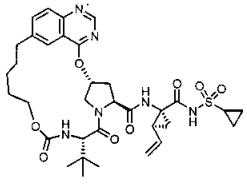
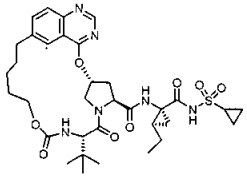
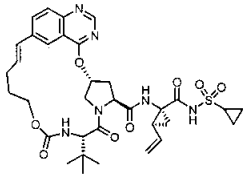
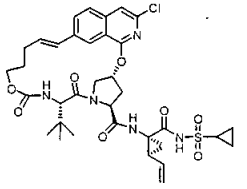
Ej.	Estructura	Nombre	EMBR $(M+H)^+$	Preparados usando los intermedios apropiados de acuerdo con el procedimiento siguiente.	Int.
106, **III-12**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-23-metoxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	726,5	Véase ejemplo 15	A1, B2, C1
107, **III-124**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*R*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-	728,6	Véase ejemplo 15	A3, B2, C1

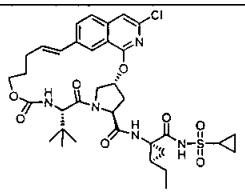
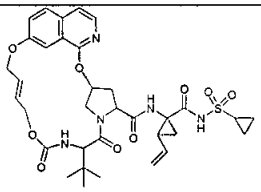
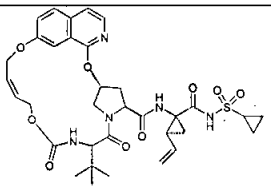
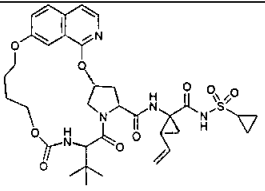
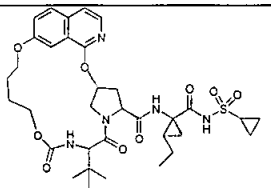
		k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida			
108, **III-125**		(2*R*,4*S*,7*S*)-7-ciclobutil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	738,5	Véase ejemplo 15	A1, B13, C1
109, **III-126**		(2*R*,4*S*,7*S*)-7-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	740,6	Véase ejemplo 15	A3, B13, C1
110, **III-127**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16-dodecahidro-2*H*-17,19-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	768,6	Véase ejemplo 15	A1, B25, C1
111, **III-128**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*R*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-24-metoxi-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15,16-dodecahidro-2*H*-17,19-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	770,7	Véase ejemplo 15	A3, B25, C1

112, **III-129**		(2*R*,4*S*,7*S*-14*E*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-23-metoxi-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-etanodiilideno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	778,6	Véase ejemplo 14	A1, B23, C1
113, **III-130**		(2*R*,4*S*,7*S*-14*E*)-7-ciclohexil-*N*-((1*R*,2*R*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-23-metoxi-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	780,6	Véase ejemplo 14	A3, B23, C1
114, **III-131**		(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-23-metoxi-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	780,5	Véase ejemplo 15	A1, B23, C1
115, **III-132**		(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-23-metoxi-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	782,6	Véase ejemplo 15	A3, B23, C1
116, **III-133**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-23-metoxi-12,12-dimetil-	738,3	Véase ejemplo 14, diastereómeros separados	A1, B46, C1

		6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida			
117, **III-134**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-23-metoxi-12-metil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	738,3	Véase ejemplo 14, diastereómeros separados	A1, B46, C1
118, **III-135**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-23-metoxi-12-metil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	740,2	Véase ejemplo 15	A1, B46, C1
119, **III-136**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-23-metoxi-12-metil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	750,4	Véase ejemplo 14, diastereómeros separados	A1, B48, C1
120, **III-137**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-23-metoxi-12-metil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	750,4	Véase ejemplo 14, diastereómeros separados	A1, B48, C1

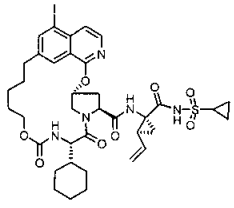
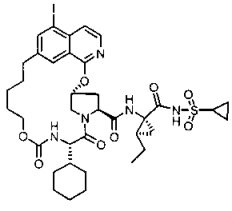
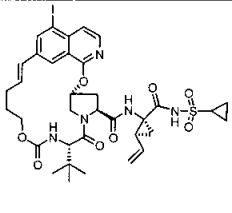
121, **III-138**		(2*R*,4*S*,7*S*,12S)-7-ciclopentil--((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-23-metoxi-12-metil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	752,4	Véase ejemplo 15, diastereómeros separados	A1, B48, C1
122, **III-139**		(2*R*,4*S*,7*S*,12*R*)-7-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-23-metoxi-12-metil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	752,5	Véase ejemplo 15, diastereómeros separados	A1, B48, C1
123, **III-140**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-23-metoxi-12-metil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	764,3	Véase ejemplo 14, diastereómeros separados	A1, B39, C1
124, **III-141**		(2*R*,4*S*,7*S*,12*S*,14*E*)-7ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-23-metoxi-12-metil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	764,3	Véase ejemplo 14, diastereómeros separados	A1, B39, C1
125, **III-142**		(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-23-metoxi-12-metil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	766,4	Véase ejemplo 15	A1, B39, C1

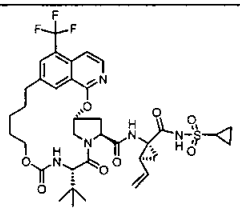
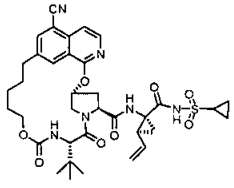
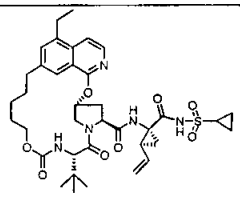
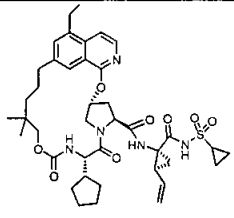
126, **III-20**		(15*S*,18*S*,20*R*)-15-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahidro-7*H*,18*H*-4,6-eteno-17,20-metanopirimido[4,5-*k*][1,10,3,6]dioxadiazaciclononadecina-18-carboxamida	697,5	Véase ejemplo 15	A1, B2, C2
127, **III-143**		(15*S*,18*S*,20*R*)-15-*terc*-butil-*N*-((1*R*,2*R*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahidro-7*H*,18*H*-4,6-eteno-17,20-metanopirimido[4,5-*k*][1,10,3,6]dioxadiazaciclononadecina-18-carboxamida	699,5	Véase ejemplo 15	A3, B2, C2
128, **III-34**		(7*E*,15*S*,18*S*,20*R*)-15-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-13,16-dioxo-10,11,13,14,15,16,19,20-octahidro-9*H*,18*H*-4,6-eteno-17,20-metanopirimido[4,5-*k*][1,10,3,6]dioxadiazaciclononadecina-18-carboxamida	695,4	Véase ejemplo 14	A1, B2, C2
129, **III-31**		(2*R*,4*S*,7*S*-14*E*)-7-*terc*-butil-20-cloro-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)--6,9-dioxo-3,4,6,7,8,9,12,13,14,15-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	728,5	Véase ejemplo 14	A1, B2, C3

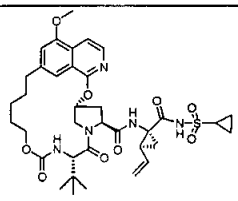
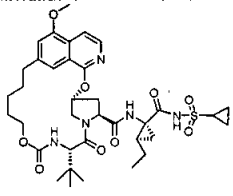
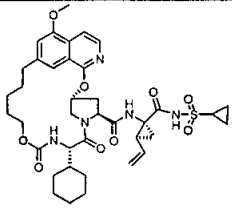
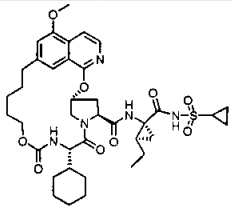
130, **III-32**		(2*R*,4*S*,7*S*-14*E*)-7-*terc*-butil-20-cloro-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	730,5	Véase ejemplo 14	A3, B2, C3
131, **III-144**		(2*R*,4*S*,7*S*-14*E*)-7-*terc*-butil-*N*-((1*S*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,14-octahidro-2*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	696,5	Véase ejemplo 14, isómeros de olefina separados	A1, B49, C4
132, **III-145**		(2*R*,4*S*,7*S*,12*Z*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,14-octahidro-2*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	696,5	Véase ejemplo 14, isómeros de olefina separados	A1, B49, C4
133, **III-146**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,14-octahidro-2*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	698,4	Véase ejemplo 15	A1, B49, C4
134, **III-147**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahidro-2*H*-16,18-eteno-2,5-metanopirido[2,3-	700,5	Véase ejemplo 15	A3, B49, C4

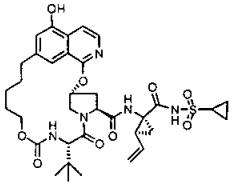
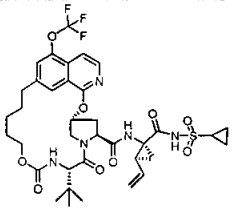
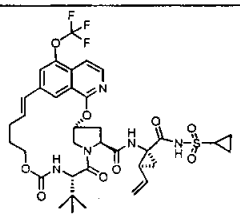
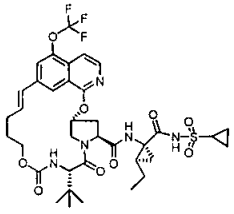
		k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida			

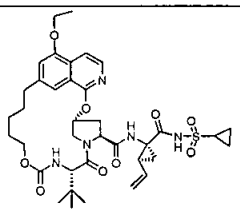
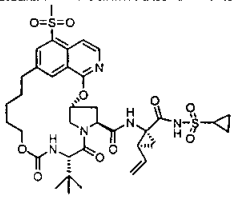
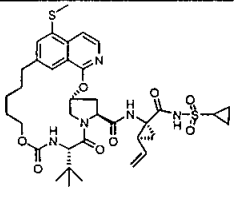
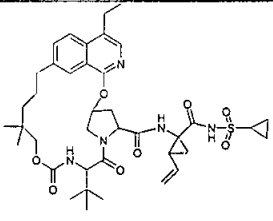
Usando los procedimientos apropiados y los intermedios A, B y C apropiados, se prepararon los siguientes compuestos.

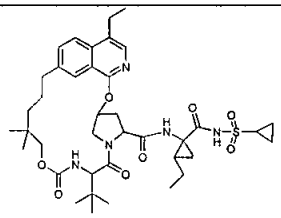
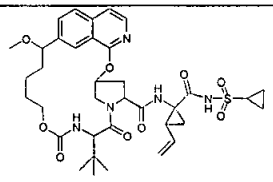
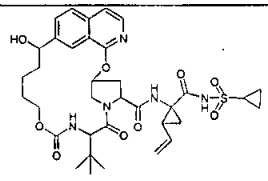
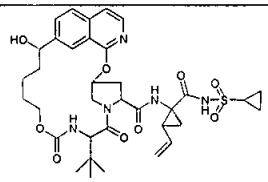
Ej.	Estructura	Nombre	EMBR (M+H)$^+$	Preparados usando los intermedios apropiados de acuerdo con el procedimiento siguiente.	Int.
135, **III-148**		(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-22-yodo-6,9-dioxo-7-fenil-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	848,4	Véase ejemplo 13	A1, B8
136, **III-149**		(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-22-yodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	850,5	Véase ejemplo 13	A3, B8
137, **III-150**		(2*R*,4*S*,7*S*-14*E*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-22-yodo-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-	820,2	Véase ejemplo 14, etapa 5	A1, D1

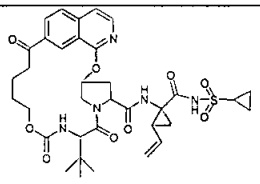
		carboxamida			
138, **III-151**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-22-(trifluorometil)-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	764,3	Véase ejemplo 14, etapas 4 y 5	A1, D5
139, **III-152**		(2*R*,4*S*,7*S*)-7-*terc*-butil-22-ciano-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	721,6	Véase ejemplo 14, etapas 4 y 5	A1, D6
140, **III-153**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-22-ciano-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	724,7	Véase ejemplo 14, etapas 4 y 5	A1, D7
141, **III-154**		(2*R*,4*S*,7*S*)-7-ciclopentil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-22-etil-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodililideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	764,4	Véase ejemplo 14, etapas 4 y 5	A1, D8

142, **III-155**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-22-metoxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	726,7	Véase ejemplo 14, etapa 5	A1, D9
143, **III-156**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*R*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-22-metoxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	728,5	Véase ejemplo 14, etapa 5	A3, D9
144, **III-157**		(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-22-metoxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	752,5	Véase ejemplo 14, etapa 5	A1, D10
145, **III-158**		(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-22-metoxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	754,5	Véase ejemplo 14, etapa 5	A3, D10

146, **III-159**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-22-hidroxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	712,5	Véase ejemplo 14, etapa 5	A1, D11
147, **III-160**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-22-(trifluorometoxi)-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	780,5	Véase ejemplo 15	A1, D15
148, **III-161**		(2*R*,4*S*,7*S*-14*E*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-22-(trifluorometoxi)-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	778,4	Véase ejemplo 14, etapas 4 y 5	A1, D15
149, **III-162**		(2*R*,4*S*,7*S*-14*E*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-6,9-dioxo-22-(trifluorometoxi)-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	780,5	Véase ejemplo 14, etapas 4 y 5	A3, D15

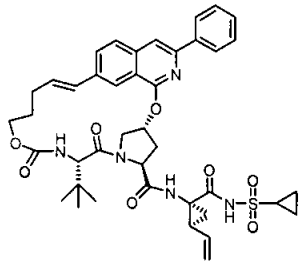
150, **III-163**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-22-etoxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	740,5	Véase ejemplo 14, etapas 4 y 5	A1, D12
151, **III-164**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-22-(metilsulfonil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	774,5	Véase ejemplo 14, etapas 4 y 5	A1, D13
152, **III-165**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-22-(metiltio)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	742,5	Véase ejemplo 14, etapas 4 y 5	A1, D14
153, **III-166**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-19-etil-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	752,6	Véase ejemplo 14, etapas 4 y 5	A1, D16

154, **III-167**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*R*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-etilciclopropil)-19-etil-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	754,5	Véase ejemplo 14, etapas 4 y 5	A3, D16
155, **III-168**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-15-metoxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	726,3	Véase ejemplo 14, etapa 5	A1, D2
156, **III-169**		(2*R*,4*S*,7*S*,15*R*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-15-metoxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	712,6	Véase ejemplo 14, etapas 4 y 5, diastereómeros separados	A1, D3
157, **III-170**		(2*R*,4*S*,7*S*,15*R*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-15-hidroxi-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	712,6	Véase ejemplo 14, etapas 4 y 5, diastereómeros separados	A1, D3

158, **III-171**		(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9,15-trioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida	710,5	Véase ejemplo 14, etapas 4 y 5	A1, D4

EJEMPLO 159

(2*R*,4*S*,7*S*,14*E*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-20-fenil-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-172**)

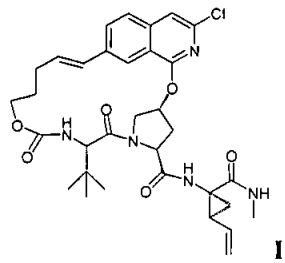


III-172

A una solución de (2R,4S,7S,14E)-7-terc-butil-20-cloro-N-((1R,2S)-1-{[(ciclopropilsulfonil) amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2H,11H-16,18-(etanodiilideno)-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (EJEMPLO 129, **III-31**) (25 mg, 0,034 mmol) in THF (2 ml) se añadió ácido fenilbórico (5,6 mg, 0,0447 mmol), carbonato de cesio (56 mg, 0,16 mmol) y triciclohexilfosfina (1,0 mg, 0,34 mmol). A esta mezcla se añadió $Pd_2(dba)_3$ (1,6 mg, 0,00172 mmol) y la mezcla se calentó a 80°C durante 2 horas. La reacción se concentró y se purificó mediante HPLC en fase reversa dando compuesto del título (20 mg) como una espuma. EMBR (ESI) *m/z* 770,6 [$(M+H)^+$; calcd. para $C_{41}H_{48}N_5O_8S$: 770,3].

EJEMPLO 160

(2*R*,4*S*,7*S*-14*E*)-7-*terc*-butil-20-cloro-*N*-((1*R*,2*S*)-1-[(metilamino)carbonil]-2-vinilciclopropil}-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-173**)

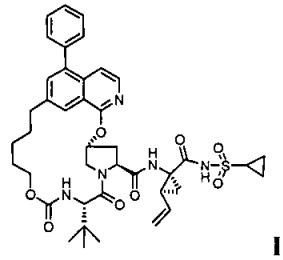


III-173

A una solución de (2*R*,4*S*,7*S*,14*E*)-7-*terc*-butil-20-cloro-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (EJEMPLO 129, **III-31**) (20 mg, 0,0275 mmol) en THF (1 ml) se añadió metilamina acuosa al 40% y la mezcla se calentó en un reactor de microondas a 180°C durante 30 min. La mezcla de reacción se concentró y purificó mediante HPLC en fase reversa dando 2 mg de producto como espuma. EMBR (ESI) $^{m/z}$ 638,5 [(M+H)+; calcd. para $C_{33}H_{41}ClN_5O_6$: 638,3].

EJEMPLO 161

(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-22-fenil-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-174**)

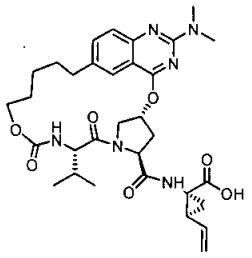


III-174

A un tubo sellado que contiene (2R,4S,7S)-7-terc-butil-N-((1R,2S)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-22-yodo-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-38**) (EJEMPLO 13) (17 mg, 0,021 mmol) en tolueno (1 ml) se añadió ácido fenilbórico (3 mg, 1,1 mmol), carbonato de sodio 2M (0,021 ml, 0,041 mmol), y tetrakis(trifenilfosfina)paladio (1 mg, 0,001 mmol). La mezcla de reacción se calentó a 80°C durante 10 h. La mezcla de reacción se diluyó con EtOAc, se lavó con HCl 1N, salmuera, se secaron los productos orgánicos, y se concentraron a un sólido amarillo. El aceite resultante se purificó mediante HPLC en fase reversa produciendo el compuesto del título como un sólido amarillo. (5 mg). EMBR (ESI) m/z 772,7 [(M+H)+; calcd. para $C_{41}H_{50}N_5O_8S$: 772,3].

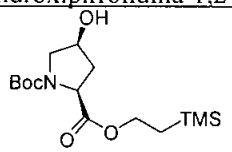
EJEMPLO 162

Ácido (1*R*,2*S*)-1-({[(15*S*,18*S*,20*R*)-2-(dimetilamino)-15-isopropil-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahidro-7*H*,18*H*-4,6-(etanodiilideno)-17,20-metanopirimido[4,5-*k*][1,10,3,6]dioxadiazaciclononadecin-18-il]carbonil}amino)-2-vinilciclopropanocarboxílico (**III-175**)



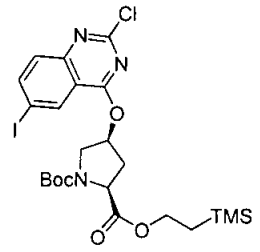
III-175

Etapa 1: 2-[2-(trimetilsilil)etil] (2*S*,4*S*)-4-hidroxipirrolidina-1,2-dicarboxilato de 1-*terc*-butilo



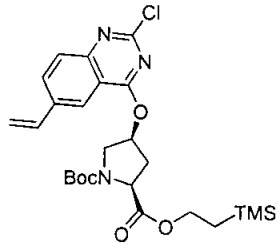
A una solución de (2*S*,4*S*)-4-hidroxipirrolidina-1,2-dicarboxilato de 1-*terc*-butil-2-metilo (1,0 g, 4,08 mmol) en THF (30 ml) y agua (6 ml) enfriada a 0°C se añadió una solución 1 M de NaOH (6,12 ml, 6,12 mmol). La mezcla se agitó a esta temperatura durante 2 h. En este momento, TLC (100% Et_2O) indicó la consunción completa del material de partida y formación de un compuesto más polar (tinción con $KMnO_4$). El THF se retiró después a vacío, y el pH de la fase de agua se ajustó a 2-3 con HCl 1 N. La mezcla se extrajo después con EtOAc, se secó sobre $MgSO_4$, y el disolvente se retiró a vacío. CL-EM indicó que el producto principal tuvo la masa deseada. El compuesto en bruto se llevó en PhMe (30 ml), O-2-trimetilsilil-N,N'-diisopropilisourea (T. Eicher, M. Ott, A. Speicher *Synthesis*, 1996, 755-762) (1,99 g, 8,15 mmol) se añadió, y la mezcla se sometió a reflujo durante 2 h. En este tiempo, se añadió EtOAc al 30%/hexanos (10 ml) y se filtró la mezcla. El disolvente se eliminó después a vacío, y el producto en bruto se purificó sobre sílice (EtOAc al 40%/hex) proporcionando el compuesto del título (1,23 g). EMBR $(M+H)^+ = 332,2$.

