Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 05-117348

54. **TÍTULO** COMPUESTOS INHIBIDORES DE LA HEPATITIS C

51. **CLASIFICACIÓN INTERNACIONAL** A61P31/00 ; A61K31/47

71. **SOLICITANTE** BOEHRINGER INGELHEIM INTERNATIONAL GMBH

DOMICILIO Ingelheim am Rhein, República Federal de Alemania

74. **APODERADO** EMILIO FERRERO

C.C. 438.019 de Usaquén.

22. **BOGOTÁ, D. C.,** 18/11/2005.

(FORMA P-10)

SS

0-12 05

90971 -Imprenta nacional de Colombia- 2004

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA I COMERCIO
Radicacion : 05117348 00000000 Folios: 397
Fecha (AMD): 2005-11-18 17:35:08 ción
Remite : 011 PCT-PATENT 379 FASE NAC:1 411 PRESENTAC:
Dependencia: 2020 DIVISION DE NUEVAS SOLICITUDES

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL 21-Dic-05

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)

Nombre: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**
sociedad constituida y existente bajo las leyes de República Federal de Alemania..

Dirección: Binger strasse 173, 55216
Ingelheim am Rhein
Alemania

Domicilio: Ingelheim am Rhein
Alemania

IDENTIFICACIÓN
C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número ____

3 REPRESENTANTE O APODERADO

Nombre: EMILIO FERRERO
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@camvp.com.
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN
C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 438.019 T.P 31.929

4 INVENTOR (ES) (72)

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5 PCT (86)

Solicitud Internacional No. PCT/CA2004/000750 Fecha: 19 mayo de 2004
Publicación Internacional No. WO 2004/103996 A1 Fecha: 2 de diciembre de 2004

6 **Título (54)**

C MPUEST S INHIBID RES DE LA HEPATITIS C

7 **Clasificación Internacional (51)** C07D 417/04 ; A61P31/00 ; A61K31/47

8 **Prioridad** SI☒ NO☐

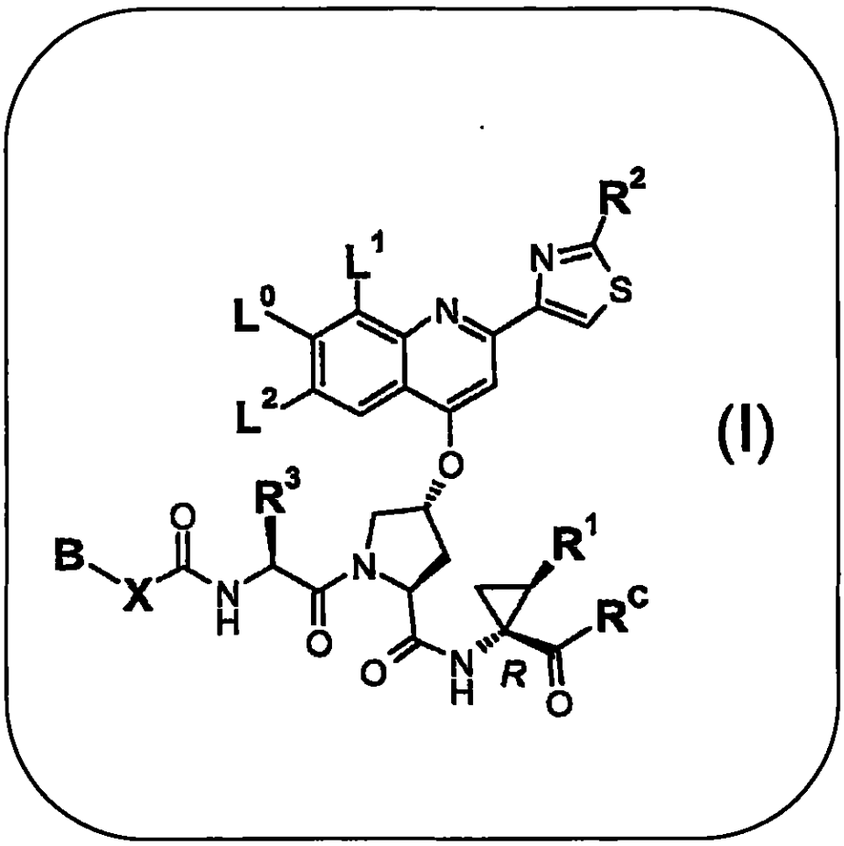
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	21 DE MAYO DE 2003	60/472.709

9 **Comprobante de pago No.:** 05-87.641 **Fecha:** 15 de Noviembre de 2005

10 **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 443.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar 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 12x12
- ☐ 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.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

(11) **FIGURA CARACTERÍSTICA**



(I)

(12) Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : _____

C.C. 436.019 de Usaquén T.P. 31.929

JDF

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2004/103996 **A1**
   Descripción:
   Páginas 141 en el idioma original
   Páginas _____ en español
   Reivindicaciones: Número (s) 56
   Figuras: Número (s) 0
2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.
3. ☒ **Forma PCT/ISA/237.** Opinión Escrita De La Administración Encargada De La Búsqueda Internacional.
3. ☒ **Forma PCT/IPEA/401.** PCT Demand
4. ☒ Extracto de publicación.

NO HUBO MODIFICACIONES EN FASE INTERNACIONAL

CONSULADO GENERAL DE COLOMBIA

MUNICH

Nr. 169

El Cónsul General de Colombia

C E R T I F I C A

Que el Dr. Hanns Paul Tüttenberg -----, quién autentica la firma del signatario en el presente documento, ejercía en la fecha allí indicada las funciones de Presidente del Tribunal Regional en Mainz. ----------

Que la firma BOEHRINGER INGELHEIM INTERNATIONAL GmbH, domiciliada en 55216 Ingelheim am Rhein, Registro Mercantil Nr. HR B 1063 del Juzgado Municipal de Bingen ----------
está constituída y ejerce su objeto social de conformidad con las leyes de la República Federal de Alemania.

Que los señores Dr. DIETER LADDIN Y Dr. GERHARD HUBER ----------

quien (es) firman el presente documento tiene (n) facultad legal suficiente para representar a la mencionada firma y otorgar poderes en su nombre.

Que ha tenido a la vista la documentación que prueba lo anterior.

Munich, 18 de Diciembre de 1995

RICARDO MOSQUERA MESA
CONSUL GENERAL DE COLOMBIA

CONSULADO GENERAL MUNICH

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL DOCUMENTO QUE HE TENIDO A LA VISTA
15 NOV 2005
MANUEL SUAREZ MEDINA
NOTARIO

Derechos para la Nación US $ 6.-
Fondo Rotatorio US $ 100.-
Tasa consular US $ 1 x DM 1,60 = DM 169.60 **PAGADO**

MINISTERIO DE RELACIONES EXTERIORES

0 5 1 0 0 5

DOCUMENTO DE SE...
LAS FUNCIONES INDICA...

NO SE ASUME RESPONSABILIDAD DEL TEXTO

ENE -4 A 11: 44

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C

1-104 5133

15 NOV 2005

IAL DE COLOMBIA

CAVELIER
ABOGADOS
EDIFICIO SISAL
CARRERA 4ª No. 72-35
BOGOTA, D.E. - COLOMBIA

For patents, utility models, industrial designs, trademarks, commercial names, trade emblems, slogans.

Para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, lemas comerciales.

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

9255
0569

I (we), the undersigned/Yo (nosotros), abajo firmado (s)
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

of/domiciliado (s) en D-55216 Ingelheim am Rhein,
GERMANY

por el presente nombramos a GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO, tpa. 31929; y LUZ CLEMENCIA DE PAEZ, tpa. 23555; domiciliados en la Carrera 4ª Nº 72-35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1º del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales; administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO, tpa. 31929; and LUZ CLEMENCIA DE PAEZ, tpa. 23555; domiciled at Carrera 4ª Nº 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact of its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition, and to authorize the said attorneys to represent me (us) before authorities or persons, with or without jurisdiction, especially those administrative, administrative-contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Ingelheim am Rhein, 12.12.1995
Given and signed this/Dado y firmado hoy

BOEHRINGER INGELHEIM
In/en INTERNATIONAL GMBH

ppa. ppa.

Dr. Dieter Laudien — Dr. Gerhard Huber
Signature — Firma

LEGALIZACION

El Señor Cónsul de Colombia debe expedir un *certificado consular* sobre (1) la existencia legal de la compañía que otorga el poder, (2) que ésta ejerce su objeto social, y (3) que las personas que otorgan el poder están autorizadas para darlo. A este efecto les solicitamos que muestren al Señor Cónsul las pruebas que acreditan esos hechos (1), (2) y (3).

LEGALIZATION

The Colombia Consul must issue a *consular certificate* on the legal existence of the company which grants the Power-of-Attorney, (2) that it is in actual exercise of its company purposes, and (3) that the persons who execute the Power of Attorney is autorized to do so. To this effect, please show the Consul the evidence to prove the above facts (1), (2) and (3).

EL COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

15 NOV 2005

JUAN MANUEL BOTERO MEDINA
NOTARIO

NOTA PARA EL SEÑOR CONSUL DE COLOMBIA: Según los artículos 65 del C. de P.C. y 480 del C. de Co., si el poderdante es una sociedad, el Señor Cónsul debe certificar que tuvo a la vista las pruebas de su existencia, que ejerce su objeto social y que quien confiere el poder es su representante.

UR.Nr. 2659 / 95 V

Vorseitige, vor mir gefertigte Namensunterschriften der Herren:

1. Dr. Dieter L a u d i e n, Dipl.-Chemiker, wohnhaft in 55127 Mainz,.

2. Dr. Gerhard H u b e r, Rechtsanwalt, wohnhaft in 55411 Bingen,

- mir bekannt -

beglaubige ich hiermit.

Gleichzeitig bescheinige ich aufgrund heutiger Einsichtnahme in das Handelsregister des Amtsgerichts Bingen, daß die Firma Boehringer Ingelheim International GmbH mit Sitz in Ingelheim am Rhein im Handelsregister des Amtsgerichts Bingen unter HR B 1063 eingetragen ist und daß die Herren Dr. Laudien und Dr. Huber als Prokuristen gemeinschaftlich zur Vertretung der Gesellschaft berechtigt sind.

Ingelheim am Rhein, den 12. Dezember 1995/hün

SEGUNDO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE ME FUE PUESTO A LA VISTA
15 NOV 2005
JUAN MANUEL BOTERO
NOTARIO

Notariatsverweser
anstelle des Notars
Prof. Dr. Weirich in Ingelheim

Landgericht Mainz

Landgericht Mainz

- 910 E 1 -

Die Echtheit vorstehender Unterschrift des Notarassessors Dr. Peter Wirth - Notariatsverweser anstelle des Notars Prof. Dr. Weirich in Ingelheim und die Echtheit des beigedrückten Dienst - ~~Schempedor~~ - siegels werden hierdurch bestätigt. Zugleich wird bescheinigt, daß der Vorgenannte zur Vornahme der Amtshandlung gesetzlich befugt war.

Mainz, den dreizehnten Dezember neunzehnhundertfünfundneunzig
Der Präsident des Landgerichts

(Dr. Hans Paul Tüttenberg)

Landgericht Mainz

Kostenberechnung:
Gebühr für Legalisation
(Wert: DM 5.000.-)
JVKostO. v. 26.7.1957
BGBl. I S. 861
DM 20.-
11. DEZ. 1995
Mainz, den
Amtsinspektor

TRADUCCION OFICIAL No. 5133

de un documento escrito en Alemán, el cual para su identificación se sella con el sello de la traductora, lo mismo que la presente.-

---

(A continuación del poder conferido a GERMAN CAVELIER, tpa. 832; GONZALO PERDOMO, tpa. 831; EMILIO FERRERO tpa, 31929; y LUZ CLEMENCIA DE PAEZ, tpa 23555; domiciliados en la Carrera 4 No. 72-35, Bogotá, Colombia, por la BOEHRINGER INGELHEIM INTERNATIONAL GMBH, domiciliada en D-55216 Ingelheim am Rhein, RFA, a través de sus representantes los Srs. Dr. Dieter Laudien y Dr. Gerhard Huber:)

LUZ AMANDA DE HERRERA
TRADUCTORA
Resolución No. 599 Ministerio

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
15 NOV 2005
JUAN MANUEL GUTIERREZ MEDINA
NOTARIO

Legalización

Protocolo notarial No. 2659/95 V

Certifico la autenticidad de las firmas antecedentes puestas ante mí por los señores:

1. Dr. Dieter Laudien, Dipl. Chim., domiciliado en 55127 Mainz,

2. Dr. Gerhard Huber, abogado, domiciliado en 55411 Bingen

a quienes conozco en persona.

Igualmente certifico, por haber examinado en la fecha el Registro de Comercio del Juzgado Municipal de Bingen, HR B 1063, que la firma Boehringen Ingelheim International GmbH, domiciliada en Ingelheim am Rhein, está inscrita bajo el No. HR B 1063 en el Registro de Comercio del Juzgado Municipal de Bingen y que los señores Dr. Laudien y Dr. Huber, en su calidad de apoderados, están facultados para representar conjuntamente a la sociedad.

LUIZ ARMIJOS DE HOYOS
TRADUCTOR-INTERPRETE OFICIAL
Resolución No. 599 Ministerio

Ingelheim am Rhein, 12 de diciembre de 1995/hün

Fdo.: firma ilegible
El notario suplente
del notario de Ingelheim
Prof. Dr. Weirich

(Hilo y oblea roja en relieve:)
El notario suplente - Ingelheim

(dos sellos redondos en tinta del Tribunal Regional de Mainz)

CUMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
15 NOV 2005
JUAN MANUEL BOTERO MEDINA

910 E 1

Se certifica la autenticidad de la firma antecedente del Dr. Peter Wirth, como notario suplente del Prof. Dr. Weirich, notario de Ingelheim, y la del sello oficial que la acompaña. Igualmente se certifica que el mencionado notario estaba facultado para realizar ese acto oficial.

Mainz, trece de diciembre de mil novecientos noventa y cinco

El Presidente del Tribunal Regional

(E) Fdo.: firma ilegible

(Dr. Hanns Paul Tütt[illegible])

Costas

Derechos de legalización
(Valor:DM 5.000,-)
JVKostO del 26 de julio 1957
Gacetas Oficial I Pag. 861
DM 20,--
Mainz, 13 de diciembre de 1995
Fdo.: firma ilegible
Inspector

EN ESPAÑOL: La legalización de las firmas antecedentes por el Consulado de Colombia en Munich bajo el No. 1[illegible] de, 1[illegible] de diciembre de 1995, y por el Ministerio de Relaciones Exteriores de Colombia bajo el No. 051606 del 4 de enero de 1[illegible].

Pagados derechos y Fondo Rotatorio US$ 1[illegible]

ES TRADUCCION FIEL Y COMPLETA, de la [illegible] en los archivos de estas oficinas para su confr[illegible].