Etapa 2: 1-terc-butil 2-[2-(trimetilsilil)etil] (2S,4S)-4-[(2-cloro-6-yodoquinazolin-4-il)oxi]pirrolidina-1,2-dicarboxilato



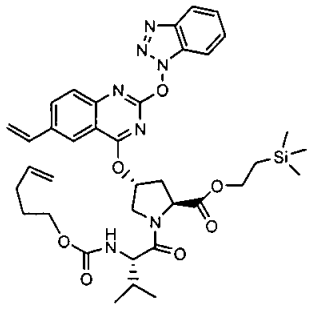
A una solución del producto de la etapa 1 (1,02 g, 3,08 mmol) y 2,4-dicloro-6-yodoquinazolina (1,0 g, 3,08 mmol) (M. C. Benutti y col., *J. Med. Chem.* **1988**, *31*, 2136-2145) en tolueno (25 ml) se añadió hidruro de sodio al 60% (600 mg, en exceso) y la mezcla de reacción se agitó a temperatura ambiente durante 45 min. La mezcla de reacción se fraccionó cuidadosamente entre tampón de citrato de pH 5,2 frío y EtOAc. La fase orgánica se lavó con agua y salmuera, se secó sobre Na_2SO_4 y el disolvente se evaporó. El producto en bruto se purificó mediante cromatografía en sílice (EtOAc hexano 0-30%) dando el compuesto del título (0,76 gm).

Etapa 3: 1-terc-butil 2-[2-(trimetilsilil)etil] (2S,4S)-4-[(2-cloro-6-vinilquinazolin-4-il)oxi]pirrolidina-1,2-dicarboxilato



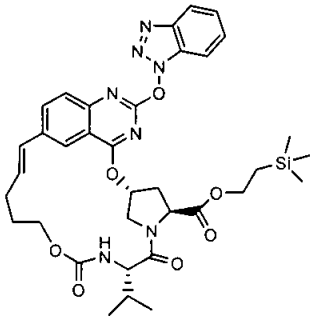
El compuesto del título se preparó a partir de (2S,4S)-4-[(2-cloro-6-iodoquinazolin-4-il)oxi]pirrolidina-1,2-dicarboxilato de 1-terc-butil 2-[2-(trimetilsilil)etil] como se describe en la etapa 3 del ejemplo 1.

Etapa 4: 2-(trimetilsilil)etil N-[(pent-4-en-1-iloxi)carbonil]-L-valil-(4R)-4-{[2-(1H-1,2,3-benzotriazol-1-iloxi)-6-vinilquinazolin-4-il]oxi}-L-prolinato



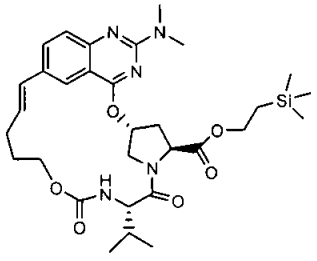
Una solución of 1-terc-butil 2-[2-(trimetilsilil)etil] (2S,4S)-4-[(2-cloro-6-vinilquinazolin-4-il)oxi]pirrolidina-1,2-dicarboxilato (495 mg, 0,95 mmol) en EtOAC (10 ml) se enfrió a 0°C y se hizo burbujear a su través cloruro de hidrógeno durante 30 min. Se hizo burbujear a su través nitrógeno durante 5 min, el disolvente se evaporó y el residuo se azeotropó con EtOAc (x3). El residuo se disolvió en DMF (5 ml) y se añadieron DIPEA (479 µl, 2,67 mmol), intermedio B3 (307 mg, 1,34 mmol) y TBTU (472 mg, 1,47 mmol). La mezcla de reacción se agitó a temperatura ambiente durante toda una noche y se fraccionó entre tampón de citrato pH 5,2 y EtOAc. La fase orgánica se lavó con agua, $NaHCO_3$ saturado, salmuera, se secó sobre Na_2SO_4 y el disolvente se evaporó. El producto en bruto se purificó mediante cromatografía en sílice (EtOAc hexano 5-50%) dando el compuesto del título (0,76 gm). EMBR $(M+H)^+$ = 702,3.

Etapa 5: 2-(trimetilsilil)etil (7*E*,15*S*,18*S*,20*R*)-2-(1*H*-1,2,3-benzotriazol-1-iloxi)-15-isopropil-13,16-dioxo-10,11,13,14,15,16,19,20-octahidro-9*H*,18*H*-4,6-(etanodiilideno)-17,20-metanopirimido[4,5-*k*][1,10,3,6]dioxadiazaciclononadecina-18-carboxilato



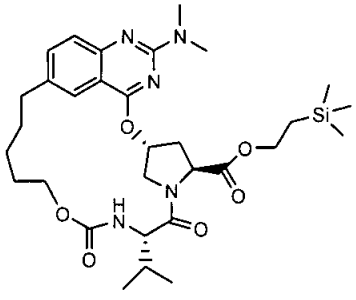
Según el compuesto del título se preparó a partir del producto de la etapa 7 usando el procedimiento descrito en la etapa 4 del ejemplo 1.

Etapa 6: 2-(trimetilsilil)etil (7*E*,15*S*,18*S*,20*R*)-2-(dimetilamino)-15-isopropil-13,16-dioxo-10,11,13,14,15,16,19,20-octahidro-9*H*,18*H*-4,6-(etanodiilideno)-17,20-metanopirimido[4,5-*k*][1,10,3,6]dioxadiazaciclononadecina-18-carboxilato:



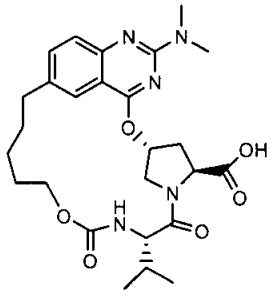
A una solución del producto a partir de la etapa 4 (130 mg, 0,185 mmol) en DCM (2 ml) se añadió una solución de dimetilamina 2,0 M en THF (0,5 ml, 1,0 mmol) y la mezcla se agitó a temperatura ambiente durante 3 h. Se añadió dimetilamina 2,0 M adicional en THF (0,5 ml, 1,0 mmol) y la reacción se agitó durante 18 horas adicionales. La mezcla de reacción se concentró a un aceite y se cromatografió en sílice usando una elución de gradiente de diclorometano a acetona al 5%/diclorometano dando el compuesto del título como un aceite (92 mg). EMBR $(M+H)^+ = 612,4$.

Etapa 7: 2-(trimetilsilil)etil (15*S*,18*S*,20*R*)-2-(dimetilamino)-15-isopropil-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahidro-7*H*,18*H*-4,6-(etanodiilideno)-17,20-metanopirimido[4,5-*k*][1,10,3,6]dioxadiazaciclononadecina-18-carboxilato



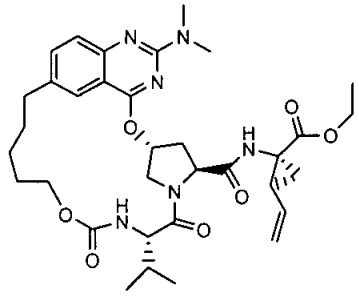
A una solución del aceite de etapa 5 (92 mg, 0,151 mmol) en acetato de etilo (20 ml) y bajo nitrógeno se añadió paladio al 10% en carbono (20 mg) y la mezcla se agitó bajo nitrógeno (1,01325 x 10^5 pascales (1 atm)) durante 18 horas. La mezcla de reacción se filtró y se concentró a vacío dando el producto como un aceite (92 mg). EMBR $(M+H)^+ = 614,3$.

Etapa 8: ácido (15*S*,18*S*,20*R*)-2-(dimetilamino)-15-isopropil-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahidro-7*H*,18*H*-4,6-(etanodiilideno)-17,20-metanopirimido[4,5-*k*][1,10,3,6]dioxadiazaciclononadecina-18-carboxílico



A una solución del aceite de la etapa 6 (92 mg, 0,151 mmol) en THF (5 ml), bajo nitrógeno, se añadió una solución de fluoruro de tetrabutilamonio 1,0 M en THF (0,9 ml, 0,90 mmol). La mezcla de reacción se agitó durante 0,5 hr y después se concentró a vacío dando un aceite. EMBR $(M+H)^+ = 514$.

Etapa 9: (1*R*,2*S*)-1-({[(15*S*,18*S*,20*R*)-2-(dimetilamino)-15-isopropil-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahidro-7*H*,18*H*-4,6-(etanodiilideno)-17,20-metanopirimido[4,5-*k*][1,10,3,6]dioxadiazaciclononadecin-18-il]carbonil}amino)-2-vinilciclopropanocarboxilato de etilo



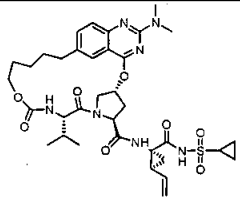
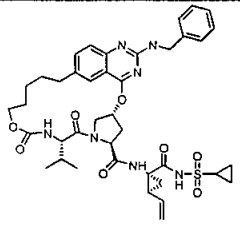
El aceite de la etapa 7 se disolvió en DMF (2 ml) y diisopropilamina (80 µL, 0,45 mmol), y se añadió clorhidrato del éster etílico del ácido (2R,3S)-3-vinil-2-aminociclopropil-carboxílico (intermedio A2) (44 mg, 0,23 mmol), seguido por TBTU (36 mg, 0,23 mmol) y la mezcla de reacción se agitó a TA durante 1 hora. La mezcla se diluyó con EtOAc (20 ml), se lavó con ácido cítrico pH 5,2 (10 ml), bicarbonato de sodio acuoso al 10% (10 ml), se secó sobre Na_2SO_4, se filtró y se concentró a vacío dando un aceite, se cromatografió en sílice (acetato de etilo al 30-100%/hexanos) dando el compuesto del título como un aceite, (45 mg). EMBR $(M+H)^+ = 651,4$.

Etapa 10: ácido (1*R*,2*S*)-1-({[(15*S*,18*S*,20*R*)-2-(dimetilamino)-15-isopropil-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahidro-7*H*,18*H*-4,6-(etanodiilideno)-17,20-metanopirimido[4,5-*k*][1,10,3,6]dioxadiazaciclononadecin-18-il]carbonil}amino)-2-vinilciclopropanocarboxílico (**III-175**)

A una solución del aceite de la etapa 8 (45 mg, 0,068 mmol) en THF (2 ml) se añadió una solución de hidróxido de litio (16 mg, 0,68 mmol) en agua (0,4 ml) y la mezcla se agitó a 40°C durante 8 h. La mezcla de reacción se diluyó con ácido clorhídrico 1N (0,7 ml) y se purificó mediante HPLC en

fase reversa dando el compuesto del título como una espuma (45 mg) después de concentración. RMN ^{1}H (500 Mhz, CD_3OD) δ 8,69 (s, 1H), 7,82 (d, 1H, J = 1,7 Hz), 7,79 (dd, 1H, J = 8,5 y 1,9 Hz), 7,68 (d, 1H, J = 8,5 Hz), 6,25 (m,1H), 5,84 (m, 1H), 5,27 (dd,1H, J = 16,8 y 1,5 Hz), 5,09 (dd, 1H, J = 10,3 y 1,7 Hz), 4,71 (d, 1H, J = 1,7 Hz), 4,66 (t, 1H, J = 10,0 Hz), 4,17 (m, 1H), 4,02 (m, 2H), 3,73 (m, 2H), 3,44 (sa, 6H), 2,86 (m, 1H), 2,69 (m, 1H), 2,19 (dd, 1H, J = 17,6 y 8,8 Hz), 2,02 (m, 1H), 1,80 (m,1H), 1,68 (m, 2H), 1,40-1,55 (m, 3H), 1,10-1,30 (m, 2H), 1,02 (d, 6H) ppm; EMBR (ESI) *m/z* 623,3 [$(M+H)^+$; calcd. para $C_{32}H_{43}N_6O_7$: 623,3].

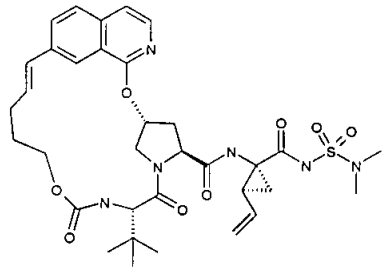
Usando los procedimientos apropiados y los intermedios A, B y C apropiados, se prepararon los siguientes compuestos.

Ej.	Estructura	Nombre	EMBR $(M+H)^+$	Preparados usando los intermedios apropiados de acuerdo con el procedimiento siguiente.	Int.
163, **III-176**		(15*S*,18*S*,20*R*)-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino] carbonil}-2-vinilciclopropil)-2-(dimetilamino)-15-isopropil-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahidro-7*H*,18*H*-4,6-(etanodiilideno)-17,20-metanopirimido[4,5-*k*][1,10,3,6]dioxadiazaciclononadecina-18-carboxamida	726,6	Ejemplo 162	A1
164, **III-177**		(15*S*,18*S*,20*R*)-2-(bencilamino)-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino] carbonil}-2-vinilciclopropil)-15-isopropil-13,16-dioxo-8,9,10,11,13,14,15,16,19,20-decahidro-7*H*,18*H*-4,6-	788,6	Ejemplo 162	A1, bencilamina

		(etanodiilideno)-17,20-metanopirimido[4,5-*k*][1,10,3,6]dioxadiazaciclono-nadecina-18-carboxamida			

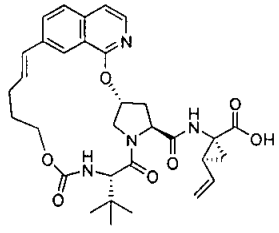
EJEMPLO 165

(2*R*,4*S*,7*S*-14*E*)-7-*terc*-butil-*N*-((1*S*,2*S*)-1-({[(dimetilamino)sulfonil]amino}carbonil)-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-178**)



III-178

Etapa 1: ácido (1R,2S)-1-({[(2R,4S,7S,14E)-7-terc-butil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2H,11H-16,18-eteno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecin-4-il]carbonil}amino)-2-vinilciclopropanocarboxílico



Se disolvió (2R,4S,7S)-7-terc-butil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxodiazaciclononadecina-4-carboxilato de etilo (EJEMPLO 10, etapa 4) (0,73 g, 0,143 mmol) en THF (20 ml) y EtOH (10 ml) y se añadió una solución de LiOH en agua (257 mg en 10 ml). La mezcla de reacción se agitó a temperatura ambiente durante 1,5 h después de lo que el análisis por HPLC indicó la reacción completa, se añadió HCl 3M (0,2 ml) y la mezcla se evaporó a un sólido. El sólido se fraccionó entre EtOAc (20 ml) y agua (20 ml), la fase orgánica, se secó sobre Na_2SO_4, se filtró y se concentró a una espuma que se usó sin purificación adicional.

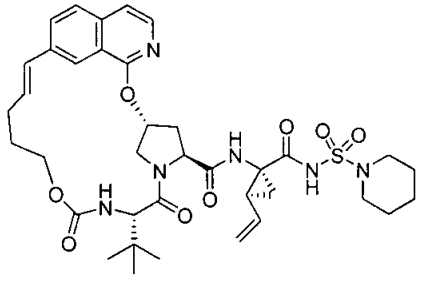
EMBR $(M+H)^+ = 591,5$.

Etapa 2: (2*R*,4*S*,7*S*,14*E*)-7-*terc*-butil-*N*-[(1*R*,2*S*)-1-({[(dimetilamino)sulfonil]amino}carbonil)-2-vinilciclopropil]-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-178**)

Al producto de la etapa 1 (100 mg, 0,169 mmol), N,N-dimetilsulfamida (84 mg, 0,677 mmol), DIPEA (0,148 ml, 0,847 mmol), y DMAP (83 mg, 0,677 mmol) en DMF (3 ml) se añadió DBU (0,115 ml, 0,762 mmol) y la mezcla se agitó durante 5 min. Se añadió HATU (70,8 mg, 0,186 mmoles) y la mezcla se agitó durante 18 horas. Se añadió HATU (15 mg) adicional y la mezcla se agitó durante unas 3 horas adicionales. La mezcla se purificó después mediante HPLC prep. dando 65 mg del compuesto del título como una espuma. RMN ^{1}H (500 MHz, $CDCl_3$) δ 9,62 (s, 1H), 8,26 (s, 1H), 7,89 (d, 1H, J = 6,1 Hz), 7,64 (d, 1H, J = 8,3 Hz), 7,50 (dd, 1H, J = 1,7 y 8,3 Hz), 7,20 (d, 1H, J = 5,8 Hz), 7,17 (s, 1H), 6,50 (d, 1H, J = 15,8 Hz), 6,36 (m, 1H), 5,82 (m, 1H), 5,66 (m, 2H), 5,17 (dd, 1H, J = 0,8 y 17,1 Hz), 5,09 (dd, 1H, J = 0,8 y 10,3 Hz), 4,61(d, 1H, J = 10,3 Hz), 4,48 (m, 3H), 3,94 (m, 2H), 2,83 (s, 6H), 2,73 (m, 1H), 2,46 (m, 1H), 2,38 (m, 2H), 2,00 (m, 2H), 1,85 (m, 2H), 1,34 (m, 1H), 1,08 (s, 9H). EMBR (ESI) *m/z* 697,5 [(M+H)$^+$; calcd. para $C_{34}H_{45}N_6O_8S$: 697,3].

EJEMPLO 166

(2*R*,4*S*,7*S*-14*E*)-7-*terc*-butil-6,9-*N*-((1*R*,2*S*)-1-{[(piperidin-1-ilsulfonil)amino]carbonil}-2-vinilciclopropil)-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-179**)

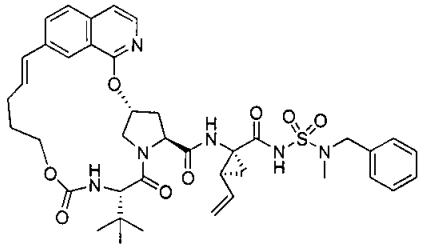


III-179

El EJEMPLO 166 se preparó de acuerdo con el procedimiento descrito por EJEMPLO 165 usando piperidina-1-sulfonamida en etapa 2. EMBR (ESI) *m/z* 737,5 [(M+H)$^+$; calcd. para $C_{37}H_{49}N_6O_8S$: 737,3].

EJEMPLO 167

(2*R*,4*S*,7*S*,14*E*)-*N*-{(1*R*,2*S*)-1-[({[bencil(metil)amino]sulfonil}amino)carbonil]-2-vinilciclopropil}-7-*terc*-butil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-180**)

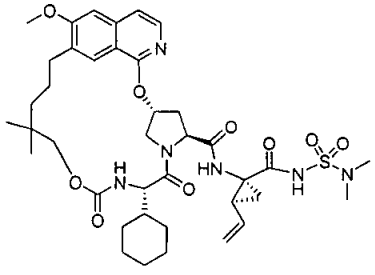


III-180

El EJEMPLO 167 se preparó de acuerdo con el procedimiento descrito por el EJEMPLO 165 usando piperidina-1-sulfonamida en etapa 2. EMBR (ESI) *m/z* 773,6 [(M+H)$^+$; calcd. para $C_{40}H_{49}N_6O_8S$: 773,3].