Santafé de Bogotá, 6 de enero de 1996.

JUAN MANUEL BOTERO MEDINA
NOTARIO

LUZ ARRIAGA DE [illegible]
TRADUCTORA E INTERPRETE OFICIAL

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA HAGO CONSTAR QUE LA FIRMA DE

C. C.

CONCIDE CON LA REGISTRADA POR EL (ELLA) EN ESTA NOTARIA

09 ENE 1996

SANTAFE DE BOGOTA D.C.

NOTARIA SEXTA
PABLO MENDEZ BABAJAS
Notario Sexto Encargado

NO SE ASUME RESPONSABILIDAD DEL TEXTO

16 ENE 96 A 11:33

JEFE DE SOLICITUDES
SANTAFE DE BOGOTA D.C.

MINISTERIO DE RELACIONES EXTERIORES

CUYA FIRMA

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CORRIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

15 NOV 2005

JUAN MANUEL BOLERO MEDINA
NOTARIO

TELEFAX: (57) (1) 2[illegible]
TELEX 43679 CAVE CO
(23)7407373 CAVE UC

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4ª, No. 72-35
BOGOTA 8, COLOMBIA

CORREO ELECTRONICO MUNDIAL: CAVE
TELEFONO (57) (1) 2120100
CABLES: CAVELEYES

Señor Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Poderdante: BOEHRINGER INGELHEIM INTERNATIONAL GMBH

Poder conferido el: 12-12-95

Yo, GERMAN CAVELIER, obrando en mi calidad de apoderado principal del poderdante arriba mencionado atentamente manifiesto a Usted que sustituyo el poder que me ha sido conferido en la persona del doctor EMILIO FERRERO, Abogado con Tarjeta Profesional No. 31.929, con todas las facultades que me fueron conferidas.

Hago la anterior sustitución conforme al artículo 66 del Código de Procedimiento Civil ya que [illegible] sustitutos faltan en este momento.

Señor Jefe,

NOTARIA SEXTA DEL CIRCULO DE BOGOTA D.C.
FOTOCOPIA COINCIDE CON EL ORIGINAL
15 NOV 2005
JUAN MANUEL BOTERO MARIÑA
NOTARIO

GERMAN CAVELIER
T.P.A. No. 832
C.C. No. 2.877.924 de Bogotá

Acepto:

EMILIO FERRERO
T.P.A. Nº 31.929
C.C. No. 438.019 de Usaquén

2e-780-2

NOTARIA SEXTA DE BOGOTA

RECONOCIMIENTO Y PRESENTACION PERSONAL

Bogotá,,D. C. 11 ENE 1996

Ante M, PABLO MENDEZ BARAJAS S.

NOTARIO SEXTO ENCARGADO DEL CIRCULO DE BOGOTA,

Compareció(eron)

quien(es) exhibió(eron) la(s) C. 2877924
4338014

y la(s) Libreta(s) Militar(es)

domiciliado(s) en Bogotá y declaró(aron) que la(s) firma(s) que aparecen(n) en el presente documento es(son) la(s) suya(s) y que el contenido del mismo es cierto.
En constancia se firma esta Diligencia.

EL SUSCRITO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE ME TUVO A LA VISTA

15 NOV 2005

JUAN MANUEL BOTERO MEDINA
NOTARIO

12.

CONSULADO GENERAL DE COLOMBIA
MONTREAL, CANADA

AUTENTICACION No. 1631

El suscrito Cónsul General de Colombia

CERTIFICA:

Que **MICHEL POULIN** quien firma y otorga autenticidad al presente documento, ejercía legalmente en la fecha allí expresada el cargo de **SECRETARIO DE LA CAMARA DE NOTARIOS DE LA PROVINCIA DE QUEBEC - CANADA,** jurisdicción de este Consulado General, y que la firma y sello que en el documento aparecen como suyos, son los que usa y acostumbra en sus actos oficiales.

El Cónsul no asume ninguna responsabilidad por el contenido del documento.

Montreal, 11 de Octubre de 2005

Derechos Pagados: US$24.00
Fondo Rotatorio: US$15.00
Impuesto de Timbre: US$9.00

EDUARDO CAMACHO BARCO
Cónsul General de Colombia
Montreal, Canadá

MINISTERIO DE RELACIONES EXTERIORES

172660

Eduardo Gnecco.

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2005 OCT 25 P 1:14

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

Chambre des notaires du Québec

4832

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CANADA
PROVINCE OF QUEBEC

I, the undersigned, Michel Poulin, Secretary of the *Chambre des notaires du Québec*, a professional order duly constituted in virtue of the *Notarial Act* and the *Professional Code*, having its Head Office at Montreal, do hereby certify under my oath of office:

THAT Mtre Jean Yves Lacasse , Notary at Montreal , is a member of the *Ordre des notaires du Québec* since the 2nd day of July 1986 , date of his entry on the Roll of the Order;

That since that date, Mtre Lacasse has always been entered on the Roll of the Chambre des notaires du Québec ;

THAT his signature affixed to the attached document corresponds to that filed in my office in accordance with the *Notarial Act*.

IN WITNESS WHEREOF, I have signed the present certificate at Montreal, on this Tuesday, October 11, 2005.

Michel Poulin, Notary
Secretary

Membre de l'Union internationale du notariat latin

Tour de la Bourse, 800, Place-Victoria, bureau 700, case postale 162, Montréal (Québec) H4Z 1L8
Téléphone : (514) 879-1793 • Télécopieur : (514) 879-1923
admin@cdnq.org

75416

13
14

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, D – COLOMBIA

374

CESION

Yo, (nosotros) abajo firmado (s)

1. **Montse LLINAS-BRUNET**
2. **Murray D. BAILEY**
3. **Punit BHARDWAJ**
4. **Josée BORDELEAU**

Domiciliado(s)

en

1. **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**
2. **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**
3. **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**
4. **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**

Declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención:

Compuestos inhibidores de la hepatitis C

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad

Boehringer Ingelheim International GmbH

constituida y existente de conformidad con las leyes de

Alemania

domiciliada en **Binger Strasse 173, 55216 Ingelheim, Alemania**

Todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente de invención correspondiente en la República de Colombia.

ASSIGNMENT

I (we), the undersigned

1. **Montse LLINAS-BRUNET**
2. **Murray D. BAILEY**
3. **Punit BHARDWAJ**
4. **Josée BORDELEAU**

of

1. **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**
2. **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**
3. **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**
4. **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**

state(s) under oath to be sole and true inventor(s) of the invention:

"HEPATITIS C INHIBITOR COMPOUNDS"

state as well, that assign, without reservations or limitations in favour of **Boehringer Ingelheim International GmbH**

a corporation constituted and existing in conformity with the laws of

Germany

domiciled in **Binger Strasse 173, 55216 Ingelheim, Germany**

all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent invention, in the Republic of Colombia

Dado y firmado hoy/Given and signed this OCT 07 2005

en/in Laval Quebec Canada

Firma/Signature

Montse LLINAS-BRUNET

Murray D. BAILEY

Punit BHARDWAJ

Josée BORDELEAU

© CAVELIER ABOGADOS
WPPODE01- 374

SWORN BEFORE ME
IN MONTREAL, QC, CANADA
ON THIS

OCT 07 2005

JEAN-YVES LACASSE
NOTAIRE

44 15

CERTIFICACIÓN NOTARIAL (INDIVIDUO)

A los _____ días del mes de _____

de 200 ___ Ante mí, Notario Público de

_____

compareció(eron) personalmente _____

_____

_____

a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede, y quien(es) tiene(n) capacidad legal para otorgarlo

NOTARIAL CERTIFICATION (INDIVIDUAL)

On this 10th day of OCTOBER

200 5 before me, a Notary Public of

QUEBEC, CANADA

personally appeared M. LIVOS-BLANT,

M.O. BRIAND, P. BRIAND AND —

J. BRIAND

to me known, and known to me to be the person(s) who executed that foregoing document, and who has(have) legal capacity to execute it.