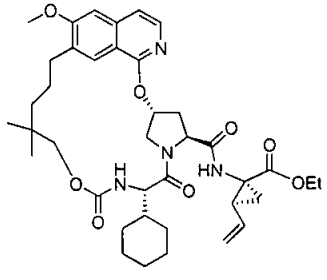
EJEMPLO 168

(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-[(1*R*,2*S*)-1-{[(dimetilamino)sulfonil]amino}carbonil)-2-vinilciclopropil]-23-metoxi-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etenodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-181**)



III-181

Etapa 1: (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-ciclohexil-23-metoxi-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecin-4-il]carbonil}amino)-2-vinilciclopropanocarboxilato de etilo



Se preparo (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-ciclohexil-23-metoxi-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-

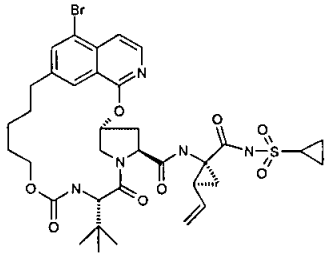
k][1,10,3,6]dioxadiazaciclononadecin-4-il]carbonil}amino)-2-vinilciclopropanocarboxilato de etilo usando el procedimiento descrito por EJEMPLO 15 usando intermedios A2, B23 y C1. EMBR $(M+H)^+$ = 705,6.

Etapa 2: (2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-({[(dimetilamino)sulfonil]amino}carbonil-2-vinilciclopropil]-23-metoxi-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida

El EJEMPLO 168 se preparó de acuerdo con el procedimiento descrito por el ejemplo 165 usando (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-ciclohexil-23-metoxi-12,12-dimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecin-4-il]carbonil}amino)-2-vinilciclopropanocarboxilato de etilo en Etapa 1. EMBR (ESI) *m/z* 783,6 $[(M+H)^+$; calcd. para $C_{39}H_{55}N_6O_9S$: 783,4].

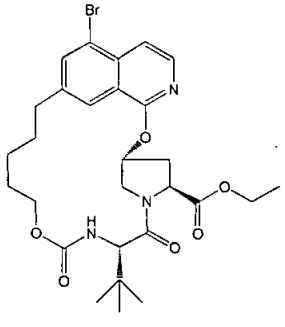
EJEMPLO 169

(2S,4S,7S)-22-bromo-7-terc-butil-N-((1R,2S)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-182**)

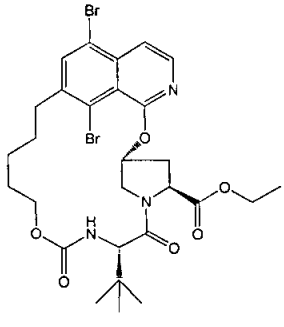


III-182

Etapa 1: (2*R*,4*S*,7*S*)-22-bromo-7-*terc*-butil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (**III-186**) y (2*R*,4*S*,7*S*)-17,22-dibromo-7-*terc*-butil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de etilo (**III-187**)



III-186



III-187

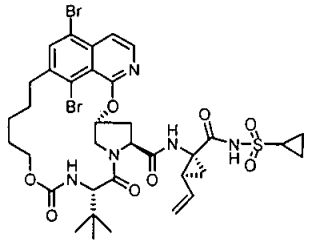
Los compuestos **III-186** y **III-187** se prepararon de acuerdo con el procedimiento dado por ejemplo 13, etapa 1 usando N-bromosuccinimida. Los compuestos mono- y di-brominados se separaron mediante HPLC en fase reversa. **III-186**: EMBR $(M+H)^+$ = 590,4. **III-187**: EMBR $(M+H)^+$ = 668,3.

Etapa 2: (2S,4S,7S)-22-bromo-7-terc-butil-N-((1R,2S)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-etanodiilideno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-182**)

Se preparó EJEMPLO 169 a partir de **III-186** usando el procedimiento descrito por ejemplo 14, etapas 4 y 5. EMBR (ESI) *m/z* 774,5 $[(M+H)^+$; calcd. para $C_{35}H_{45}BrN_5O_8S$: 774,2].

EJEMPLO 170

(2S,4S,7S)-17,22-dibromo-7-terc-butil-N-((1R,2S)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2H,11H-16,18-(etanodiilideno)-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-183**)

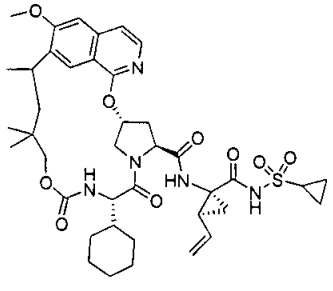


III-183

El compuesto del título se preparó a partir de **III-187** usando el procedimiento descrito por ejemplo 14, etapas 4 y 5. EMBR (ESI) *m/z* 852,5 $[(M+H)^+$; calcd. para $C_{35}H_{44}Br_2N_5O_8S$: 852,1].

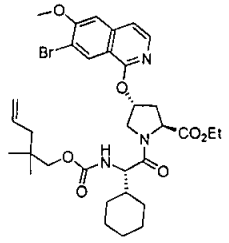
EJEMPLO 171

(2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-22-metoxi-12,12,14-trimetil-6,9-dioxo-3,4,6,7,8,9,12,13,14,15-decahidro-2*H*-15,17-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-184**)



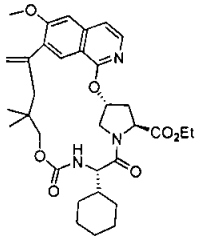
III-184

Etapa 1: (4R)-4-[(7-bromo-6-metoxiisoquinolin-1-il)oxi]-1-[(2S)-2-ciclohexil-2-({[(2,2-dimetilpent-4-en-1-il)oxi]carbonil}amino)acetil]-L-prolinato de etilo



Se preparó (4R)-4-[(7-bromo-6-metoxiisoquinolin-1-il)oxi]-1-[(2S)-2-ciclohexil-2-({[(2,2-dimetilpent-4-en-1-il)oxi]carbonil}amino)acetil]-L-prolinato de acuerdo con el procedimiento dado por ejemplo 14, etapa 1 usando intermedios B23 y C1. EMBR $(M+H)^+$ = 674,3

Etapa 2: (2R,4S,7S)-7-ciclohexil-22-metoxi-12,12-dimetil-14-metileno-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahidro-2H-15,17-eteno-2,5-metanopirido[2,3-k][1,10,3,6]dioxadiazaciclooctadecina-4-carboxilato de etilo



A una solución del producto de etapa 1 (448 mg, 0,664 mmol) disuelta en etanol (10 ml) se añadió trietilamina (0,139 ml, 0,996 mmol) y [1,1'-bis(difenilfosfino)ferroceno]dicloropaladio (II) (24,3 mg, 0,033 mmol) y la mezcla de reacción se calentó a 90°C. Después de 1 hora, se añadió catalizador adicional (5 mg) y la mezcla de reacción se agitó 18 horas adicionales a 90°C. La mezcla de reacción se concentró a vacío y se cromatografió en sílice (EtOAc al 20-50%/hexano) dando producto impuro. La purificación por HPLC prep. dio el compuesto del título (140 mg) como una espuma. EMBR $(M+H)^+$ = 594,5.

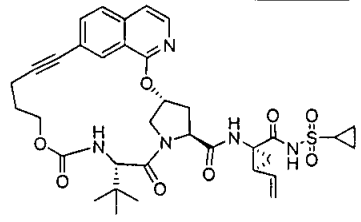
Etapa 3: (2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-22-metoxi-12,12,14-trimetil-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahidro-2*H*-15,17-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclooctadecina-4-carboxamida (**III-184**)

Se preparó (2*R*,4*S*,7*S*)-7-ciclohexil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-22-metoxi-12,12,14-trimetil-6,9-dioxo-3,4,6,7,8,9,11,12,13,14-decahidro-2*H*-15,17-eteno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclooctadecina-4-carboxamida (**III-184**) a partir del

producto de la etapa 2 de acuerdo con el procedimiento dado por el ejemplo 14, etapas 4 y 5 usando intermedio A1 en etapa 5. EMBR (ESI) *m/z* 780,6 $[(M+H)^+$; calcd. por $C_{40}H_{53}N_5O_9S$: 780,4].

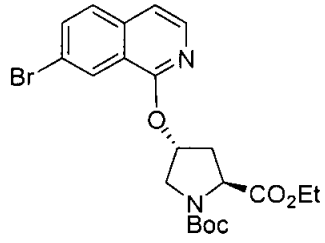
EJEMPLO 172

(2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2S)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-14,15-didehidro-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-185**)



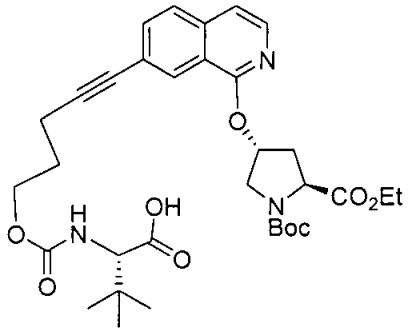
III-185

Etapa 1: ácido 1,2-pirrolidinadicarboxílico, éster 4-[(7-bromo-1-isoquinolinil)oxi]-, 1-(1,1-dimetiletil) 2-etilílico, (2*S*,4*R*)-



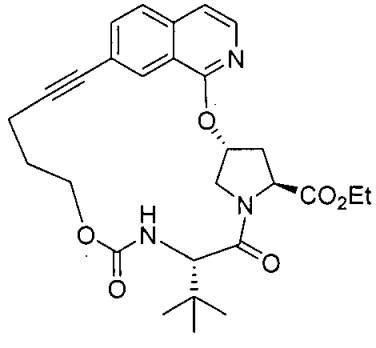
A una solución de di-*terc*-butildicarbonato (1,14 g, 5,23 mmol) en CH_3CN (15 ml) se añadió Et_3N (2,08 ml, 14,9 mmol) y clorhidrato de (4*R*)-4-[(7-bromoisoquinolin-1-il)oxi]-L-prolinato (ejemplo 10, etapa 1) (1,5 g, 3,73 mmol) a TA. Después de 15 min, se añadió DCM (150 ml) y la solución se extrajo con HCl 1 N. La fase orgánica se secó sobre K_2CO_3 y el disolvente se eliminó a vacío. El material en bruto se purificó en gel de sílice (elución de gradiente de EtOAc al 0-30% en hexanos) produciendo el compuesto del título como una espuma (1,73 g). EMBR $(M+H)^+$ Calcd. = 465,1; hallado 465,2.

Etapa 2: *N*-({[5-(1-{[(3*R*,5*S*)-1-(*terc*-butoxicarbonil)-5-(etoxicarbonil)pirrolidin-3-il]oxi}isoquinolin-7-il)pent-4-in-1-il]oxi}carbonil)-3-metil-L-valina



A una parte del producto de la etapa 1 (0,94 g, 2,02 mmol), en THF desgasificado (10 ml) y pirrolidina (10 ml) se añadió intermedio B11, 3-metil-*N*-[(pent-4-in-1-iloxi)carbonil]-L-valina (0,8 g, 3,33 mmol), $Pd(PPh_3)_4$ (58 mg, 0,05 mmol), y CuI (19 mg, 0,1 mmol). La mezcla se calentó después a 70°C durante 2 h. La mezcla se vertió después dentro de una mezcla de agua y EtOAc y el pH se ajustó a ~1 con HCl 1 N. La fase orgánica se separó después, se secó sobre $MgSO_4$, y el disolvente se evaporó. El producto en bruto se purificó en gel de sílice (elución de gradiente de EtOAc al 20-100% en hexanos) produciendo el compuesto del título como una espuma (1,2 g). EMBR $(M+H)^+$ Calcd. = 626,3; hallado 626,4.

Etapa 3: (2*R*,4*S*,7*S*)-7-*terc*-butil-6,9-dioxo-14,15-didehidro-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de 7-etilo



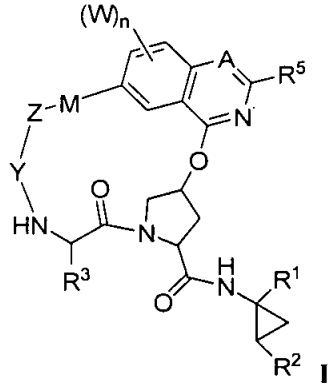
A una parte del producto de etapa 2 (0,93 g, 1,49 mmol), se añadió HCl/dioxano (37 ml, 4M, 148 mmol). La mezcla se agitó durante 30 min y después el disolvente se eliminó a vacío. Se añadió después DCM (400 ml) a la mezcla junto con DIEA (1,3 ml, 7,4 mmol) y HATU (622 mg, 1,6 mmol). Después de 20 h, el disolvente se eliminó a vacío y el producto en bruto se purificó en gel de sílice (elución de gradiente de EtOAc 0-60% en hexanos) produciendo el compuesto del título como una espuma (0,11 g). EMBR $(M+H)^+$ Calcd. = 508,3; hallado 508,4.

Etapa 4: (2*R*,4*S*,7*S*)-7-*terc*-butil-*N*-((1*R*,2*S*)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-6,9-dioxo-14,15-didehidro-3,4,6,7,8,9,12,13-octahidro-2*H*,11H-16,18-(etanodiilideno)-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxamida (**III-172**)

El compuesto del título se preparó a partir de (2*R*,4*S*,7*S*)-7-*terc*-butil-6,9-dioxo-14,15-didehidro-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-(etanodiilideno)-2,5-metanopirido[2,3*k*][1,10,3,6]dioxadiazaciclononadecina-4-carboxilato de 7-etilo e intermedio A1 usando el procedimiento descrito en ejemplo 14, etapas 4 y 5. EMBR (ESI) *m/z* 692,3 $[(M+H)^+$; calcd. para $C_{35}H_{42}N_5O_8S$: 692,3].

REIVINDICACIONES

1. Un compuesto de fórmula (**I**):



I

en la que:

n es 1 ó 2;

R^1 es CO_2R^{10}, $CONR^{10}SO_2R^6$, $CONR^{10}SO_2NR^8R^9$, o tetrazolilo;

R^2 es alquilo C_1-C_6, alquenilo C_2-C_6 o cicloalquilo C_3-C_8, en los que dicho alquilo, alquenilo o cicloalquilo está opcionalmente sustituido con 1 a 3 halo;

R^3 es alquilo C_1-C_8, cicloalquilo C_3-C_8, cicloalquil C_3-C_8(alquilo C_1-C_8), aril(alquiloC_1-C_8), o Het, en los que arilo es fenilo o naftilo y dicho alquilo, cicloalquilo, o arilo está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, y $CON(R^{10})_2$;

Het es un anillo cíclico saturado de 5-6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, en el que dicho anillo está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, y $CON(R^{10})_2$;

R^4 es H, alquilo C_1-C_8, cicloalquil C_3-C_8(alquil C_1-C_8), o aril(alquiloC_1-C_8); en los que arilo es fenilo o naftilo y dicho alquilo, cicloalquilo, o arilo está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)^2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO^2R10, C(O)R10, y $CON(R^{10})_2$;

R^5 es H, halo, OH, alcoxi C_1-C_6, alquilo C_1-C_6, CN, CF_3, SR^{10}, SO_2(alquilo C_1-C_6), cicloalquilo C_3-C_8, cicloalcoxi C_3-C_8, haloalquilo C_1-C_6, $N(R^7)_2$, arilo, heteroarilo o heterociclilo; en el que arilo es fenilo o naftilo, heteroarilo es un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y heterociclilo es un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en los que dicho arilo, heteroarilo, heterociclilo, cicloalquilo, cicloalcoxi, alquilo o alcoxi está opcionalmente sustituido con 1 a 4 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^7)_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), cicloalquilo C_3-C_6, cicloalcoxi C_3-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, S(O)(alquilo C_1-C_6), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, y $CON(R^{10})_2$; en los que los 2 sustituyentes adyacentes de dicho cicloalquilo, cicloalcoxi, arilo, heteroarilo o heterociclilo se toman opcionalmente conjuntamente para formar un anillo cíclico de 3-6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S;

R^6 es alquilo C_1-C_8, cicloalquilo C_3-C_8, cicloalquil C_3-C_8(alquilo C_1-C_5), arilo, aril(alquilo C_1-C_4), heteroarilo, heteroaril(alquilo C_1-C_4), heterociclilo, o heterociclil(alquilo C_1-C_8), en los que dicho alquilo, cicloalquilo, arilo, heteroarilo, o heterociclilo está opcionalmente sustituido con 1 a 2 sustituyentes W'; y en los que cada arilo es independientemente fenilo o naftilo, cada heteroarilo es independientemente un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y cada heterociclilo es independientemente un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un anillo de carbono o nitrógeno;

Y es C(=O), SO_2, o C(=N-CN);

Z es $C(R^{10})_2$, O, o $N(R^4)$;

M es alquileno C_1-C_{12} o alquenileno C_2-C_{12} o alquinileno C_2-C_{12}, en el que dicho alquileno o alquenileno está opcionalmente sustituido con 1, 2 ó 3 sustituyentes seleccionados del grupo constituido por alquilo

C_1-C_8, cicloalquil C_3-C_8(alquilo C_1-C_8), y aril(alquilo C_1-C_8); en los que 2 sustituyentes en átomos de carbono adyacentes de M se toman opcionalmente conjuntamente para formar un anillo cíclico de 3-6 miembros que contienen 0-3 heteroátomos seleccionados de N, O y S, o 2 sustituyentes en el mismo átomo de carbono de M opcionalmente se toman conjuntamente para formar un anillo cíclico de 3-6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S;

A es $C(R^{11})$ o N;

cuando R^5 es distinto de H, R^{11} es H, alquilo C_1-C_6, halo, OR^{10}, SR^{10}, o $N(R^{10})_2$;

cuando R^5 es H, halo, R^{11} es H, alquilo C_1-C_6, halo, OH, alcoxi C_1-C_6,CN, CF_3, SR^{10}, SO_2(alquilo C_1-C_6), cicloalquilo C_3-C_8, cicloalcoxi C_3-C_8, haloalquilo C_1-C_6, $N(R^7)_2$, arilo, heteroarilo o heterociclilo; en el que arilo es fenilo o naftilo, heteroarilo es un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y heterociclilo es un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en los que dicho arilo, heteroarilo, heterociclilo, cicloalquilo, cicloalcoxi, alquilo o alcoxi está opcionalmente sustituido con 1 a 4 sustituyentes seleccionados del grupo constituido por halo, OR^{10}, SR^{10}, $N(R^7)_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, haloalquilo C_1-C_6, halo(alcoxi C_1-C_6), cicloalquilo C_3-C_6, cicloalcoxi C_3-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, S(O)(alquilo C_1-C_6), $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, $C(O)R^{10}$, y $CON(R^{10})_2$; en los que los 2 sustituyentes adyacentes de dicho cicloalquilo, cicloalcoxi, arilo, heteroarilo o heterociclilo se toman opcionalmente conjuntamente para formar un anillo cíclico de 3-6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S;

o R^5 y R^{11} se toman opcionalmente conjuntamente parar formar un anillo cíclico saturado, no aromático insaturado, o aromático de 5 a 6 miembros, que tiene 0-2 heteroátomos seleccionados de N, O y S;

cada R^7 es independientemente H, alquilo C_1-C_6, cicloalquilo C_3-C_6, cicloalquil C_3-C_6(alquilo C_1-C_5), arilo, aril(alquilo C_1-C_4), heteroarilo, heteroaril(alquilo C_1-C_4), heterociclilo, o heterociclil(alquilo C_1-C_8), en los que dicho alquilo, cicloalquilo, arilo, heteroarilo, o heterociclilo está opcionalmente sustituido con 1 a 2 sustituyentes W'; y en los que cada arilo es independientemente fenilo o naftilo, cada heteroarilo es independientemente un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y cada heterociclilo es independientemente un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo;

cada W es independientemente halo, OR^7, alquilo C_1-C_6, CN, CF_3, NO_2, SR^7, CO_2R^7, $CON(R^7)_2$, $C(O)R^7$, $N(R^{10})C(O)R^7$, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), cicloalquilo C_3-C_8, cicloalcoxi C_3-C_8, haloalquilo C_1-C_6, $N(R^7)_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), halo(alcoxi C_1-C_6), $NR^{10}SO_2R^7$, $SO_2N(R^7)_2$, $NHCOOR^7$, $NHCONHR^7$, arilo, heteroarilo o heterociclilo; en los que arilo es fenilo o naftilo, heteroarilo es un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y heterociclilo es un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en los que 2 restos W adyacentes se toman opcionalmente conjuntamente con los átomos a los que están unidos para formar un anillo cíclico no aromático insaturado, saturado, o aromático de 5 ó 6 miembros que tiene 0-2 heteroátomos seleccionados de N, O y S;

cada W' es independientemente H, halo, OR^{10}, alquilo C_1-C_6, CN, CF_3, NO_2, SR^{10}, CO_2R^{10}, $CON(R^{10})_2$, $C(O)R^{10}$, $N(R^{10})C(O)R^{10}$, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), cicloalquilo C_3-C_8, cicloalcoxi C_3-C_8, haloalquilo C_1-C_6, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), halo(alcoxi C_1-C_6), $NR^{10}SO_2R^{10}$, $SO_2N(R^{10})_2$, $NHCOOR^{10}$, $NHCONHR^{10}$, arilo, heteroarilo o heterociclilo; en los que arilo es fenilo o naftilo, heteroarilo es un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo, y heterociclilo es un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en los que 2 restos W' adyacentes se toman opcionalmente conjuntamente con los átomos a los que están unidos para formar un anillo cíclico no aromático, o aromático saturado, insaturado que tiene 0-2 heteroátomos seleccionados de N, O y S;