_____ NOTARIO PÚBLICO-NOTARY PUBLIC _____

SWORN BEFORE ME
IN MONTREAL, QC, CANADA
THIS
OCT 07 2005

JEAN-YVES LACASSE
NOTAIRE

APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. Country: .....
   This public document
2. has been signed by .....
3. acting in the capacity of .....
4. bears the seal/stamp of .....

Certified

5. at ..... 6. the .....
7. by .....
8. No. .....
9. Seal/stamp 10. Signature

....

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WPPODE01-374

2 of 2

16

TRADUCCIÓN OFICIAL No. 10.28/05a realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia, registrado ante el Ministerio de Relaciones Exteriores de Colombia.

A continuación se traducen los sellos y legalizaciones de un documento de Cesión escrito en inglés y español por medio del cual 1. Montse LLINAS-BRUNET, 2. Murray D. BAILEY, 3. Punit BHARDWAJ, 4. Josée BORDELEAU, domiciliados en 1. 2100 Cunard Street, Laval, Québec H7S 2G5 / Canadá, 2. 2100 Cunard Street, Laval, Québec H7S 2G5 / Canadá, 3. 2100 Cunard Street, Laval, Québec H7S 2G5 / Canadá, 4. 2100 Cunard Street, Laval, Québec H7S 2G5 / Canadá, respectivamente, declaran bajo juramento ser únicos y verdaderos inventores de la invención: "*COMPUESTOS INHIBIDORES DE LA HEPATITIS C*" y declaran así mismo que ceden y transfieren, sin limitación, a favor de la sociedad Boehringer Ingelheim International GmbH una sociedad constituida y existente de conformidad con las leyes de Alemania domiciliada en Binger Strasse 173, 55216 Ingelheim, Alemania, todos los derechos inherentes a dicha invención y que dicha Compañía queda facultada para solicitar a su nombre la patente correspondiente en la República de Colombia.

Dado y firmado el 07 de Octubre de 2005 en Laval, Quebec, Canadá.

Firma Ilegible
Montse LLINAS-BRUNET

Firma Ilegible
Murray D. BAILEY

Firma Ilegible
Punit BHARDWAJ

Firma Ilegible
Josée BORDELEAU

Sello: JURAMENTADO ANTE MÍ EN
MONTREAL, QC, CANADÁ
HOY 07 DE OCTUBRE DE 2005

Firma Ilegible
JEAN-YVES LACASSE
NOTARIO

Certificación Notarial (Individuo) del 6 de octubre de 2005 por medio de la cual se certifican las firmas de M. LLINAS-BRUNET, M.D. BAILEY, P. BHARDWAJ y J. BORDELEAU en el anterior documento y su capacidad legal para otorgarlo.

Sello: JURAMENTADO ANTE MÍ EN
MONTREAL, CANADÁ
HOY 07 DE OCTUBRE DE 2005

Firma Ilegible
JEAN-YVES LACASSE
NOTARIO

CANADÁ
PROVINCIA DE QUÉBEC

Yo, el suscrito, Michel Poulin, Secretario de la *Chambre des notaires du Québec*, (Cámara de Notarios de Québec) una asociación profesional debidamente constituida en virtud de la *Ley Notarial* y del *Código Profesional*, cuya Oficina Principal está ubicada en Montreal, por el presente certifico bajo mí juramento de oficio:

QUE el Señor Jean Yves Lacasse, Notario de Montreal, es un miembro de la *Ordre des notaries du Québec* (Asociación de Notarios de Québec)desde el 2 de Julio de 1986, fecha de su inscripción en la Lista de la Asociación.

QUE desde ese día, el Señor Lacasse siempre ha permanecido inscrito en la Lista de la Asociación de la Chambre des notaires du Québec;

QUE la firma que fue fijada en el documento adjunto corresponde a la suya presentada ante mí oficina en concordancia con la Ley Notarial.

EN TESTIMONIO DE LO CUAL, he firmado el presente certificado en Montreal hoy Martes 11 de Octubre de 2005.

Firma Ilegible

Michel Poulin, Notario
Secretario

75416

Sellos parciales del Consulado de Colombia de Montreal, Canadá

Se anexa autenticación No. 1031 del Consulado de Colombia en Montreal, Canadá, con fecha del 11 de Octubre de 2005, en donde se autentica la firma anterior del Señor MICHEL POULIN y de su cargo como SECRETARIO DE LA CÁMARA DE NOTARIOS DE LA PROVINCIA DE QUÉBEC - CANADÁ.

Pagado el Impuesto de Timbre y Fondo de Rotatorio.

Firmado por Eduardo Camacho Barco, Cónsul General de Colombia en Montreal, Canadá.

Legalización de la firma anterior por parte del Jefe de Legalizaciones del Ministerio de Relaciones Exteriores en Bogotá D.C. bajo el número **172660** con fecha del 25 de Octubre de 2005.

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.
DVZ/ID-7209/WPCL002G/COLO 09255-841-030-1

DIEGO F. VARGAS Z.
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLES – INGLES - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S) DE

Diego Felipe Rodriguez Salcedo

COINCIDE(N) CON LA FIRMA REGISTRADA POR EL (ELLOS) EN ESTA NOTARIA

SANTAFE DE BOGOTA, 31 OCT 2005

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2005 OCT 31 A 11:25

JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.

MINISTERIO DE RELACIONES EXTERIORES

174551

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

MONTREAL

19

CONSULADO GENERAL DE COLOMBIA
MONTREAL, CANADA

AUTENTICACION No. 1030

El suscrito Cónsul General de Colombia

CERTIFICA:

Que **MICHEL POULIN** quien firma y otorga autenticidad al presente documento, ejerce legalmente en la fecha allí expresada el cargo de **SECRETARIO DE LA CAMARA DE NOTARIOS DE LA PROVINCIA DE QUEBEC - CANADA,** jurisdicción de este Consulado General, y que la firma y sello que en el documento aparecen como suyos, son los que usa y acostumbra en sus actos oficiales.

El Cónsul no asume ninguna responsabilidad por el contenido del documento.

Montreal, 11 de Octubre de 2005

Derechos Pagados: US$24.00
Fondo Rotatorio: US$15.00
Impuesto de Timbre : US$9.00

EDUARDO SAMACHO BARCO
Cónsul General de Colombia
Montreal, Canadá

CONSULADO GENE

MONTR

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 OCT 25 P 1:16

DEPT. DE LEGALIZACIONES
SUBDIRECCIÓN DE BOGOTÁ D.C.

MINISTERIO DE RELACIONES
EXTERIORES

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

Chambre des notaires du Québec

4832

20

CANADA
PROVINCE OF QUEBEC

I, the undersigned, Michel Poulin, Secretary of the *Chambre des notaires du Québec*, a professional order duly constituted in virtue of the *Notarial Act* and the *Professional Code*, having its Head Office at Montreal, do hereby certify under my oath of office:

THAT Mtre Jean Yves Lacasse , Notary at Montreal , is a member of the *Ordre des notaires du Québec* since the 2nd day of July 1986 , date of his entry on the Roll of the Order;

That since that date, Mtre Lacasse has always been entered on the Roll of the Chambre des notaires du Québec ;

THAT his signature affixed to the attached document corresponds to that filed in my office in accordance with the *Notarial Act*.