R^8 es alquilo C_1-C_8, cicloalquilo C_3-C_8, cicloalquil C_3-C_8 cicloalquil(alquilo C_1-C_8), arilo, aril(alquilo C_1-C_4), heteroarilo, heterociclilo, heteroaril(alquilo C_1-C_4), o heterociclil(alquilo C_1-C_8), en los que dicho alquilo, cicloalquilo, arilo, heteroarilo o heterociclilo está opcionalmente sustituido con 1 a 4 sustituyentes seleccionados del grupo constituido por arilo, cicloalquilo C_3-C_8, heteroarilo, heterociclilo, alquilo C_1-C_6, halo(alcoxi C_1-C_6), halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, $C(O)R^{10}$, haloalquilo C_1-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R^{10}, y $C(O)N(R^{10})_2$; en el que cada arilo es independientemente fenilo o naftilo; cada heteroarilo es independientemente un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y cada heterociclilo es independientemente un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en el que los 2 sustituyentes adyacentes de dicho

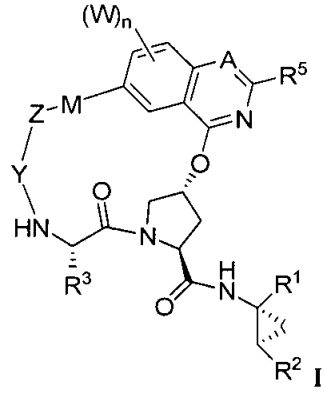
cicloalquilo, cicloalcoxi, arilo, heteroarilo o heterociclilo se toman opcionalmente conjuntamente para formar un anillo cíclico de 3 a 6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S;

R^9 es alquilo C_1-C_8, cicloalquilo C_3-C_8, cicloalquil C_3-C_8 (alquilo C_1-C_8), alcoxi C_1-C_8, cicloalcoxi C_3-C_8, arilo, aril(alquilo C_1-C_4), heteroarilo, heterociclilo, heteroaril(alquilo C_1-C_4), o heterociclil(alquilo C_1-C_8), en los que dicho alquilo, cicloalquilo, alcoxi, cicloalcoxi, arilo, heteroarilo o heterociclilo está opcionalmente sustituido con 1 a 4 sustituyentes seleccionados del grupo constituido por arilo, cicloalquilo C_3-C_8, heteroarilo, heterociclilo, alquilo C_1-C_6, halo(alcoxi C_1-C_6), halo, OR^{10}, SR^{10}, $N(R^{10})_2$, N(alquil C_1-C_6)O(alquilo C_1-C_6), alquilo C_1-C_6, $C(O)R^{10}$, haloalquilo C_1-C_6, NO_2, CN, CF_3, SO_2(alquilo C_1-C_6), S(O)(alquilo C_1-C_6), $NR^{10}SO_2R^6$, $SO_2N(R^6)_2$, $NHCOOR^6$, $NHCOR^6$, $NHCONHR^6$, CO_2R_{10}, y $C(O)N(R^{10})_2$; en el que cada arilo es independientemente fenilo o naftilo; cada heteroarilo es independientemente un anillo aromático de 5 ó 6 miembros que tiene 1, 2 ó 3 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y cada heterociclilo es independientemente un anillo no aromático saturado o insaturado de 5 a 7 miembros que tiene 1, 2, 3 ó 4 heteroátomos seleccionados de N, O y S, unidos a través de un carbono o nitrógeno de anillo; y en la que los 2 sustituyentes adyacentes de dicho cicloalquilo, cicloalcoxi, arilo, heteroarilo o heterociclilo se toman opcionalmente conjuntamente para formar un anillo cíclico de 3 a 6 miembros que contiene 0-3 heteroátomos seleccionados de N, O y S;

o R^8 y R^9 se toman opcionalmente conjuntamente, con el átomo de nitrógeno al que están unidos, para formar un anillo monocíclico de 4-8 miembros que contienen 0-2 heteroátomos adicionales seleccionados de N, O y S; y

cada R^{10} es independientemente H o alquilo C_1-C_6.

2. El compuesto de la reivindicación 1, en el que el compuesto es de fórmula **III**:



III.

3. El compuesto de la reivindicación 2, en el que R^1 es CO_2R^{10} o $CONR^{10}SO_2R^6$.

4. El compuesto de la reivindicación 3, en el que R^1 es CO_2H.

5. El compuesto de la reivindicación 3, en el que R^1 es $CONHSO_2R^6$.

6. El compuesto de la reivindicación 5, en el que R^1 es $CONHSO_2R^6$ en el que R^6 es cicloalquilo C_3-C_8, alquilo C_1-C_8, arilo, o aril(alquilo C_1-C_4).

7. El compuesto de la reivindicación 3, en el que R^2 es alquilo C_1-C_4 o alquenilo C_2-C_4.

8. El compuesto de la reivindicación 7, en el que R^3 es cicloalquilo C_5-C_6 o alquilo C_1-C_8 opcionalmente sustituido con 1 a 3 sustituyentes halo.

9. El compuesto de la reivindicación 8, en el que R^5 es H, halo, arilo, heteroarilo o $N(R^7)_2$.

10. El compuesto de la reivindicación 9, en el que R^5 es H o halo.

11. El compuesto de la reivindicación 9, en el que R^5 es arilo o heteroarilo.

12. El compuesto de la reivindicación 9, en el que Y es C=O.

13. El compuesto de la reivindicación 12, en el que Z es O, NH, N(alquilo C_1-C_8) o $C(R^{10})_2$.

14. El compuesto de la reivindicación 13, en el que M es alquileno C_4-C_7 insustituido o alquenileno C_4-C_7 insustituido.

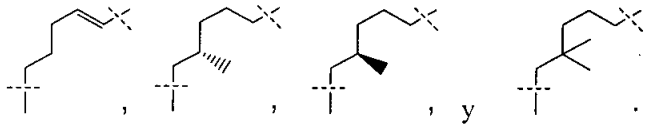
15. El compuesto de la reivindicación 14, en el que n es 1 y W es H, alcoxilo C_1-C_6, alquilo C_1-C_6, OH, halo, $N(R^7)_2$ en el que R^7 es H o alquilo C_1-C_6.

16. El compuesto de la reivindicación 15, en el que A es N.

17. El compuesto de la reivindicación 15, en el que A es $C(R^{11})$ en el que R^{11} es H, alquilo C_1-C_6, alcoxi C_1-C_6, hidroxi o halo.

18. El compuesto de la reivindicación 10, en el que R^2 es alquenilo C_2-C_4, R^5 es H, R^6 es cicloalquilo C_3-C_8, W es R^7 o H, Y es C(=O), Z es O, y n es 1.

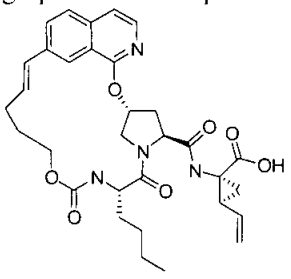
19. El compuesto de la reivindicación 18, en la que M se selecciona del grupo constituido por:



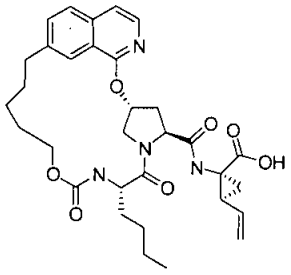
20. El compuesto de la reivindicación 19, en el que R^3 es alquilo C_5-C_6 o alquilo C_3-C_5.

21. El compuesto de la reivindicación 20, en el que R^6 es cicloalquilo C_3-C_5.

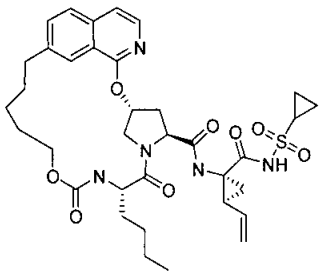
22. El compuesto de la reivindicación 1, en el que el compuesto se selecciona del grupo constituido por compuestos **III-1** a **III-38**:



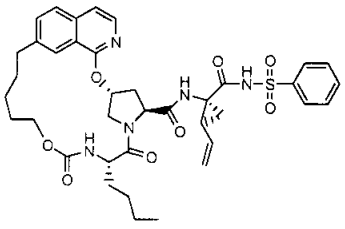
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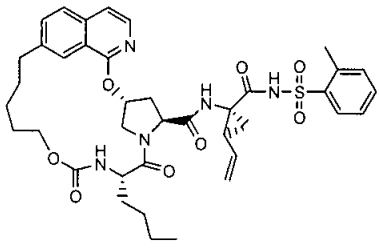
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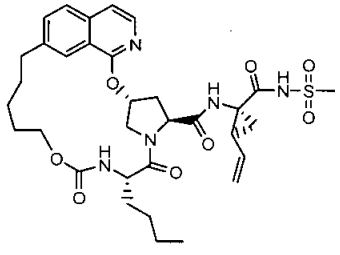
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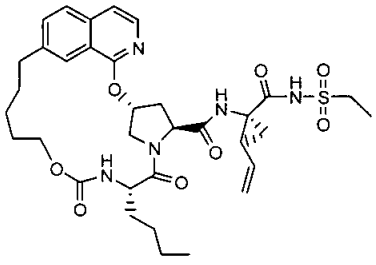
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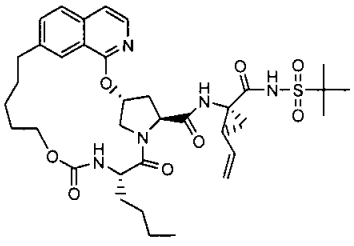
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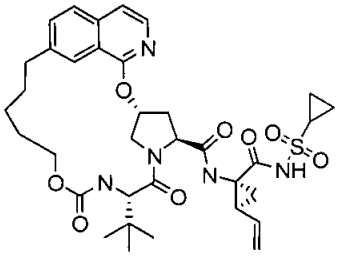
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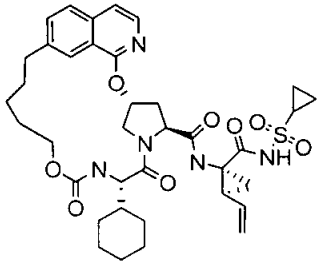
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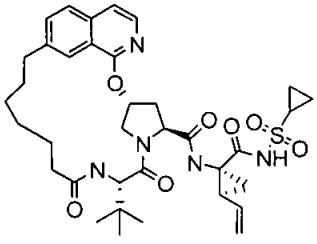
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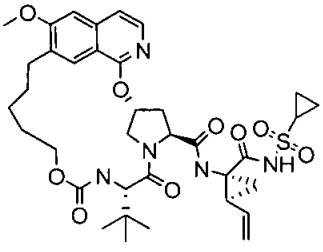
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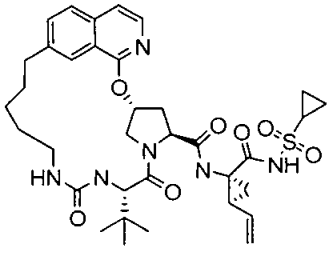
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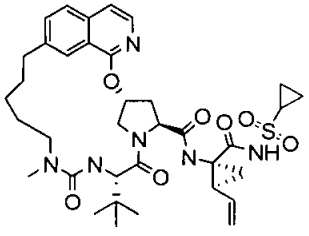
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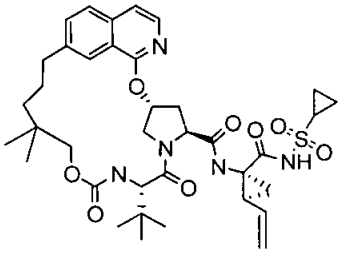
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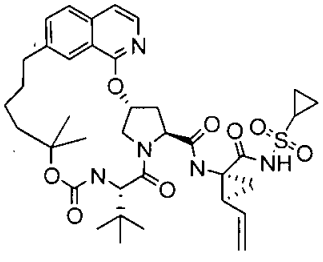
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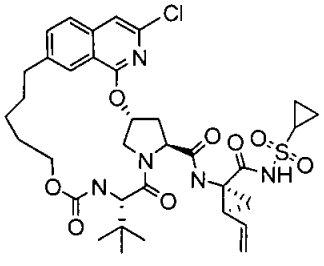
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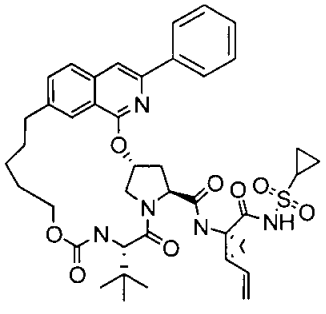
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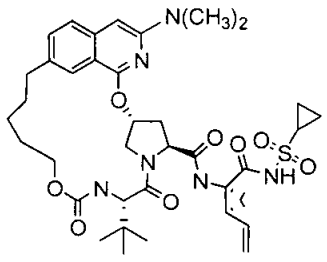
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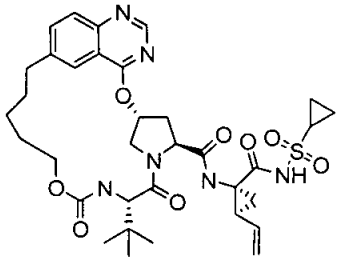
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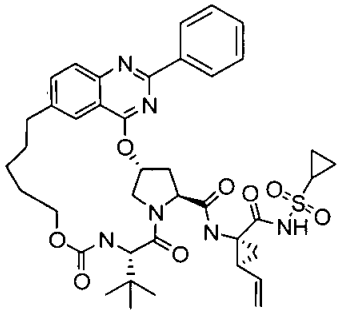
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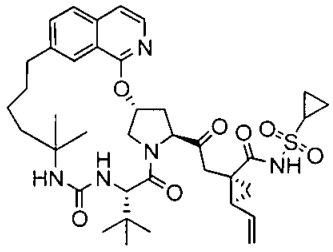
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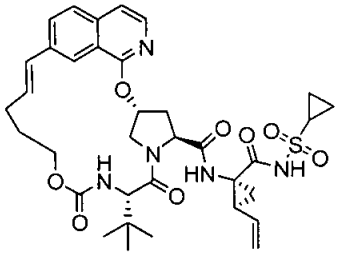
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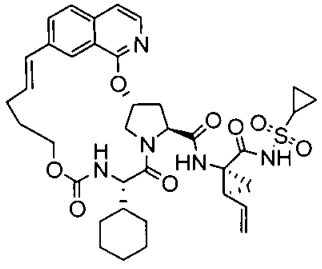
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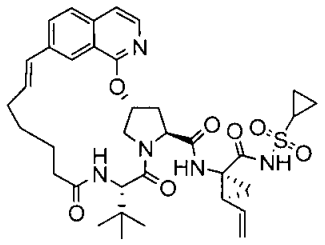
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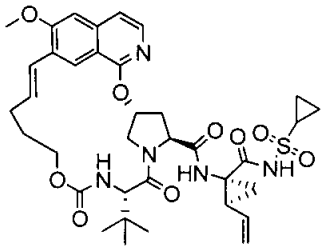
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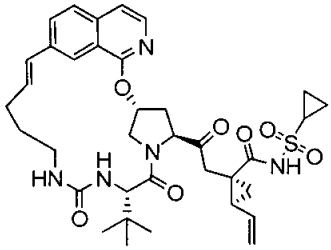
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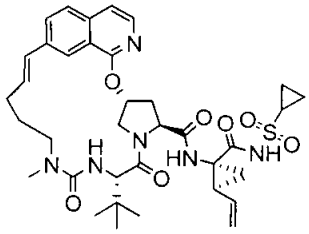
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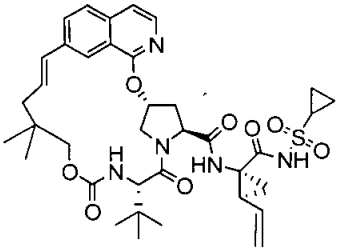
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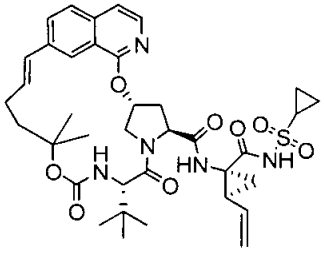
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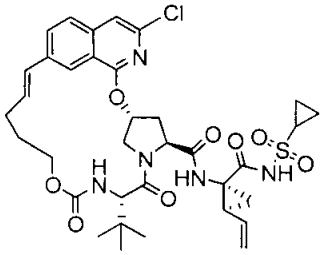
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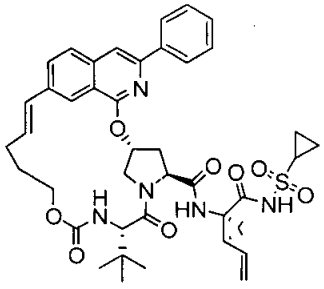
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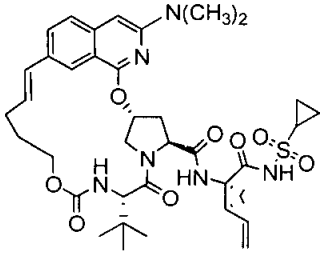
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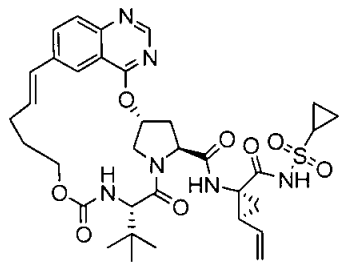
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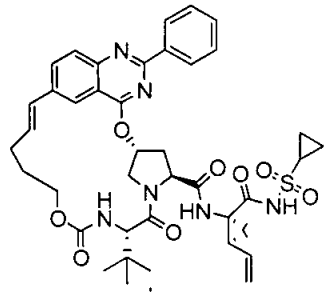
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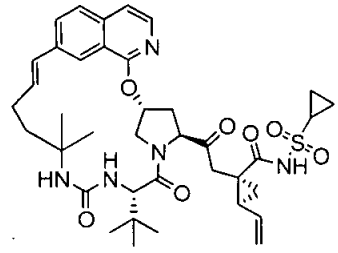
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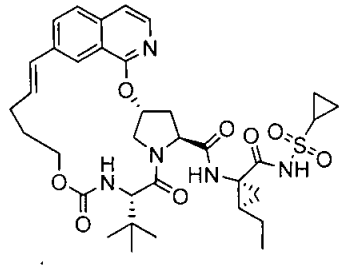
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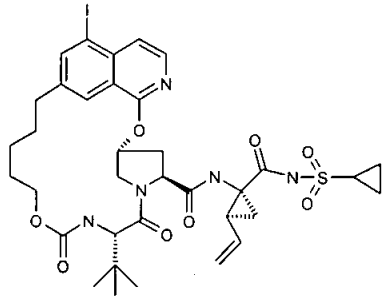
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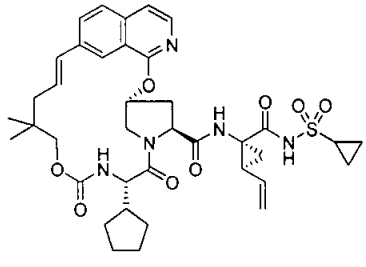


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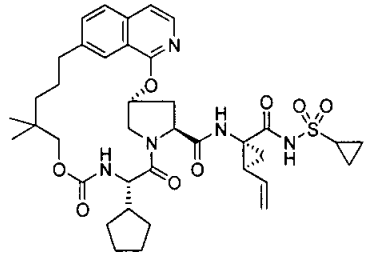


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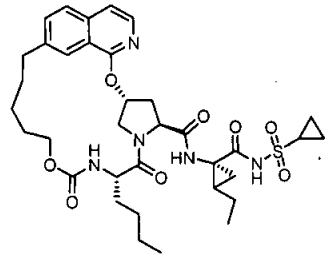
23. El compuesto de la reivindicación 1, en el que el compuesto se selecciona del grupo constituido por compuestos **III-39** a **III-187**:



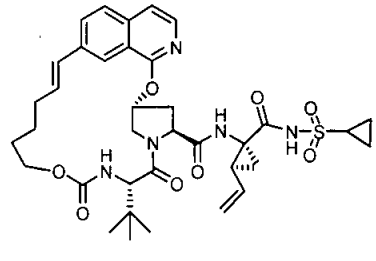
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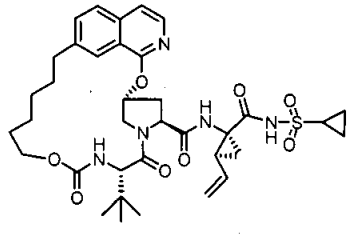
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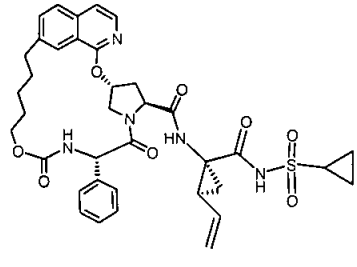
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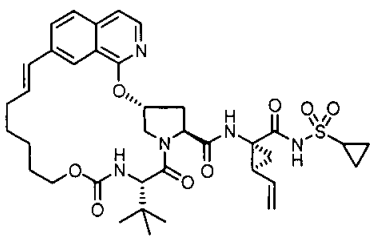
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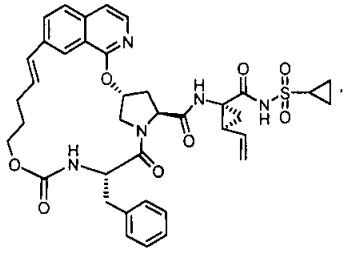
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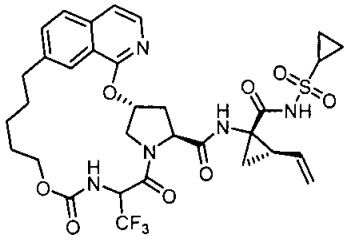
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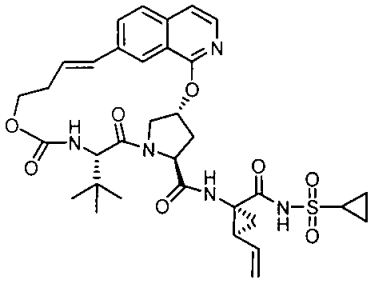
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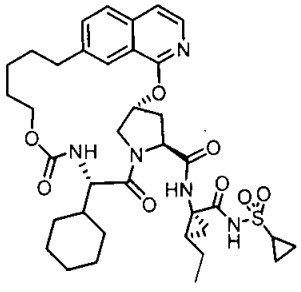
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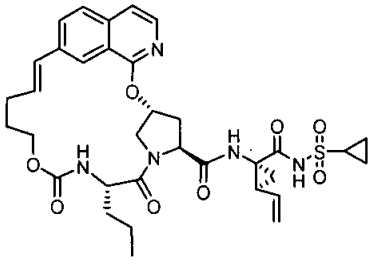
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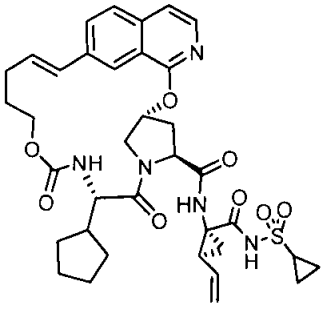
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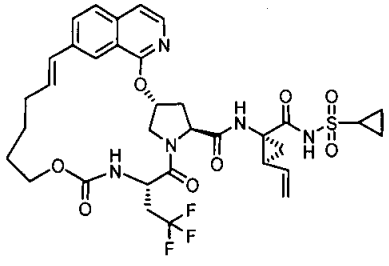
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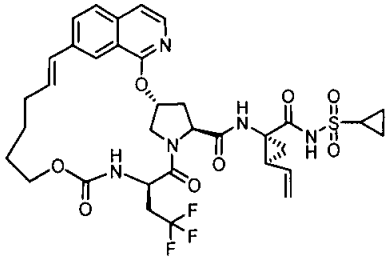
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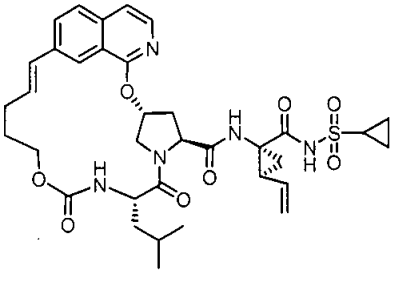
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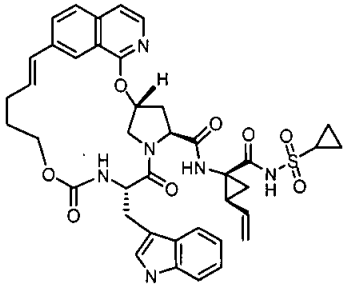
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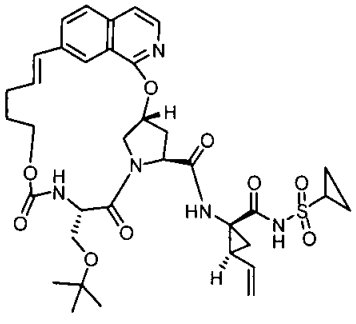
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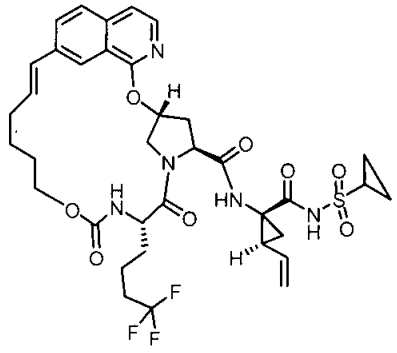
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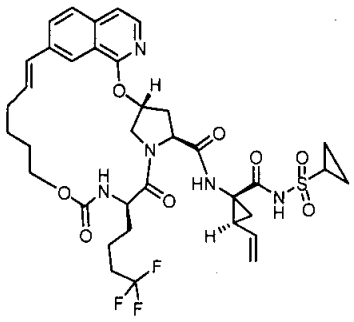
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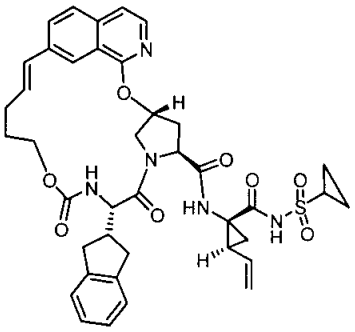
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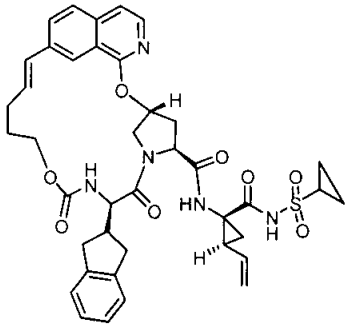
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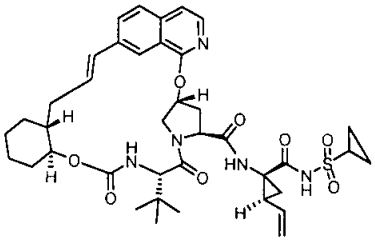
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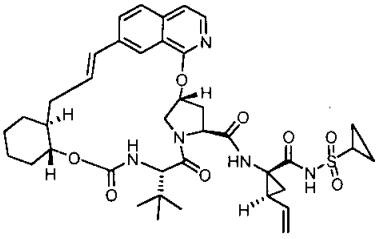
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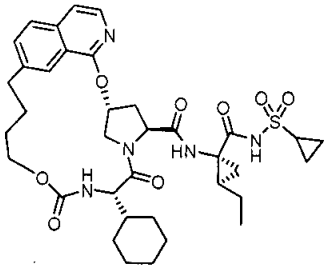
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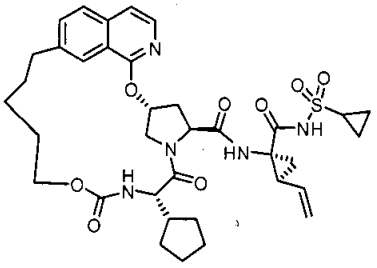
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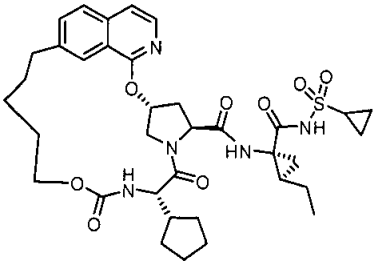
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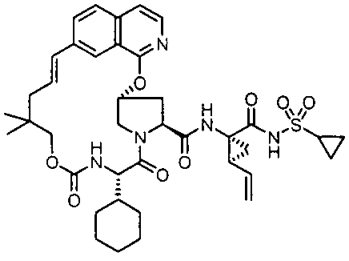
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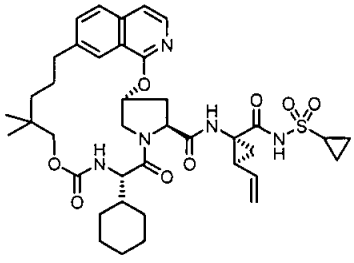
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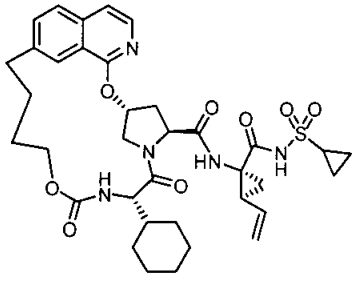
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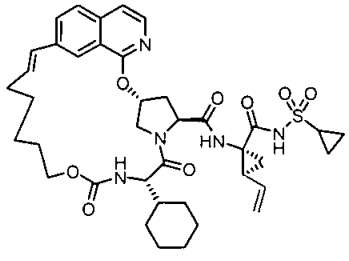
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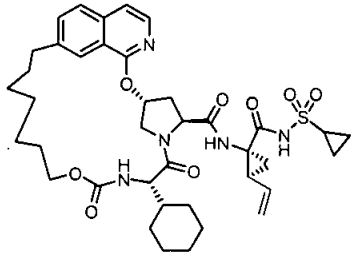
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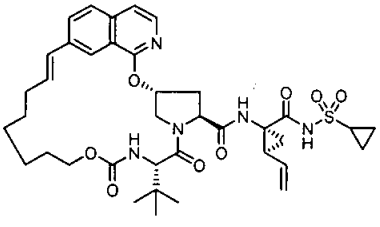
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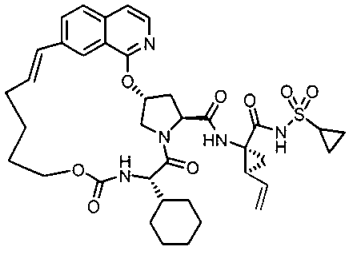
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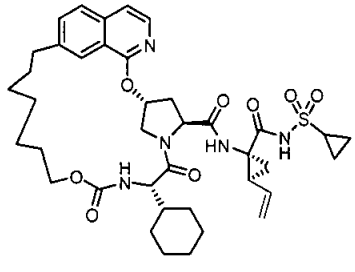
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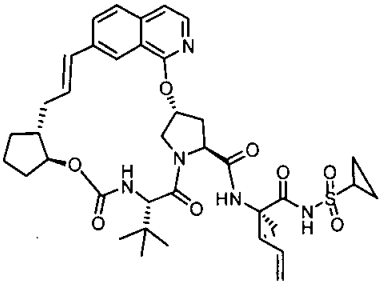
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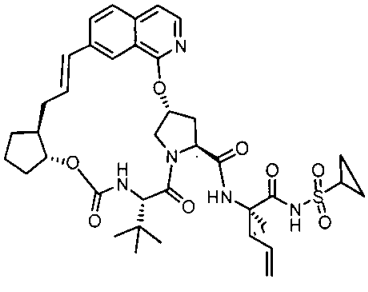
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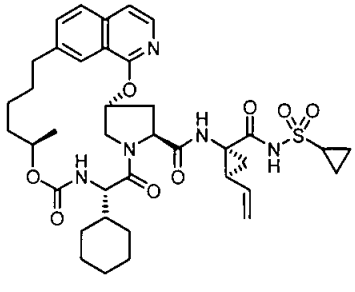
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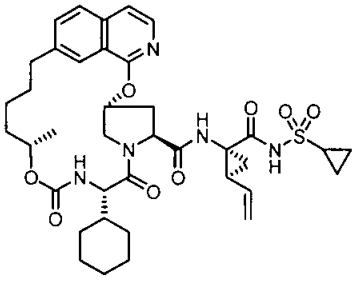
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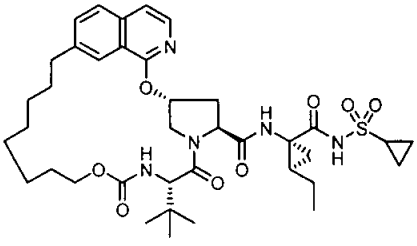
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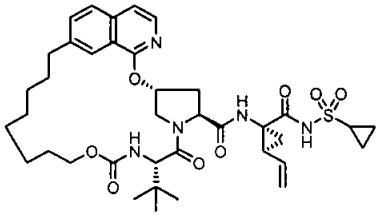
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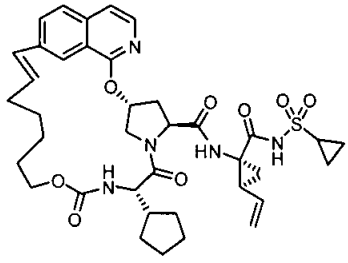
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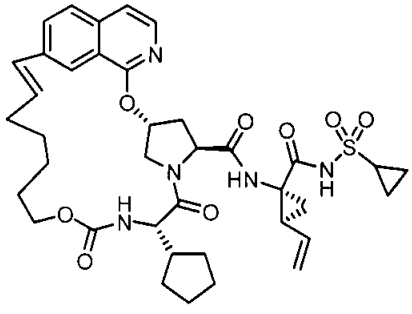
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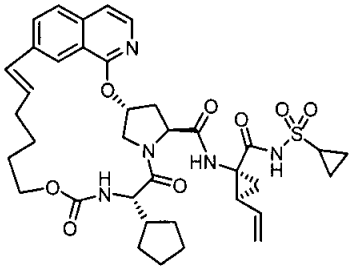
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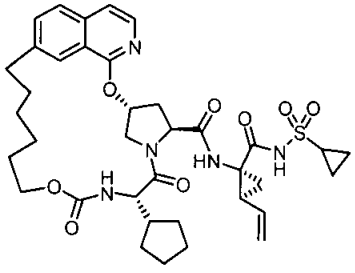
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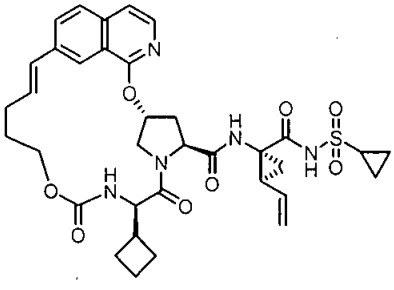
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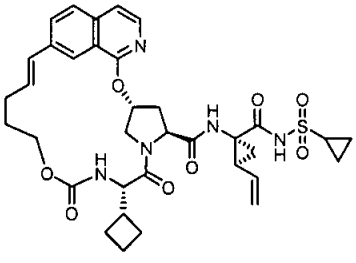
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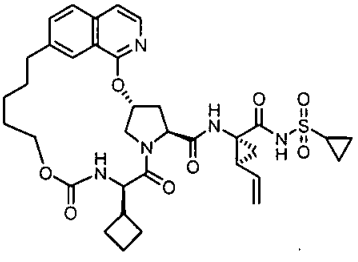
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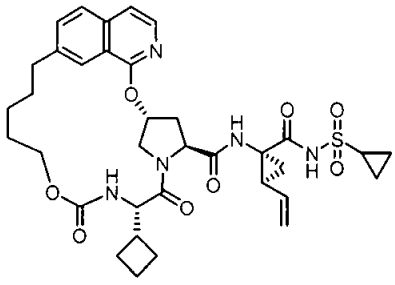
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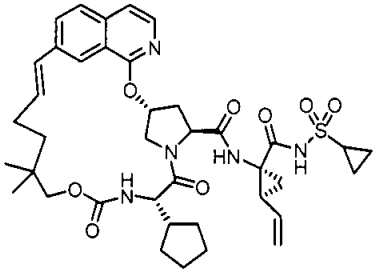
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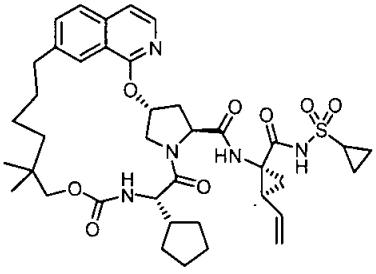
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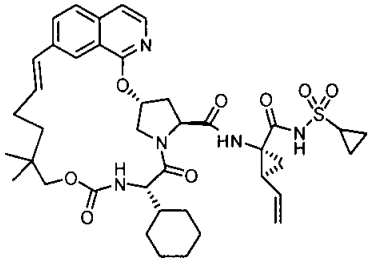
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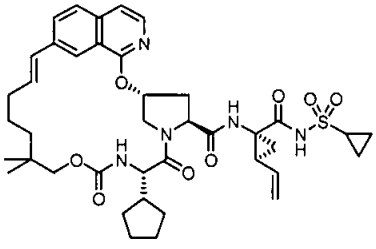
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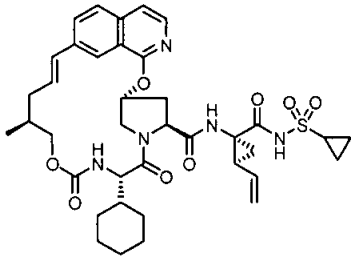
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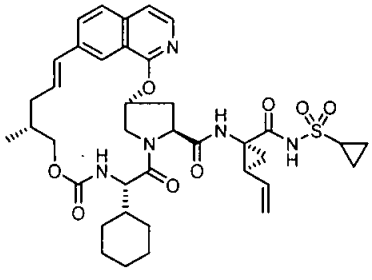
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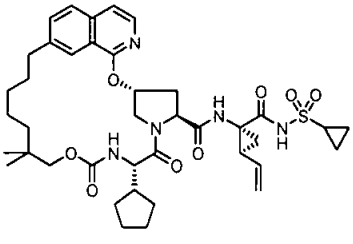
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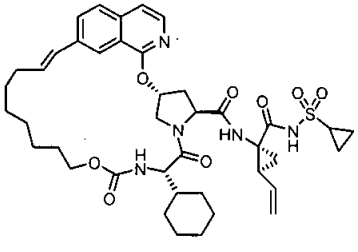
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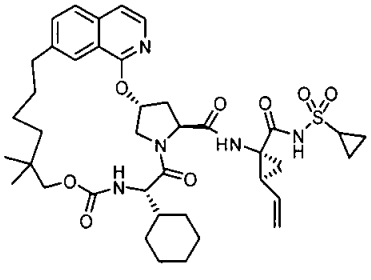
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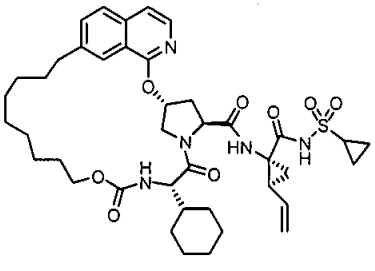
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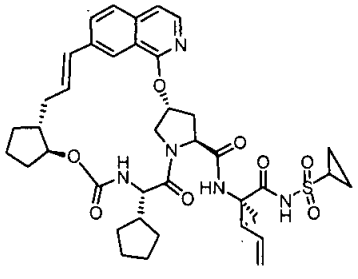
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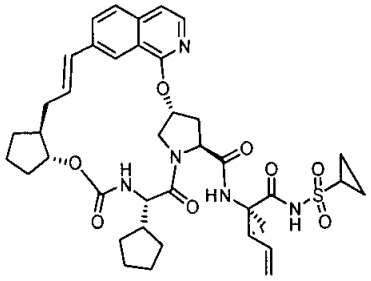
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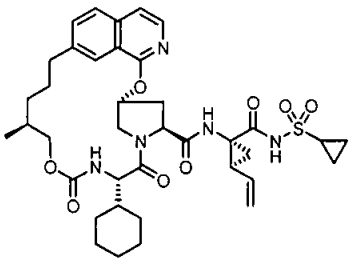
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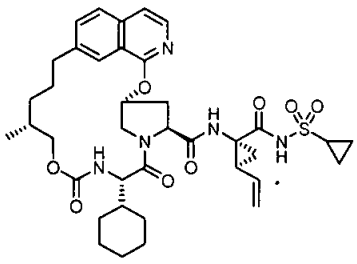
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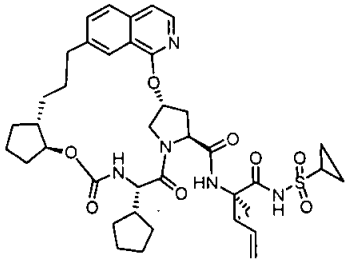
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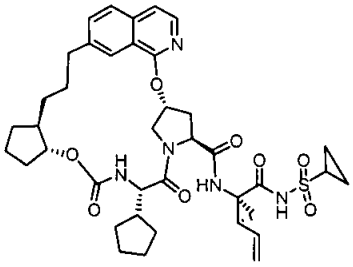
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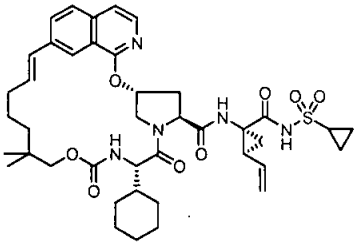
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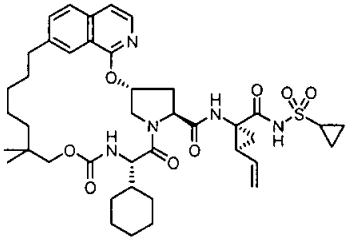
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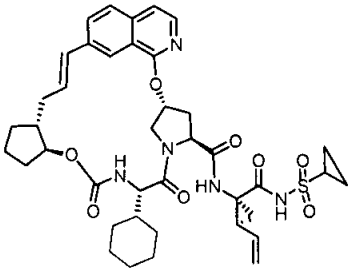
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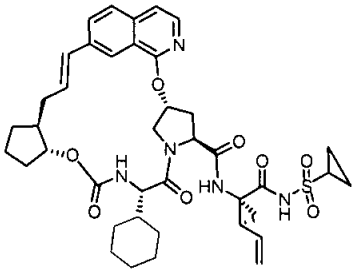
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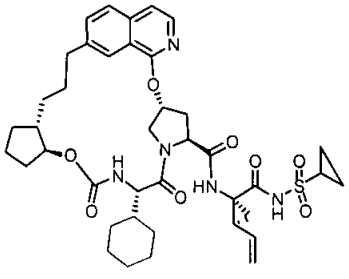
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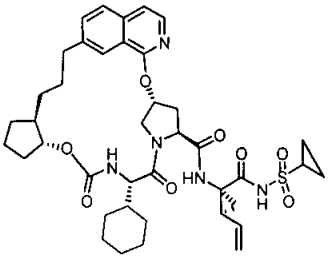
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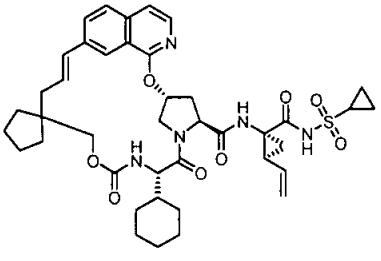
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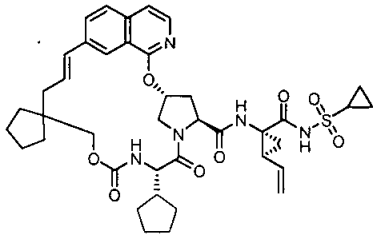
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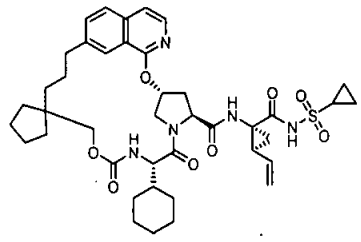
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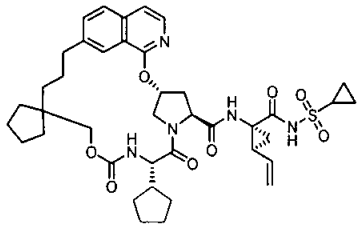
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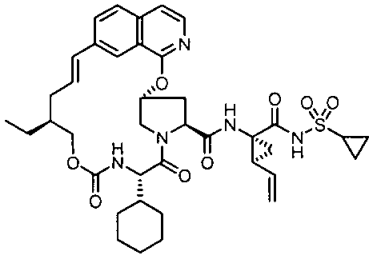
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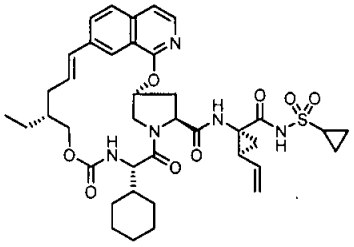
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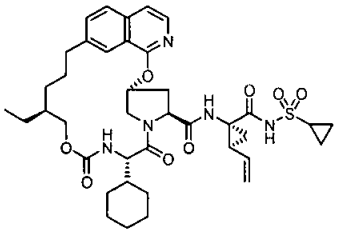
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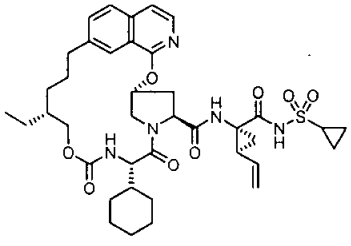
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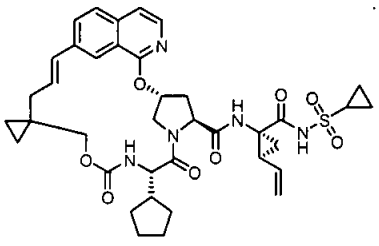
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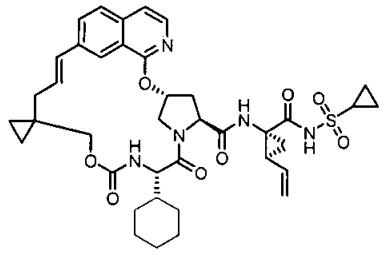
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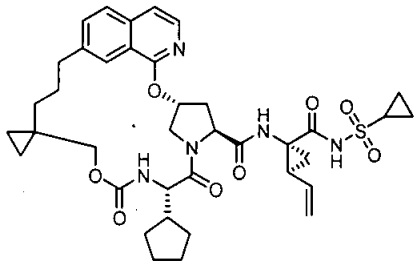
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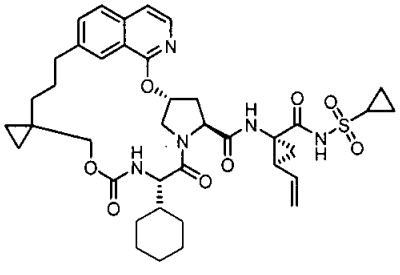
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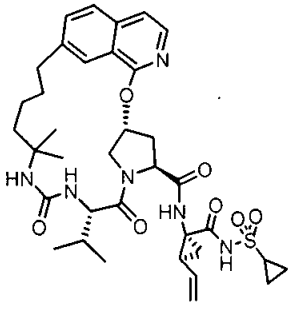
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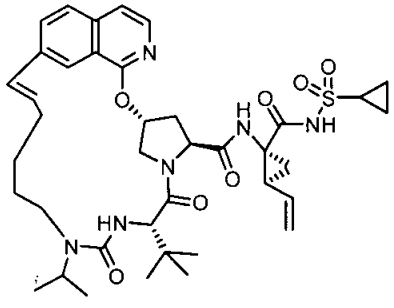
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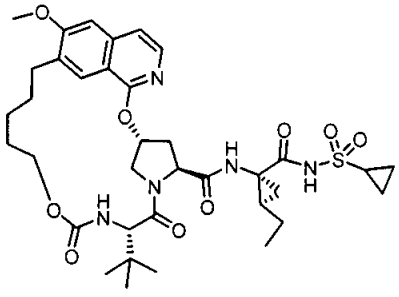
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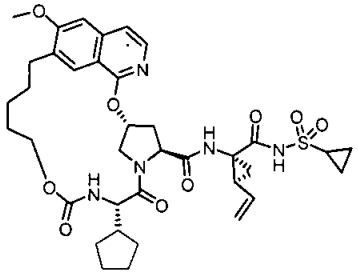
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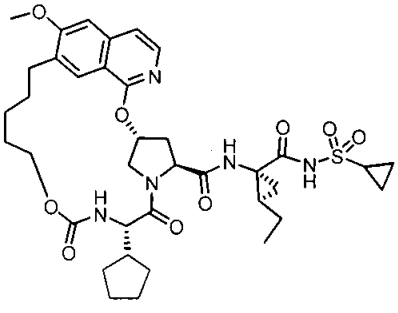
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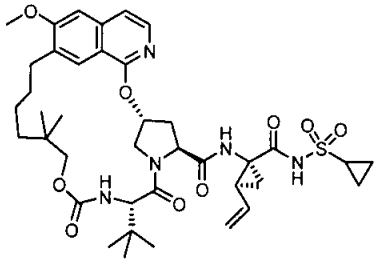
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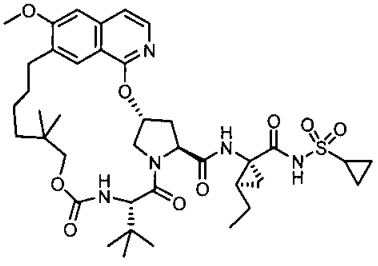
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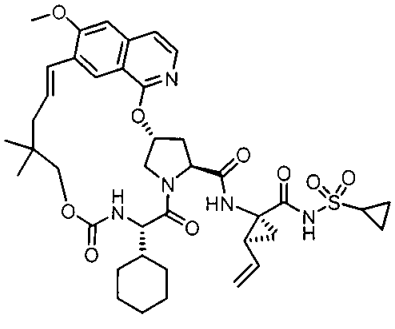
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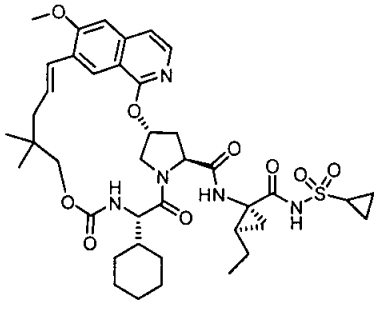
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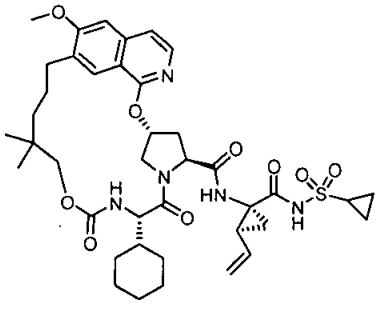
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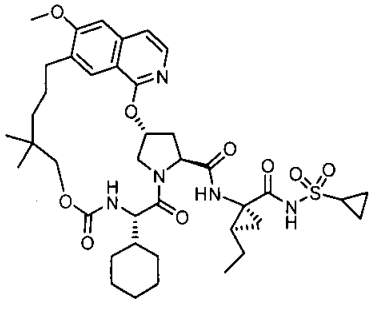
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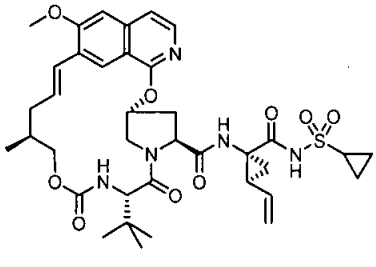
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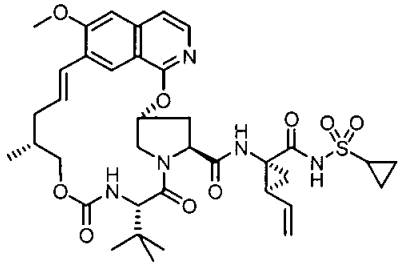
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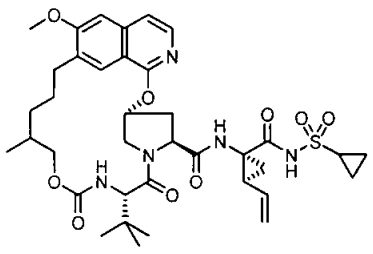
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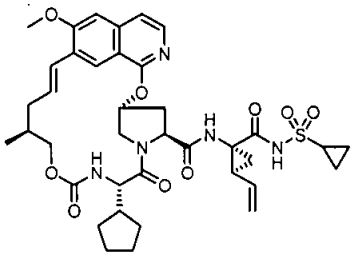
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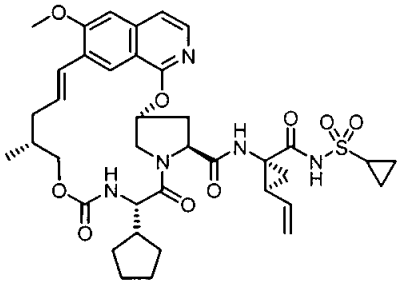
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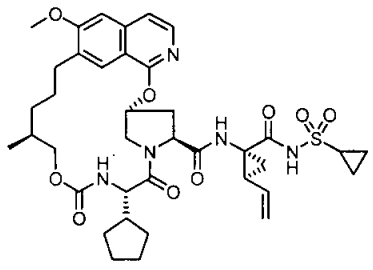
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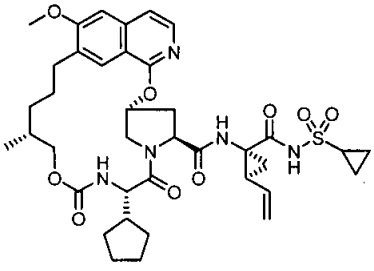
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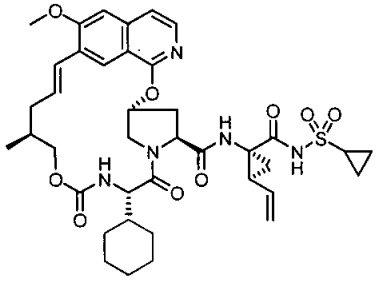
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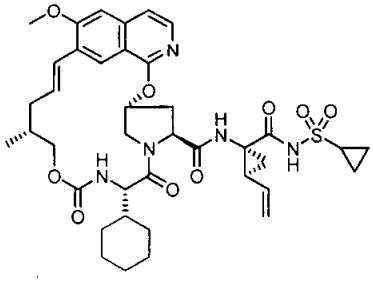
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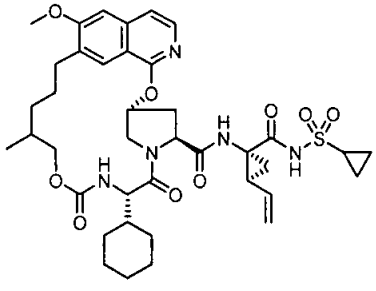
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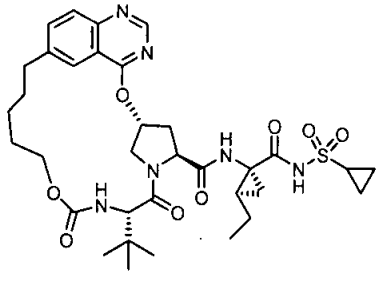
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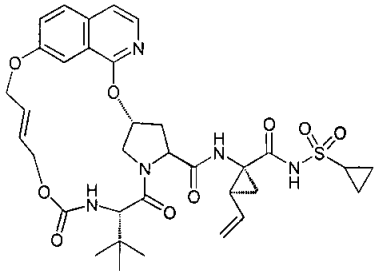
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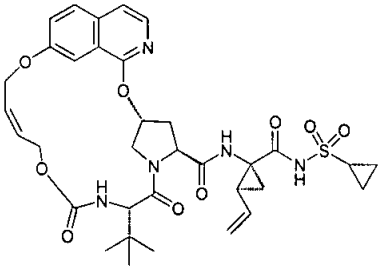
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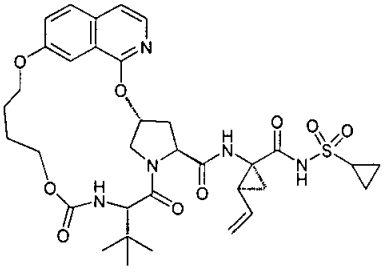
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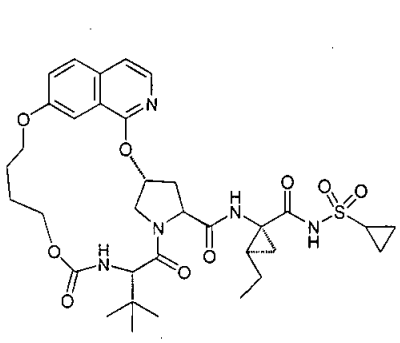
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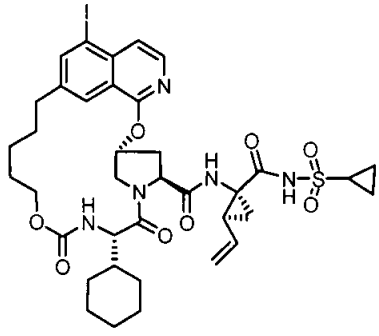
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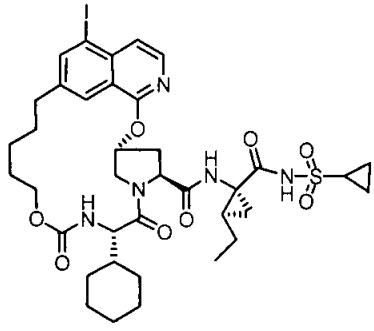
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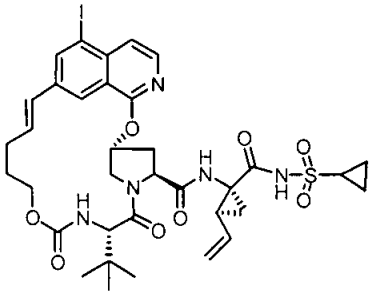
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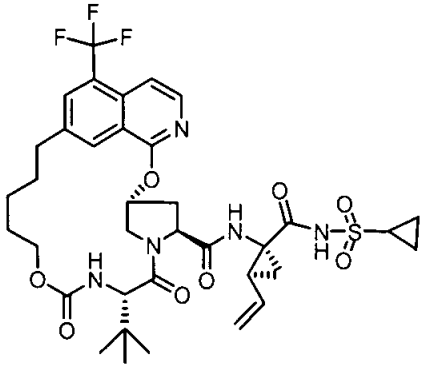
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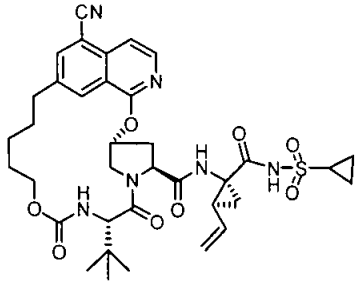
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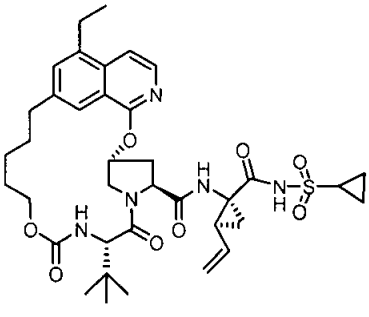
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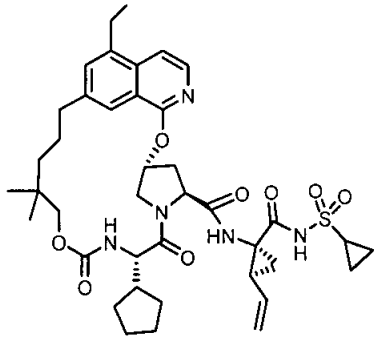
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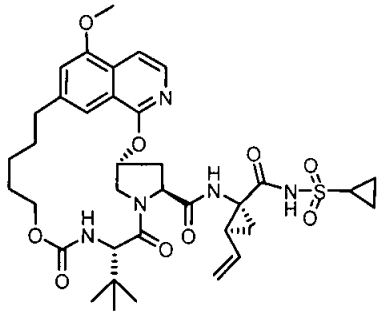
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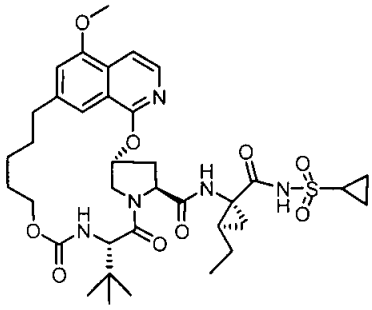
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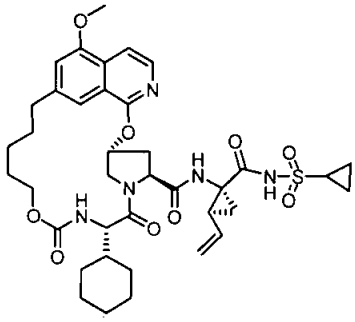
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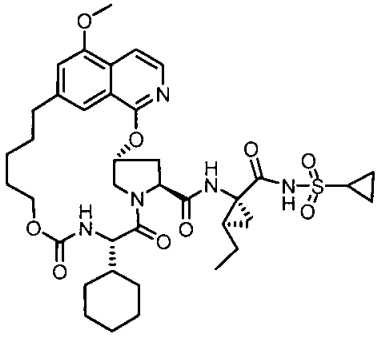
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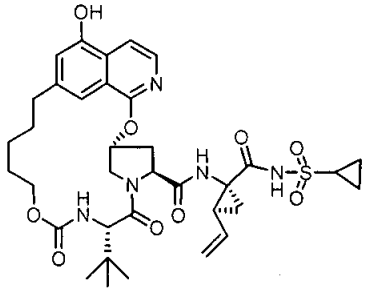
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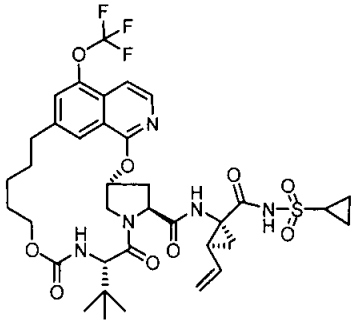
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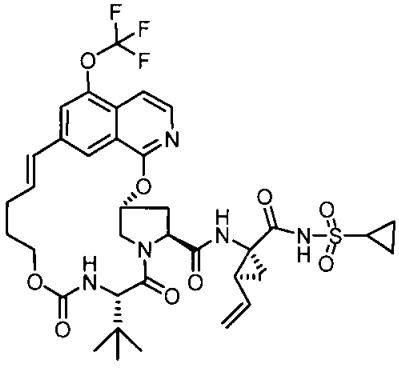
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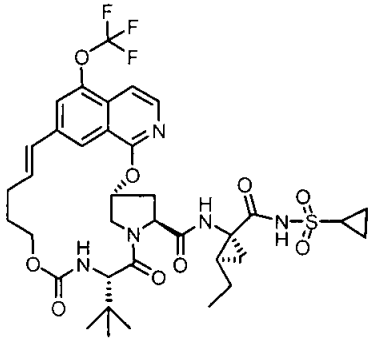
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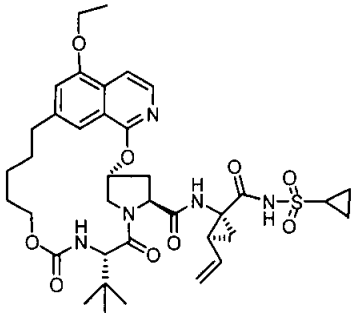
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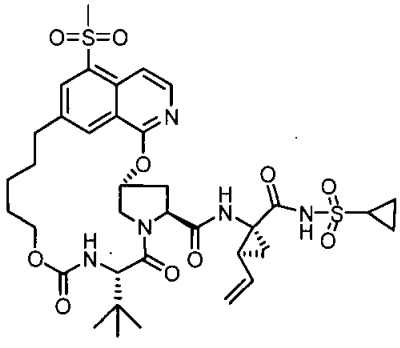
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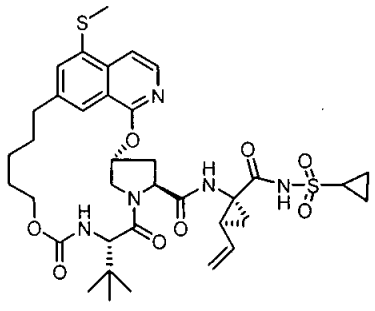
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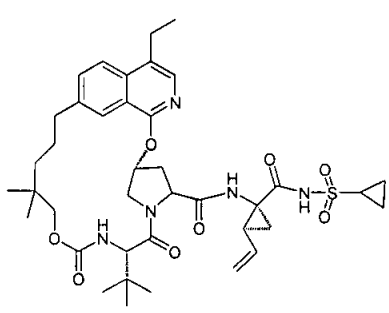
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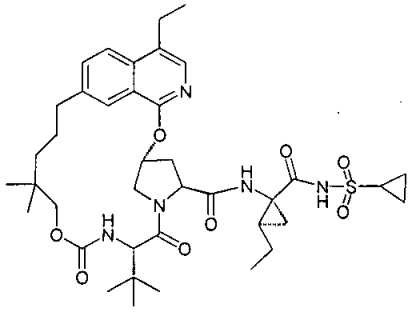
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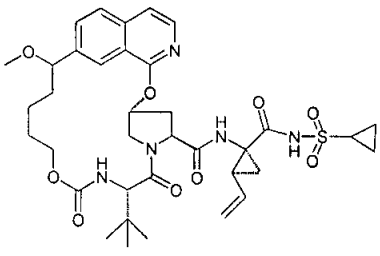
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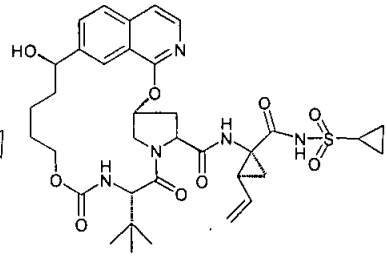
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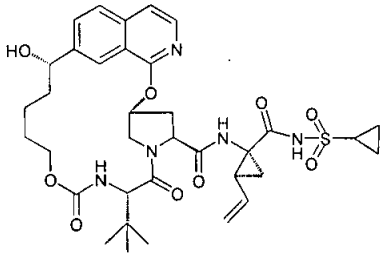
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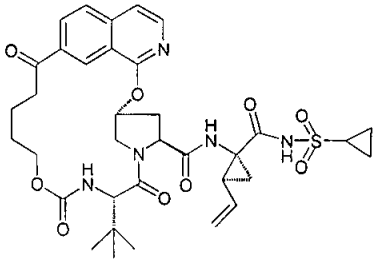
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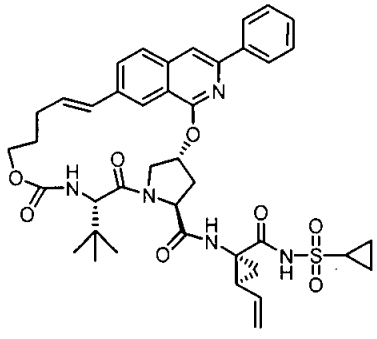
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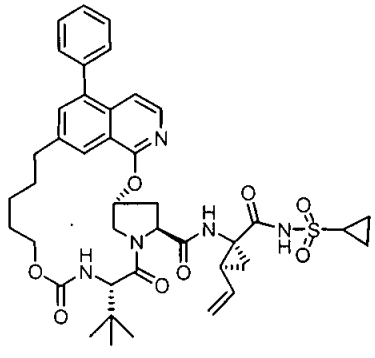
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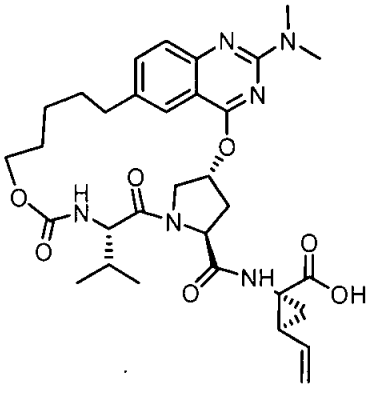