IN WITNESS WHEREOF, I have signed the present certificate at Montreal, on this Tuesday, October 11, 2005.

Michel Poulin, Notary
Secretary

Membre de l'Union internationale du notariat latin
Tour de la Bourse, 800, Place-Victoria, bureau 700, case postale 162, Montréal (Québec) H4Z 1L8
Téléphone : (514) 879-1793 • Télécopieur : (514) 879-1923
admin@cdnq.org

75415

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a Nº 72-35
BOGOTA, 8 – COLOMBIA

374

XR
21

CESION

Yo, (nosotros) abajo firmado (s)

5. **Pasquale FORGIONE**
6. **Elise GHIRO**
7. **Vida GORYS**
8. **Nathalie GOUDREAU**

Domiciliado(s)

en

5. **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**
6. **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**
7. **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**
8. **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**

Declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención:

Compuestos Inhibidores de la hepatitis C

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad

Boehringer Ingelheim International GmbH

constituida y existente de conformidad con las leyes de

Alemania

domiciliada en **Binger Strasse 173, 55216 Ingelheim, Alemania**

todos los derechos inherentes a dicha invención y que la citada compañía queda facultada para solicitar en su nombre la patente de invención correspondiente en la República de Colombia.

ASSIGNMENT

I (we), the undersigned

5. **Pasquale FORGIONE**
6. **Elise GHIRO**
7. **Vida GORYS**
8. **Nathalie GOUDREAU**

of

5. **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**
6. **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**
7. **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**
8. **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**

state(s) under oath to be sole and true inventor(s) of the invention:

"HEPATITIS C INHIBITOR COMPOUNDS"

state as well, that assign, without reservations or limitations in favour of **Boehringer Ingelheim International GmbH**

a corporation constituted and existing in conformity with the laws of

Germany

domiciled in **Binger Strasse 173, 55216 Ingelheim, Germany**

all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent invention, in the Republic of Colombia

Dado y firmado hoy/Given and signed this OCT 0 7 2005

en/in Laval, Quebec Canada

Firma/Signature

Pasquale FORGIONE | Elise GHIRO | Vida GORYS | Nathalie GOUDREAU

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WPPODE01- 374

SWORN BEFORE ME
IN MONTREAL, QC, CANADA
ON THIS
OCT 0 7 2005

JEAN-YVES LACASSE
NOTAIRE

CERTIFICACIÓN NOTARIAL (INDIVIDUO)

A los _____ días del mes de _____

de 200 ___ Ante mí, Notario Público de

_____

compareció(eron) personalmente _____

_____

_____

a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede, y quien(es) tiene(n) capacidad legal para otorgarlo

NOTARIAL CERTIFICATION (INDIVIDUAL) 72

On this 6th day of OCTOBER

200 5 before me, a Notary Public of

QUEBEC, CANADA

personally appeared P. Fournier, R. Guido, U. Gorys and N. Gonzalez

to me known, and known to me to be the person(s) who executed that foregoing document, and who has(have) legal capacity to execute it.

_____ NOTARIO PÚBLICO-NOTARY PUBLIC _____

SWORN BEFORE ME
IN MONTRÉAL, QC, CANADA
ON THIS

OCT 0 7 2005

JEAN-YVES LACASSE
NOTAIRE

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: .....
   This public document
2. has been signed by .....
3. acting in the capacity of .....
4. bears the seal/stamp of .....

Certified

5. at ..... 6. the .....
7. by .....
8. No. .....
9. Seal/stamp 10. Signature

....

© CAVELIER ABOGADOS
WPPODE01-374

TRADUCCIÓN OFICIAL No. 10.28/05b realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia, registrado ante el Ministerio de Relaciones Exteriores de Colombia.

A continuación se traducen los sellos y legalizaciones de un documento de Cesión escrito en inglés y español por medio del cual 5. Pasquale FORGIONE, 6. Elise GHIRO, 7. Vida GORYS, 8. Nathalie GOUDREAU, domiciliados en 5. 2100 Cunard Street, Laval, Québec H7S 2G5 / Canadá, 6. 2100 Cunard Street, Laval, Québec H7S 2G5 / Canadá, 7. 2100 Cunard Street, Laval, Québec H7S 2G5 / Canadá, 8. 2100 Cunard Street, Laval, Québec H7S 2G5 / Canadá, respectivamente, declaran bajo juramento ser únicos y verdaderos inventores de la invención: "*COMPUESTOS INHIBIDORES DE LA HEPATITIS C*" y declaran así mismo que ceden y transfieren, sin limitación, a favor de la sociedad **Boehringer Ingelheim International GmbH** una sociedad constituida y existente de conformidad con las leyes de Alemania domiciliada en Binger Strasse 173, 55216 Ingelheim, Alemania, todos los derechos inherentes a dicha invención y que dicha Compañía queda facultada para solicitar a su nombre la patente correspondiente en la República de Colombia.

Dado y firmado el 07 de Octubre de 2005 en Laval, Quebec, Canadá.

Firma Ilegible	*Firma* Ilegible	Firma *Ilegible*	*Firma Ilegible*
Pasquale FORGIONE	Elise GHIRO	Vida GORYS	Nathalie GOUDREAU

Sello: JURAMENTADO ANTE MÍ EN
MONTREAL, QC, CANADÁ
HOY 07 DE OCTUBRE DE 2005

Firma Ilegible
JEAN-YVES LACASSE
NOTARIO

Certificación Notarial (Individuo) del 6 de octubre de 2005 por medio de la cual se certifican las firmas de P. FORGIONE, E. GHIRO, V. GORYS, N. GOUDREAU en el anterior documento y su capacidad legal para otorgarlo.

Sello: JURAMENTADO ANTE MÍ EN
MONTREAL, QC, CANADÁ
HOY 07 DE OCTUBRE DE 2005

Firma Ilegible
JEAN-YVES LACASSE
NOTARIO

CANADÁ
PROVINCIA DE QUÉBEC

Yo, el suscrito, Michel Poulin, Secretario de la *Chambre des notaires du Québec*, (Cámara de Notarios de Québec) una asociación profesional debidamente constituida en virtud de la *Ley Notarial* y del *Código Profesional*, cuya Oficina Principal está ubicada en Montreal, por el presente certifico bajo mí juramento de oficio:

QUE el Señor Jean Yves Lacasse, Notario de Montreal, es un miembro de la *Ordre des notaries du Québec* (Asociación de Notarios de Québec)desde el 2 de Julio de 1986, fecha de su inscripción en la Lista de la Asociación.

QUE desde ese día, el Señor Lacasse siempre ha permanecido inscrito en la Lista de la Asociación de la Chambre des notaires du Québec;

QUE la firma que fue fijada en el documento adjunto corresponde a la suya presentada ante mí oficina en concordancia con la Ley Notarial.

25 83

EN TESTIMONIO DE LO CUAL, he firmado el presente certificado en Montreal hoy Martes 11 de Octubre de 2005.

Firma Ilegible

Michel Poulin, Notario
Secretario

75415

Sellos parciales del Consulado de Colombia de Montreal, Canadá

Se anexa autenticación No. 1030 del Consulado de Colombia en Montreal, Canadá, con fecha del 11 de Octubre de 2005, en donde se autentica la firma anterior del Señor MICHEL POULIN y de su cargo como SECRETARIO DE LA CÁMARA DE NOTARIOS DE LA PROVINCIA DE QUÉBEC - CANADÁ.