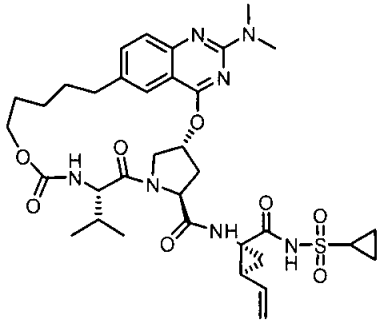
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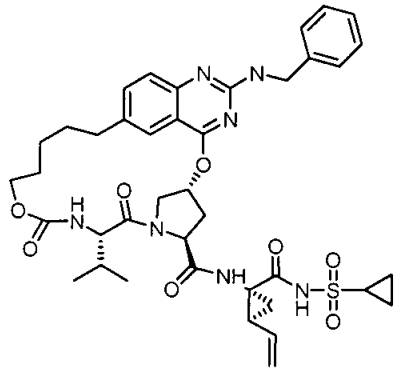
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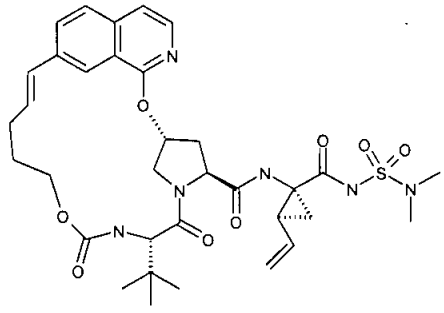




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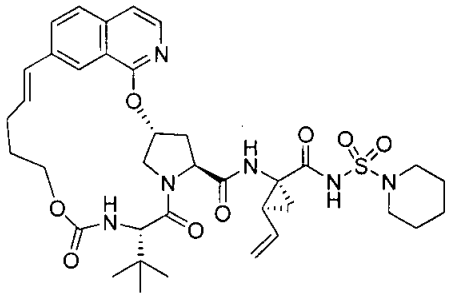


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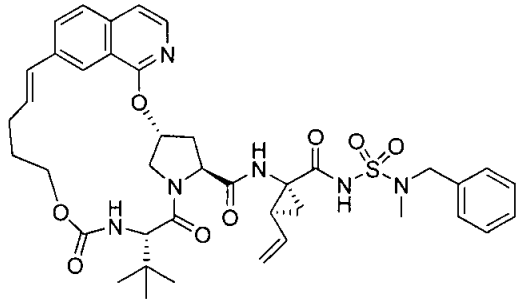


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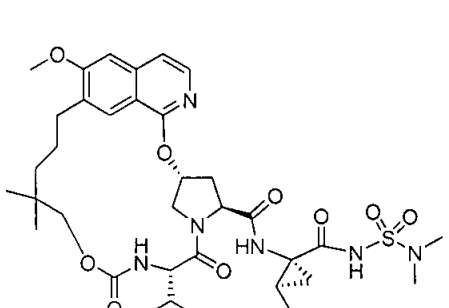
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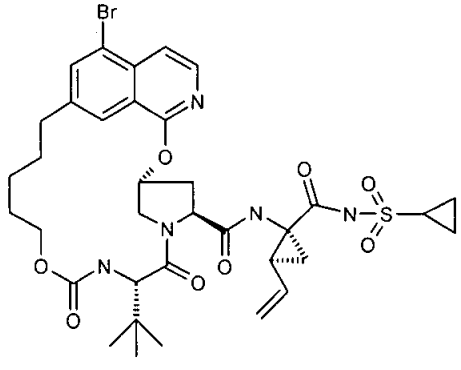
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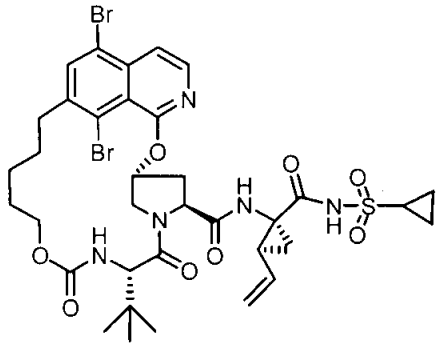


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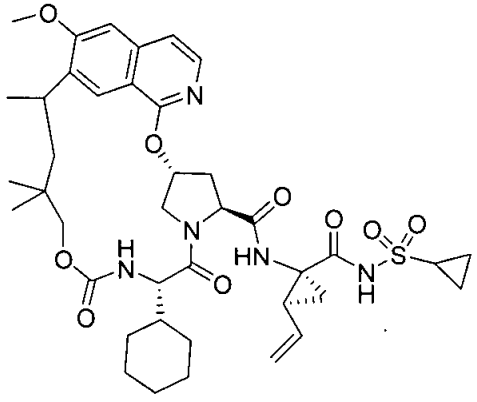
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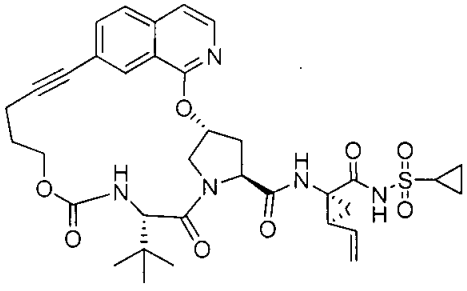




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III-185

24. El compuesto de la reivindicación 1, en el que el compuesto es ácido (1*R*,2*S*)-1-({[(2*R*,4*S*,7*S*)-7-terc-butil-6,9-dioxo-3,4,6,7,8,9,12,13-octahidro-2*H*,11*H*-16,18-etanodiilideno-2,5-metanopirido[2,3-*k*][1,10,3,6]dioxadiazaciclononadecin-4-il]carbonil}amino)-2-vinilciclopropanocarboxílico.

25. Una composición farmacéutica que comprende una cantidad efectiva de un compuesto de una cualquiera de las reivindicaciones 1-24, y un vehículo farmacéuticamente aceptable.

26. La composición farmacéutica de la reivindicación 25, que comprende adicionalmente un segundo agente terapéutico seleccionado del grupo constituido por un agente antiviral VHC, un inmunomodulador, y un agente antiinfeccioso.

27. La composición farmacéutica de la reivindicación 26, en la que el agente antiviral de VHC es un antiviral seleccionado del grupo constituido por un inhibidor de proteasa de VHC y un inhibidor de polimerasa NS5B de VHC.

28. Un uso de un compuesto de una cualquiera de las reivindicaciones 1-24 en la preparación de un medicamento para inhibir actividad de proteasa NS3 de VHC en un sujeto en necesidad del mismo.

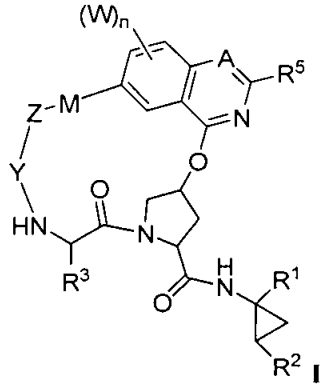
29. Un uso de un compuesto de una cualquiera de las reivindicaciones 1-24 en la preparación de un medicamento para prevenir o tratar infección por VHC en un sujeto en necesidad del mismo.

30. El uso de la reivindicación 29, en el que dicho medicamento comprende adicionalmente al menos un segundo agente terapéutico seleccionado del grupo constituido por un agente antiviral VHC, un inmunomodulador, y un agente antiinfeccioso.

31. El uso de la reivindicación 30, en el que el agente antiviral contra VHC es un antiviral seleccionado del grupo constituido por un inhibidor de proteasa de VHC y un inhibidor de polimerasa NS5B de VHC.

RESUMEN DE LA DESCRIPCIÓN

La presente invención se refiere a compuestos macrocíclicos de fórmula (**I**) que son útiles como inhibidores de la proteasa NS3 del virus de la hepatitis C (VHC), su síntesis, y su uso para tratar o prevenir la infección de VHC.



I

Patent Department (RSP NO REPLY) 1) Reply to Search By 331 2/12/07

DEC 15 2006

RECEIVED MERCK & CO.

RICHARD S. PARR

2) Reply to Written w/ Demand (RSP NO REPLY) By 6/1/07

From the INTERNATIONAL SEARCHING AUTHORITY

2006 DEC 13 PM 2:44

PCT

To:

MERCK & CO., INC.
126 East Lincoln Avenue
Rahway, NJ 07065-0907
ETATS-UNIS D'AMERIQUE

PATENT DOCKET

PAT. REG. COORD
DOCKET
ATTORNEY
MAINTENANCE
CASE REFERENCE CLERK
OTHER

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

RECEIVED 01/3/07 Crw

(PCT Rule 44.1)

Applicant's or agent's file reference PCT 22021Y	Date of mailing *(day/month/year)* 12/12/2006
International application No. PCT/US2006/029635	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant MERCK & CO., INC.	International filing date *(day/month/year)* 28/07/2006

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority	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	Federico Bonomelli

Form PCT/ISA/220 (October 2005) *(See notes on accompanying sheet)*

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT 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.
PCT 22021Y		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2006/029635	28/07/2006	01/08/2005
Applicant		
MERCK & CO., INC.		

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 4 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:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:
   MACROCYCLIC PEPTIDES AS HCV NS3 PROTEASE INHIBITORS

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

INTE ATIONAL SEARCH REPORT

rnational application No
PCT/US2006/029635

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K5/08 C07K5/10 C07K7/06 A61K38/06 A61K38/07
A61K38/08 A61P31/14

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)
C07K A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
1 Y	WO 03/064455 A2 (BOEHRINGER INGELHEIM CA LTD [CA]; LLINAS-BRUNET MONTSE [CA]; GORYS VID) 7 August 2003 (2003-08-07) abstract examples claims	1-31
2 Y	WO 00/09543 A2 (BOEHRINGER INGELHEIM CA LTD [CA]; LLINAS BRUNET MONTSE [CA]; BAILEY MU) 24 February 2000 (2000-02-24) abstract examples claims	1-31

-/--

[X] Further documents are listed in the continuation of Box C. [X] See patent family 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
23 November 2006	12/12/2006

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	Stix-Malaun, Elke

2

Form PCT/ISA/210 (second sheet) (April 2005)

INT..NATIONAL SEARCH REPORT

..nternational application No
PCT/US2006/029635

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	POUPART ET AL: J.ORG.CHEM., vol. 66, no. 14, 2001, pages 4743-4751, XP002408789 abstract page 4744; examples 4-6,8 page 4745; table 1	1-31



Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INT. NATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/029635

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03064455 A2	07-08-2003	BR 0307297 A	21-12-2004
		CA 2369711 A1	30-07-2003
		CN 1639187 A	13-07-2005
		EP 1472278 A2	03-11-2004
		HR 20040689 A2	30-06-2005
		JP 2005524632 T	18-08-2005
		MX PA04007462 A	13-07-2005
		NZ 534929 A	31-08-2006
		US 2003181363 A1	25-09-2003
		ZA 200405639 A	01-07-2005
WO 0009543 A2	24-02-2000	AU 769738 B2	05-02-2004
		AU 5273199 A	06-03-2000
		BR 9913646 A	05-06-2001
		CA 2338946 A1	24-02-2000
		CN 1323316 A	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 A2	28-02-2002
		HU 0105144 A2	29-04-2002
		ID 27839 A	26-04-2001
		JP 2002522554 T	23-07-2002
		KR 20060083992 A	21-07-2006
		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

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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2006/029635	28.07.2006	01.08.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07K5/08 C07K5/10 C07K7/06 A61K38/06 A61K38/07 A61K38/08 A61P31/14

Applicant
MERCK & CO., INC.

1. This opinion 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 Rule 43*bis*.1(a)(i) 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

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Stix-Malaun, Elke Telephone No. +49 89 2399-8057

Form (PCT/ISA/237) (Cover Sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2006/029635

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2006/029635

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-31
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-31
Industrial applicability (IA)	Yes:	Claims	1-31
	No:	Claims	

2. Citations and explanations

see separate sheet

V REASONED STATEMENT

1. PRIOR ART

The documents cited in the International Search Report

D1: WO 03/064455 A2 (BOEHRINGER INGELHEIM CA LTD [CA]; LLINAS-BRUNET MONTSE [CA]; GORYS VID) 7 August 2003 (2003-08-07)
D2: WO 00/09543 A2 (BOEHRINGER INGELHEIM CA LTD [CA]; LLINAS BRUNET MONTSE [CA]; BAILEY MU) 24 February 2000 (2000-02-24)
D3: POUPART ET AL: J.ORG.CHEM., vol. 66, no. 14, 2001, pages 4743-4751, XP002408789

have been considered for the examination procedure.