Pagado el Impuesto de Timbre y Fondo de Rotatorio.

Firmado por Eduardo Camacho Barco, Cónsul General de Colombia en Montreal, Canadá.

Legalización de la firma anterior por parte del Jefe de Legalizaciones del Ministerio de Relaciones Exteriores en Bogotá D.C. bajo el número **172661** con fecha del 25 de Octubre de 2005.

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.
DVZ/ID-7210/WPCL002G/COLO 09255-841-030-1

DIEGO F. VARGAS
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLÉS – INGLÉS - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA

COMO NOTARIO SEXTO DEL CIRCULO DE SANTA
BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S)
Diego Felipe
Vargas Zabaleta
C[illegible]INCIDE(N) CON LA FIRMA REGISTRADA POR
EL (ELLOS) EN ESTA NOTARIA
SANTAFE DE BOGOTA. 31 OCT 2005

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 OCT 31 A 11: 26

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

MINISTERIO DE RELACIONES
EXTERIORES

174553
Diego Vargas

CUYA FIRMA APARECE EN EL
DOCUMENTO DESCRIPTERA
LAS FUNCIONES INDICADAS

26

CONSULADO GENERAL DE COLOMBIA
MONTREAL, CANADA

AUTENTICACION No. 1029

El suscrito Cónsul General de Colombia

CERTIFICA

Que MICHEL POULIN quien firma y otorga autenticidad al presente documento, ejercía legalmente en la fecha allí expresada el cargo de **SECRETARIO DE LA CAMARA DE NOTARIOS DE LA PROVINCIA DE QUEBEC - CANADA,** jurisdicción de este Consulado General, y que la firma y sello que en el documento aparecen como suyos, son los que usa y acostumbra en sus actos oficiales.

El Cónsul no asume ninguna responsabilidad por el contenido del documento.

Montreal, 11 de Octubre de 2005

Derechos Pagados: US$24.00
Fondo Rotatorio: US$15.00
Impuesto de Timbre : US$9.00

EDUARDO CAMACHO BARCO
Cónsul General de Colombia
Montreal, Canadá

MINISTERIO DE RELACIONES
EXTERIORES

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

E 172662
Eduardo Gmacho

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

2005 OCT 25 P 1:16

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

Chambre des notaires du Québec

24
27

CANADA
PROVINCE OF QUEBEC

I, the undersigned, Michel Poulin, Secretary of the *Chambre des notaires du Québec*, a professional order duly constituted in virtue of the *Notarial Act* and the *Professional Code*, having its Head Office at Montreal, do hereby certify under my oath of office:

THAT Mtre Jean Yves Lacasse , Notary at Montreal , is a member of the *Ordre des notaires du Québec* since the 2nd day of July 1986 , date of his entry on the Roll of the Order;

That since that date, Mtre Lacasse has always been entered on the Roll of the Chambre des notaires du Québec ;

THAT his signature affixed to the attached document corresponds to that filed in my office in accordance with the *Notarial Act*.

IN WITNESS WHEREOF, I have signed the present certificate at Montreal, on this Tuesday, October 11, 2005.

Michel Poulin, Notary
Secretary

CONSULADO GENERAL DE COLOMBIA

CONSULADO GENERAL DE COLOMBIA

Membre de l'Union internationale du notariat latin
Tour de la Bourse, 800, Place-Victoria, bureau 4000, case postale 162, Montréal (Québec) H4Z 1L8
Téléphone : (514) 879-1793 • Télécopieur : (514) 879-1923
admin@cdnq.org

75417

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
- BOGOTA, 8 – COLOMBIA

28 of

CESION

Yo, (nosotros) abajo firmado (s)

9 **Sylvie GOULET**
10 **Teddy HALMOS**
11 **Jean RANCOURT**

Domiciliado(s)

en

9 **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**
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declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención:

compuestos inhibidores de la hepatitis C

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad

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constituida y existente de conformidad con las leyes de

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todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente de invención correspondiente en la República de Colombia.

ASSIGNMENT

I (we), the undersigned

9 **Sylvie GOULET**
10 **Teddy HALMOS**
11 **Jean RANCOURT**

of

12 **2100, Cunard Street, Laval, Québec H7S 2G5, Canada**
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state(s) under oath to be sole and true inventor(s) of the invention:

"HEPATITIS C INHIBITOR COMPOUNDS"

state as well, that assign, without reservations or limitations in favour of **Boehringer Ingelheim International GmbH**

a corporation constituted and existing in conformity with the laws of

Germany

domiciled in **Binger Strasse 173, 55216 Ingelheim, Germany**

all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent invention, in the Republic of Colombia

Dado y firmado hoy/Given and signed this OCT 07 2005

en/in Laval, Quebec Canada

Firma/Signature

Sylvie GOULET

Teddy HALMOS

Jean RANCOURT

CAVELIER ABOGADOS
WPPODE01-374

SWORN BEFORE ME
IN MONTREAL, QC, CANADA
ON THIS OCT 07 2005

JEAN-YVES LACASSE
NOTAIRE

JEAN-YVES LACASSE
NOTAIRE

ZE
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CERTIFICACIÓN NOTARIAL (INDIVIDUO)

A los _____ días del mes de _____

de 200 ___ Ante mí, Notario Público de

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compareció(eron) personalmente _____

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a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede, y quien(es) tiene(n) capacidad legal para otorgarlo

NOTARIAL CERTIFICATION (INDIVIDUAL)

On this 6th day of October

200 5 before me, a Notary Public of

Quebec, Canada

personally appeared S. Garet, T. Holmes

Alb - J. Rancourt

_____

to me known, and known to me to be the person(s) who executed that foregoing document, and who has(have) legal capacity to execute it.

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IN MONTREAL, QC, CANADA
ON THIS

OCT 07 2005

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APOSTILLE
(Convention de La Haye du 5 octobre 1961)

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WPPODE01-374

JEAN-YVES LACASSE
NOTAIRE

TRADUCCIÓN OFICIAL No. 10.28/05c realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia, registrado ante el Ministerio de Relaciones Exteriores de Colombia.

A continuación se traducen los sellos y legalizaciones de un documento de Cesión escrito en inglés y español por medio del cual 9. Sylvie GOULET, 10. Teddy HALMOS, 11. Jean RANCOURT, domiciliados en 9. 2100 Cunard Street, Laval, Québec H7S 2G5 / Canadá, 10. 2100 Cunard Street, Laval, Québec H7S 2G5 / Canadá, 11. 2100 Cunard Street, Laval, Québec H7S 2G5 / Canadá, respectivamente, declaran bajo juramento ser únicos y verdaderos inventores de la invención: "*COMPUESTOS INHIBIDORES DE LA HEPATITIS C*" y declaran así mismo que ceden y transfieren, sin limitación, a favor de la sociedad **Boehringer Ingelheim International GmbH** una sociedad constituida y existente de conformidad con las leyes de Alemania domiciliada en Binger Strasse 173, 55216 Ingelheim, Alemania, todos los derechos inherentes a dicha invención y que dicha Compañía queda facultada para solicitar a su nombre la patente correspondiente en la República de Colombia.

Dado y firmado el 07 de Octubre de 2005 en Laval, Quebec, Canadá.