2. NOVELTY

The subject-matter of the claims is considered to be novel (Article 33(2) PCT). The essential structural difference between the claimed compounds and those of D1-D3 resides in the macrocycle including the pyrrolidine unit and the isoquinoline/benzpyrimidin unit.

3. INVENTIVE STEP

The subject-matter of the claims does not appear to fulfil the requirements of Article 33(3) PCT for the following reasons:

The problem of the present application may be seen in the provision of further macrocyclic peptides which exhibit activity against the HCV NS3 protease and which are therefore useful in the treatment of hepatitis C.

The closest state of the art for the present application is represented by D1. D1 discloses structurally similar macrocyclic peptides having the same properties. The compounds of D1 exhibit the same key structural features: cyclopropaneacid, pyrrolidinoxy, chinoline linked via peptide chains. In contrast to the present application the macrocycle is formed between the cyclopropane unit and the

pyrrolidine unit whereas presently the isoquinoline unit is linked via a macrocycle with the pyrrolidine unit.

From D2 and D3 it is derivable (see passages of the ISR) that variation in this respect is possible without losing the alleged activity as long as the key structural features are present (see above).

In view of the close structural relationship to the compounds of D1 it is considered that the man skilled in the art would regard the new compounds of the application as obvious alternatives to the known compounds.

Accordingly beneficial effects have to be demonstrated. In the absence of comparative tests or further information it is not possible to acknowledge inventive step.

Bitte beachten Sie, dass angeführte Nichtpatentliteratur (wie z. B. wissenschaftliche oder technische Dokumente) je nach geltendem Recht dem Urheberrechtsschutz und/oder anderen Schutzarten für schriftliche Werke unterliegen könnte. Die Vervielfältigung urheberrechtlich geschützter Texte, ihre Verwendung in anderen elektronischen oder gedruckten Publikationen und ihre Weitergabe an Dritte ist ohne ausdrückliche Zustimmung des Rechtsinhabers nicht gestattet.

Veuillez noter que les ouvrages de la littérature non-brevets qui sont cités, par exemple les documents scientifiques ou techniques, etc., peuvent être protégés par des droits d'auteur et/ou toute autre protection des écrits prévue par les législations applicables. Les textes ainsi protégés ne peuvent être reproduits ni utilisés dans d'autres publications électroniques ou imprimées, ni rediffusés sans l'autorisation expresse du titulaire du droit d'auteur.

Please be aware that cited works of non-patent literature such as scientific or technical documents or the like may be subject to copyright protection and/or any other protection of written works as appropriate based on applicable laws. Copyrighted texts may not be copied or used in other electronic or printed publications or re-distributed without the express permission of the copyright holder.

XS CPRTENFRDE

BNSDOCID: <XS____2006100103CF_I_>

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-010100- -00000-0000
Fecha: 2008-02-01 17:08:26 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 342

343

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-010100- -00000-0000
Fecha: 2008-02-01 17:08:26 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 342

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Claudia M Nava Cortes
Firma Responsable

Fecha _____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
MERCK & CO, INC.

REFERENCIA	Radicación No.	8 10100
	Solicitud internacional	PCT/US2006/029635
	Fecha inicio fase nacional	01/03/2008
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	3127

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 29 FEB. 2008
adpa11

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OLARTERAISBECK
OLARTE RAISBECK FRIERI MOURE & CASTRO LTDA.

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. S.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-010100- -00002-0000
Fecha: 2008-03-11 16:00:00 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 444 RESPUESTAREQUE Folios: 13

Ref.: Expediente N°. 08-010.100

Solicitud de Patente de Invención titulada: "PEPTIDOS MACROLIDOS COMO INHIBIDORES DE LA PROTEASA NS3 DEL VHC".

Solicitante: MERCK & CO., INC.

Nuestra Ref.: P2008/000025

RESPUESTA AL OFICIO N°. 3127 NOTIFICADO POR FIJACION EN LISTA No. 58, DE FECHA 29 DE FEBRERO DE 2008 (EXAMEN DE FORMA)

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, me permito dar respuesta al auto emanado de ese Despacho, dentro del término legal previsto en el artículo 39 de la Decisión 486, en los siguientes términos:

1. En respuesta a la única observación del Examinador, me permito aportar junto al presente memorial, dos (2) documentos de cesión debidamente legalizados (el primer documento de seis inventores al solicitante, el segundo del inventor faltante al solicitante), junto con su correspondiente traducción, según lo previsto en el Art. 26- k de la Decisión 486.

Atentamente,

CARLOS R. OLARTE
C.C. N°. 79.782.747 de Bogotá
T.P. 74.295

Anexos: Documento de Cesión

APOSTILLA

(Convención de la Haya, Octubre 5, 1961)

1. PAIS: ESTADOS UNIDOS DE AMERICA ESTE DOCUMENTO PÚBLICO

2. HA SIDO FIRMADO POR BARBARA ANN COZZI

3. ACTUANDO EN SU CALIDAD DE NOTARIO PUBLICO DE NEW JERSEY

4. LLEVA EL SELLO /ESTAMPILLA DE BARBARA ANN COZZI, NOTARIO.

CERTIFICADO

5. EN TRENTON, NUEVA JERSEY

6. EL DIA 13 DE FEBRERO DE 2008

7. POR Michellene Davis, TESORERO DE NUEVA JERSEY

8. No. A317304

9. SELLO/ESTAMPILLA

10. FIRMADO

(HAY FIRMA) MICHELLENE

(SELLO DORADO): ESTADO DE NUEVA JERSEY

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RECONOCIMIENTO

ESTADO DE NUEVA JERSEY) SS:

CONDADO DE UNION)

Yo DANISE MARKOWSKI, con el presente juro que las fotocopias anexas de: cesiones y acuerdos de estados unidos, Caso No. 22021YS, titulado "**INHIBIDORES DE LA PROTEASA NS3 DEL VHC",** son autenticas, correctas y completas copias de los documentos originales por los cuales yo tengo responsabilidad de custodia.

Firma.

DENSE MARKOWSKI
Asociado de Personal II

Suscrito y Juramentado ante mi el 27 de noviembre de 2007.

(firma) BARBARA ANN COZZI
Notario Publico de New Jersey
Mi comisión vence el 30 de Noviembre de 2008

Caso Extranjero No.: 22021YS

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Caso Documento No. 22021YS
U.S. Serial No.
Fecha de presentación
Solicitud PCT No.
Fecha de presentación:

CESION Y ACUERDO

Por valor recibido, nosotros, Nigel J. Liverton, John A. McCauley, Michael T. Rudd, Joseph P. Vacca, Steven W. Ludmerer, Y David B. Olsen.

Domiciliados en
171 Forest Trail Drive, Lansdale, PA 19446; 786 Sharon Lane, Harleysville, PA 19438; 1566 Bauman Drive, Maple Glen, PA 19002; 236 Winterverry Lane, Collegiville, PA 19426; 733 Indian Creek Road, Telford, PA 18969, 100 Holl Court, North Wales, PA 19454; 1640 Quarry road, Lansdale, PA 19446 respectivamente,

con el presente vendo, cedo y transfiero a **MERCK & CO.**, una corporación del estado de New Jersey, con una sede en Lincoln Avenue, City of Rahway, Estado de New Jersey, y sus sucesores, cesionarios y representantes legales, todo mi derecho, título e interés, para todos los países, en y para ciertos inventos relacionados con "**INHIBIDORES DE LA PROTEASA NS3 DEL VHC**" descrito en una solicitud de Patente con Número de Registro de Abogado 22021YS, en la solicitud serial No. 60/704,256, radicada el 08/01/2005; Serial No. 60/724,509 Radicada el 10/07/2005; Serial No.; radicada el (es aplicable), y todos mis derechos y privilegios, incluyendo cualquiera y todos los beneficios bajo la Convención Internacional para la Protección de la Propiedad Industrial, bajo cualquiera y todas las Patentes que puedan ser conferidas, y bajo cualquiera y todas las extensiones, divisionales y re-expediciones y continuaciones de dicha solicitud por Patentes, incluyendo cualquier solicitud extranjera derivadas de la misma, equivalente, o reclamando prioridad en la misma.

Solicito que cualquiera y todos las Patentes por dichos inventos sen expedidas a dicho concesionario, o a sus sucesores, cesionarios, y representantes legales, o a sus nominados según este lo designe.

Acepto que, a solicitud, yo, sin costo alguno para dicho cesionario, pero por su cuenta, realizaré todos los juramentos legales, y haré todos los actos que sean necesarios, deseables o convenientes para asegurar y mantener las Patentes para dichos inventos en cualquiera y en todos los países para conferir titulo a dicho concesionario, o a sus sucesores, cesionarios, y representantes legales, o a sus nominados.

Nosotros, acordamos con dicho cesionario, o a sus sucesores, cesionarios, y representantes legales, que los derechos y propiedad conferidos

con el presente están libres de cualquier gravamen, y que yo tengo todo el derecho para transferir los mismos como se expresa en el presente.

Con el presente autorizo a mi apoderado Richard S. Parr, o a un abogado con Poder de Representación en esta solicitud, del mencionado MERCK & CO., Inc, para insertar el Nr(s) de Serie, Solicitud PCT Nr(s) y Fecha(s) de Radicado de dicha solicitud(s) cuando sean conocidos.

Firmado en West Point PA el día 13 del mes de julio de 2006.

(Fdo) Nigel J. Liverton
(Fdo) Michael T. Rudd,
(Fdo) Steven W. Ludmerer
(Fdo) John A. McCauley
(Fdo) Joseph P. Vacca
(Fdo) David B. Olsen

Provincia de Pennsylvania
Condado de Montgomery

Personalmente comparecieron ante mi los citados Nigel J. Liverton, John A. McCauley, Michael T. Rudd, Joseph P. Vacca, Steven W. Ludmerer, David B. Olsen conocido para mi como la persona que ejecutó el instrumento que antecede y reconoció que dicho instrumento es de su libre acto y escritura a los 13 días del mes de julio de 2006.

(FIRMADO Y SELLADO)
GABRIELLE A. GORDON
Notario Público
Condado de Montgomery
Mi comisión vence el 26 de Noviembre de 2009

(Sello) Comisionado de Pennsylvania

Caso Documento No. 22021YS
U.S. Serial No.
Fecha de presentación
Solicitud PCT No.
Fecha de presentación:

CESION Y ACUERDO

Por valor recibido, nosotros, M.Katharine Holloway

Domiciliados en
171 Forest Trail Drive, Lansdale, PA 19446 respectivamente,

con el presente vendo, cedo y transfiero a **MERCK & CO.**, una corporación del estado de New Jersey, con una sede en Lincoln Avenue, City of Rahway, Estado de New Jersey, y sus sucesores, cesionarios y representantes legales, todo mi derecho, título e interés, para todos los países, en y para ciertos inventos relacionados con "**INHIBIDORES DE LA PROTEASA NS3 DEL VHC"** descrito en una solicitud de Patente con Número de Registro de Abogado 22021YS, en la solicitud serial No. 60/704,256, radicada el 08/01/2005; Serial No. 60/724,509 Radicada el 10/07/2005; Serial No.; radicada el (es aplicable), y todos mis derechos y privilegios, incluyendo cualquiera y todos los beneficios bajo la Convención Internacional para la Protección de la Propiedad Industrial, bajo cualquiera y todas las Patentes que puedan ser conferidas, y bajo cualquiera y todas las extensiones, divisionales y re-expediciones y continuaciones de dicha solicitud por Patentes, incluyendo cualquier solicitud extranjera derivadas de la misma, equivalente, o reclamando prioridad en la misma.

Solicito que cualquiera y todos las Patentes por dichos inventos sen expedidas a dicho concesionario, o a sus sucesores, cesionarios, y representantes legales, o a sus nominados según este lo designe.

Acepto que, a solicitud, yo, sin costo alguno para dicho cesionario, pero por su cuenta, realizaré todos los juramentos legales, y haré todos los actos que sean necesarios, deseables o convenientes para asegurar y mantener las Patentes para dichos inventos en cualquiera y en todos los países para conferir titulo a dicho concesionario, o a sus sucesores, cesionarios, y representantes legales, o a sus nominados.

Nosotros, acordamos con dicho cesionario, o a sus sucesores, cesionarios, y representantes legales, que los derechos y propiedad conferidos con el presente están libres de cualquier gravamen, y que yo tengo todo el derecho para transferir los mismos como se expresa en el presente.

Con el presente autorizo a mi apoderado Richard S. Parr, o a un abogado con Poder de Representación en esta solicitud, del mencionado

MERCK & CO., Inc, para insertar el Nr(s) de Serie, Solicitud PCT Nr(s) y Fecha(s) de Radicado de dicha solicitud(s) cuando sean conocidos.

Firmado en West Point PA el día 12 del mes de julio de 2006.

(Fdo) M. Katharine Holloway

Provincia de Pennsylvania
Condado de Montgomery

Personalmente comparecieron ante mi los citados M. Katharine Holloway conocido para mi como la persona que ejecutó el instrumento que antecede y reconoció que dicho instrumento es de su libre acto y escritura a los 12 días del mes de julio de 2006.

(FIRMADO Y SELLADO)
GABRIELLE A. GORDON
Notario Público
Condado de Montgomery
Mi comisión vence el 26 de Noviembre de 2009

(Sello) Comisionado de Pennsylvania

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APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
BARBARA ANN COZZI

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

4. BEARS THE SEAL/STAMP OF:
BARBARA ANN COZZI, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

6. THE 13TH DAY OF FEBRUARY 2008

7. BY: R. David Rousseau, NEW JERSEY TREASURER

8. NO. A317304

9. SEAL/STAMP:



10. SIGNATURE



357

COLOMBIA

STATE OF NEW JERSEY)
)SS:
COUNTY OF UNION)

I, **DENISE MARKOWSKI**, hereby swear that the attached photocopies of: U.S. Assignments and Agreements, Case No. 22021Y, entitled "HCV NS3 PROTEASE INHIBITORS", are true, correct, and complete copies of the original documents for which I have custodial responsibility.

Denise Markowski

DENISE MARKOWSKI
STAFF ASSOCIATE II

Subscribed and sworn to before me this 27th day of November, 2007.

Barbara Ann Cozzi

NOTARY PUBLIC

Foreign Case No.: 22021Y

BARBARA ANN COZZI
Notary Public of New Jersey
My Commission Expires Nov. 30, 2008

PATENT

Attorney Docket Number 22021Y 353

ASSIGNMENT AND AGREEMENT

Filing Date _____

PCT Appl. No. _____

Filing Date _____

For value received, we, ~~M. Katharine Holloway~~, Nigel J. Liverton, John A. McCauley, Michael T. Rudd, Joseph P. Vacca, Steven W. Ludmerer and David B. Olsen

of 171 Forest Trail Drive, Lansdale, PA 19446; 786 Sharon Lane, Harleysville, PA 19438; 1566 Bauman Drive, Maple Glen, PA 19002; 236 Winterberry Lane, Collegeville, PA 19426; 733 Indian Creek Road, Telford, PA 18969; 100 Holl Court, North Wales, PA 19454; 1640 Quarry Road, Lansdale, PA 19446 respectively;

hereby sell, assign and transfer to MERCK & CO., Inc., a corporation of the State of New Jersey, having an office at Lincoln Avenue, City of Rahway, State of New Jersey, and its successors, assigns and legal representatives, our entire right, title and interest, for all countries, in and to certain inventions relating to

HCV NS3 PROTEASE INHIBITORS

described in an application for Patents having Attorney Docket Number 22021Y and in application(s) Serial No. 60/704,256 filed on 08/01/2005 ; Serial No. 60/724,509 filed on 10/07/2005 ; Serial No. filed on (if applicable),

and all our rights and privileges, including any and all benefits under the International Convention for the Protection of Industrial Property, under any and all Patents which may be granted therefor, and under any and all extensions, divisionals, reissues and continuations of said application for Patents, including any foreign applications derived therefrom, equivalent thereto or claiming priority thereof.

We request that any and all Patents for said inventions be issued to said assignee, its successor, assigns and legal representatives, or to such nominees as it may designate.

We agree that, when requested, we will, without charge to said assignee but at its expense, sign all papers, take all rightful oaths, and do all acts which may be necessary, desirable or convenient for securing and maintaining Patents for said inventions in any and all countries and for vesting title thereto in said assignee, its successors, assigns and legal representatives or nominees.

We covenant with said assignee, its successors, assigns and legal representatives, that the rights and property herein conveyed are free and clear of any encumbrance, and that we have full right to convey the same as herein expressed.

This document may be executed in any number of counterparts, each of which so executed shall be deemed to be an original, but all such counterparts shall together constitute but one and the same document.

We hereby authorize our attorney, Richard S. Parr or an attorney with Power of Attorney in this application, of the said MERCK & CO., Inc., to insert **Serial No. (s), PCT Appl. No. (s)** and **Filing Date (s)** of said application(s) when known.

PATENT

Attorney Docket Number 22021Y

ASSIGNMENT AND AGREEMENT

Filing Date

PCT Appl. No.

Filing Date

Signed at West Point, PA this 13th day of July, 2006

~~M. Katharine Holloway~~

John A. McCauley

Joseph P. Vacca

David B. Olsen

Nigel J. Liverton

Michael T. Rudd

Steven W. Ludmerer

COMMONWEALTH OF PENNSYLVANIA

County of Montgomery } SS.

Personally appeared before me the above-named ~~M. Katharine Holloway~~ John A. McCauley Joseph P. Vacca David B. Olsen Nigel J. Liverton Michael T. Rudd Steven W. Ludmerer

to me known and known to me to be the person(s) who executed the foregoing instrument and acknowledged said instrument to be their free act and deed this 13th day of July, 2006.

Gabrielle A. Gordon

Notary Public

COMMONWEALTH OF PENNSYLVANIA
Notarial Seal
Gabrielle A. Gordon, Notary Public
Upper Gwynedd Twp., Montgomery County
My Commission Expires Nov. 26, 2009
Member, Pennsylvania Association of Notaries

PATENT

Attorney Docket Number 22021Y

Filing Date

PCT Appl. No.

Filing Date

ASSIGNMENT AND AGREEMENT

For value received, I, M. Katharine Holloway

residing at: 171 Forest Trail Drive, Lansdale, PA 19446 respectively,

hereby sell, assign and transfer to MERCK & CO., Inc., a corporation of the State of New Jersey, having an office at Lincoln Avenue, City of Rahway, State of New Jersey, and its successors, assigns and legal representatives, my entire right, title and interest, for all countries, in and to certain inventions relating to

HCV NS3 PROTEASE INHIBITORS

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I agree that, when requested, I will, without charge to said assignee but at its expense, sign all papers, take all rightful oaths, and do all acts which may be necessary, desirable or convenient for securing and maintaining Patents for said inventions in any and all countries and for vesting title thereto in said assignee, its successors, assigns and legal representatives or nominees.

I covenant with said assignee, its successors, assigns and legal representatives, that the rights and property herein conveyed are free and clear of any encumbrance, and that I have full right to convey the same as herein expressed.

I hereby authorize my attorney Richard S. Parr

an attorney with Power of Attorney in this application, of the said MERCK & CO., Inc., to insert the **Serial No. (s), PCT Appl. No. (s),** and **Filing Date (s)** of said application(s) when known.

Signed at West Point, PA this 12 day of July, 2006

M. Katharine Holloway

M. Katharine Holloway

PATENT

Attorney Docket Number 22021Y

Filing Date

PCT Appl. No.

Filing Date

ASSIGNMENT AND AGREEMENT

COMMONWEALTH OF PENNSYLVANIA

County of Montgomery } SS.

Personally appeared before me the above-named M. Katharine Holloway

to me known and known to me to be the person who executed the foregoing instrument and acknowledged said instrument to be

free act and deed this 12th day of July, 2006

Gabrielle A. Gordon *Notary Public*

COMMONWEALTH OF PENNSYLVANIA
Notarial Seal
Gabrielle A. Gordon, Notary Public
Upper Gwynedd Twp., Montgomery County
My Commission Expires Nov. 26, 2009
Member, Pennsylvania Association of Notaries

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 357

2020
Bogotá D.C.,

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
MERCK & CO, INC.

REFERENCIA	Radicación No.	8 10100
	Solicitud internacional	PCT/US2006/029635
	Fecha inicio fase nacional	01/03/2008
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	7279
	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, 11 DIC. 2008

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

adpa11

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Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No.08-010100

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **602** DE

FECHA **31** DE **MARZO DE 2009** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **02** DE **JULIO** DEL **2009**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ____ NO__ ___ **X** ___ _____