Firma Ilegible	*Firma* Ilegible	*Firma Ilegible*
Sylvie GOULET	Teddy HALMOS	Jean RANCOURT

Sello: JURAMENTADO ANTE MÍ EN
MONTREAL, QC, CANADÁ
HOY 07 DE OCTUBRE DE 2005

Firma Ilegible
JEAN-YVES LACASSE
NOTARIO

Certificación Notarial (Individuo) del 6 de octubre de 2005 por medio de la cual se certifican las firmas de S. GOULET, T. HALMOS,

J. RANCOURT en el anterior documento y su capacidad legal para otorgarlo.

Sello: JURAMENTADO ANTE MÍ EN
MONTREAL, QC, CANADÁ
HOY 07 DE OCTUBRE DE 2005

Firma Ilegible
JEAN-YVES LACASSE
NOTARIO

CANADÁ
PROVINCIA DE QUÉBEC

Yo, el suscrito, Michel Poulin, Secretario de la *Chambre des notaires du Québec*, (Cámara de Notarios de Québec) una asociación profesional debidamente constituida en virtud de la *Ley Notarial* y del *Código Profesional*, cuya Oficina Principal está ubicada en Montreal, por el presente certifico bajo mí juramento de oficio:

QUE el Señor Jean Yves Lacasse, Notario de Montreal, es un miembro de la *Ordre des notaries du Québec* (Asociación de Notarios de Québec)desde el 2 de Julio de 1986, fecha de su inscripción en la Lista de la Asociación.

QUE desde ese día, el Señor Lacasse siempre ha permanecido inscrito en la Lista de la Asociación de la Chambre des notaires du Québec;

QUE la firma que fue fijada en el documento adjunto corresponde a la suya presentada ante mí oficina en concordancia con la Ley Notarial.

EN TESTIMONIO DE LO CUAL, he firmado el presente certificado en Montreal hoy Martes 11 de Octubre de 2005.

Firma Ilegible

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Michel Poulin, Notario
Secretario

75417

Sellos parciales del Consulado de Colombia de Montreal, Canadá

Se anexa autenticación No. 1029 del Consulado de Colombia en Montreal, Canadá, con fecha del 11 de Octubre de 2005, en donde se autentica la firma anterior del Señor MICHEL POULIN y de su cargo como SECRETARIO DE LA CÁMARA DE NOTARIOS DE LA PROVINCIA DE QUÉBEC - CANADÁ.

Pagado el Impuesto de Timbre y Fondo de Rotatorio.

Firmado por Eduardo Camacho Barco, Cónsul General de Colombia en Montreal, Canadá.

Legalización de la firma anterior por parte del Jefe de Legalizaciones del Ministerio de Relaciones Exteriores en Bogotá D.C. bajo el número **172662** con fecha del 25 de Octubre de 2005.

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

DVZ/ID-7211/WPCL002G/COLO 09255-841-030-1

DIEGO F. VARGAS Z.
TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLES - INGLES - ESPAÑOL
RES. 0001 DE ENERO 4 DE 1999
MINISTERIO DE JUSTICIA

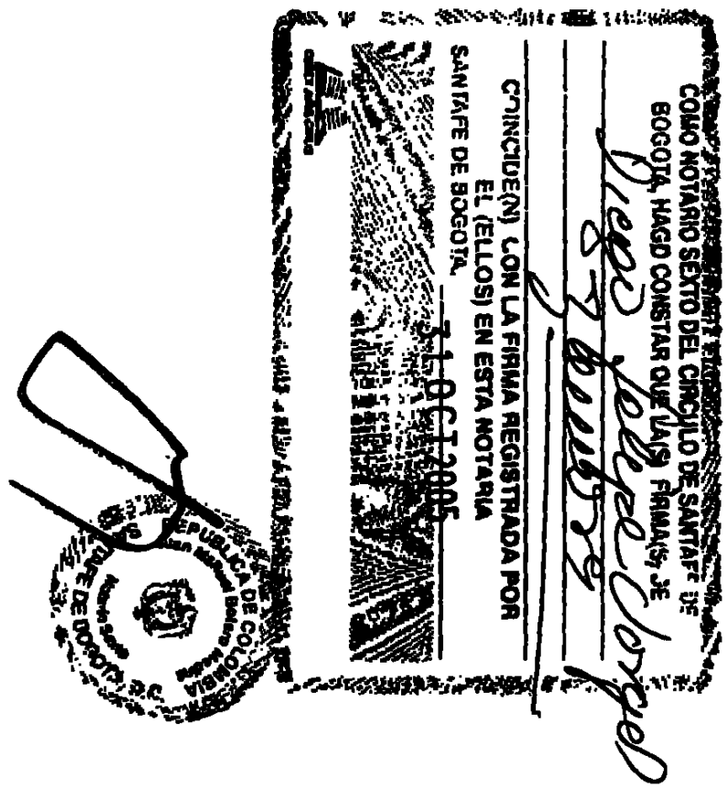
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Diego Jaramillo
CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2005 OCT 31 A 11: 25

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.



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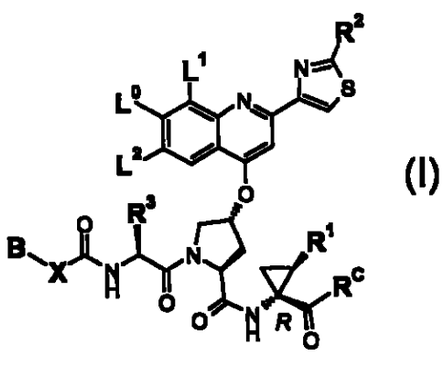
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HEPATITIS C INHIBITOR COMPOUNDS



(I)

(57) Abstract: Compounds of formula (I): wherein B, X, R^3, L^0, L^1, L^2, R^2, R^1 and R^C are defined herein. The compounds are useful as inhibitors of HCV NS3 protease for the treatment of hepatitis C viral infection.

WO 2004/103996 A1

HEPATITIS C INHIBITOR COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to compounds, processes for their synthesis, compositions and methods for the treatment of hepatitis C virus (HCV) infection. In particular, the present invention provides novel peptide analogs, pharmaceutical compositions containing such analogs and methods for using these analogs in the treatment of HCV infection.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) is the major etiological agent of post-transfusion and community-acquired non-A non-B hepatitis worldwide. It is estimated that over 200 million people worldwide are infected by the virus. A high percentage of carriers become chronically infected and many progress to chronic liver disease, so-called chronic hepatitis C. This group is in turn at high risk for serious liver disease such as liver cirrhosis, hepatocellular carcinoma and terminal liver disease leading to death.

The mechanism by which HCV establishes viral persistence and causes a high rate of chronic liver disease has not been thoroughly elucidated. It is not known how HCV interacts with and evades the host immune system. In addition, the roles of cellular and humoral immune responses in protection against HCV infection and disease have yet to be established. Immunoglobulins have been reported for prophylaxis of transfusion-associated viral hepatitis, however, the Center for Disease Control does not presently recommend immunoglobulin treatment for this purpose. The lack of an effective protective immune response is hampering the development of a vaccine or adequate post-exposure prophylaxis measures, so in the near-term, hopes are firmly pinned on antiviral interventions.

Various clinical studies have been conducted with the goal of identifying pharmaceutical agents capable of effectively treating HCV infection in patients afflicted with chronic hepatitis C. These studies have involved the use of interferon-alpha, alone and in combination with other antiviral agents. Such studies have shown that a substantial number of the participants do not respond to these

therapies, and of those that do respond favorably, a large proportion were found to relapse after termination of treatment.

Until recently, interferon (IFN) was the only available therapy of proven benefit approved in the clinic for patients with chronic hepatitis C. However the sustained response rate is low, and interferon treatment also induces severe side-effects (i.e. retinopathy, thyroiditis, acute pancreatitis, depression) that diminish the quality of life of treated patients. Recently, interferon in combination with ribavirin has been approved for patients non-responsive to IFN alone. However, the side effects caused by IFN are not alleviated with this combination therapy. Pegylated forms of interferons such as PEG-Intron® and Pegasys® can apparently partially address these deleterious side-effects but antiviral drugs still remain the avenue of choice for oral treatment of HCV.

Therefore, a need exists for the development of effective antiviral agents for treatment of HCV infection that overcome the limitations of existing pharmaceutical therapies.

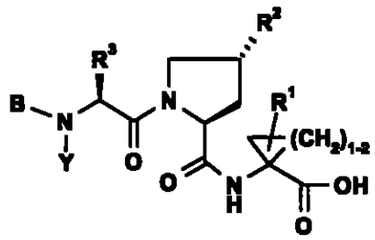
HCV is an enveloped positive strand RNA virus in the Flaviviridae family. The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural and non-structural (NS) proteins. In the case of HCV, the generation of mature nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) is effected by two viral proteases. The first one, as yet poorly characterized, cleaves at the NS2-NS3 junction (henceforth referred to as NS2/3 protease); the second one is a serine protease contained within the N-terminal region of NS3 (NS3 protease) and mediates all the subsequent cleavages downstream of NS3, both in *cis*, at the NS3-NS4A cleavage site, and in *trans*, for the remaining NS4A-NS4B, NS4B-NS5A, NS5A-NS5B sites. The NS4A protein appears to serve multiple functions, acting as a cofactor for the NS3 protease and possibly assisting in the membrane localization of NS3 and other viral replicase components. The complex formation of the NS3 protease with NS4A seems necessary to the processing events, enhancing the proteolytic efficiency at all of the

sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B is a RNA-dependent RNA polymerase that is involved in the replication of HCV.

A general strategy for the development of antiviral agents is to inactivate virally encoded enzymes that are essential for the replication of the virus.

More recently, the NS3 protease has been found to potentially have an additional impact by blocking the IFN-mediated cellular antiviral activity in the infected cell (Foy *et al.*, *Science*, 17 April 2003). This lends credence to a hypothesis that the NS3/NS4A protease may represent a dual therapeutic target, the inhibition of which may both block viral replication and restore interferon response of HCV infected cells.

In WO 00/09543, compounds of the formula



wherein a preferred meaning of R^2 is an unsubstituted or mono- or disubstituted quinolinyl residue as defined therein, are described as hepatitis C viral NS3 protease inhibitors, an enzyme essential for the replication of the hepatitis C virus.

The present invention provides tripeptide compounds that have improved potency against the HCV NS3 protease. Furthermore, compounds being highly active in cell culture are provided.

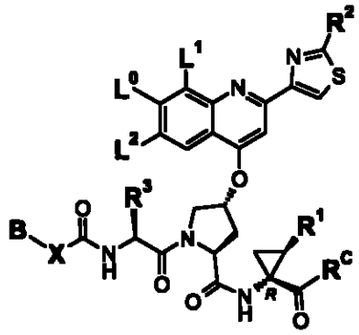
An advantage of one aspect of the present invention resides in the fact that compounds according to this invention specifically inhibit the NS3 protease and do not show significant inhibitory activity against other human serine proteases such as human leukocyte elastase (HLE), or cysteine proteases such as human liver cathepsin B (Cat B).

Compared to the compounds as disclosed in WO 00/09543, compounds as provided by this invention exhibit unexpected advantages. In general they show one or more of the following advantages:

- lower IC_{50} values in a NS3-NS4A protease assay;
- lower EC_{50} values in a cell based HCV RNA replication assay;
- better solubility; and/or
- higher plasma levels when administered orally in the rat.

SUMMARY OF THE INVENTION

Included in the scope of the invention is a racemate, diastereoisomer, or optical isomer of a compound of formula (I):



I

wherein

B is (C_{1-10})alkyl, (C_{3-7})cycloalkyl, or (C_{1-4})alkyl-(C_{3-7})cycloalkyl,

a) wherein said alkyl, cycloalkyl, and alkyl-cycloalkyl may be mono-, di- or tri-substituted with (C_{1-3})alkyl; and

b) wherein said alkyl, cycloalkyl, and alkyl-cycloalkyl may be mono- or di-substituted with substituents selected from hydroxy and O-(C_{1-4})alkyl; and

c) wherein each of said alkyl groups may be mono-, di- or tri-substituted with halogen; and

d) wherein each of said cycloalkyl groups being 4-, 5-, 6- or 7-membered having optionally one (for the 4-, 5, 6, or 7-membered) or two (for the 5-, 6- or 7-membered) -CH_2-groups not directly linked to each other replaced by -O- such that the O-atom is linked to the group **X** via at least two C-atoms;

X is O or NH;

R^3 is (C_{2-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-3})alkyl-(C_{3-7})cycloalkyl, wherein each of said alkyl, cycloalkyl, and alkyl-cycloalkyl groups may be mono-, di- or tri-substituted with (C_{1-4})alkyl;

L^0 is H, halogen, (C_{1-4})alkyl, –OH, –O-(C_{1-4})alkyl, $-NH_2$, –NH(C_{1-4})alkyl or -N$((C_{1-4})alkyl)_2$;

L^1, L^2 are each independently halogen, cyano, (C_{1-4})alkyl, -O-(C_{1-4})alkyl, -S-(C_{1-4})alkyl, -SO-(C_{1-4})alkyl, or $–SO_2$-(C_{1-4})alkyl, wherein each of said alkyl groups is optionally substituted with from one to three halogen atoms; and *either* L^1 *or* L^2 *(but not both at the same time) may also be* H; *or*

L^0 and L^1 or
L^0 and L^2 may be covalently bonded to form, together with the two C-atoms to which they are linked, a 5- or 6-membered carbocyclic ring wherein one or two $-CH_2$-groups not being directly linked to each other may be replaced each independently by -O- or NR^a wherein R^a is H or (C_{1-4})alkyl, and wherein said carbo- or heterocyclic ring is optionally mono- or di-substituted with (C_{1-4})alkyl;

R^2 is R^{20}, $-NR^{22}COR^{20}$, $-NR^{22}COOR^{20}$ $-NR^{22}R^{21}$ and $–NR^{22}CONR^{21}R^{23}$, wherein R^{20} is selected from (C_{1-6})alkyl, (C_{3-7})cycloalkyl and (C_{1-4})alkyl-(C_{3-7})cycloalkyl, wherein said cycloalkyl and alkyl-cycloalkyl may be mono-, di- or tri-substituted with (C_{1-3})alkyl;
R^{21} is H or R^{20} as defined above,
R^{22} and R^{23} are independently selected from H and methyl,

R^1 is ethyl or vinyl;

R^C is hydroxy or $NHSO_2R^B$ wherein R^B is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, phenyl, naphthyl, pyridinyl, (C_{1-4})alkyl-phenyl, (C_{1-4})alkyl-naphthyl or (C_{1-4})alkyl-pyridinyl; each of which optionally being mono-, di- or tri-substituted with substituents selected from halogen, hydroxy, cyano,

(C_{1-4})alkyl, O-(C_{1-6})alkyl, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, -NH_2, -NH(C_{1-4})alkyl and -N((C_{1-4})alkyl)$_2$, wherein (C_{1-4})alkyl and O-(C_{1-6})alkyl are optionally substituted with one to three halogen atoms; and each of which optionally being monosubstituted with nitro;

or R^8 is –N(R^{N2})R^{N1}), wherein R^{N1} and R^{N2} are independently selected from H, (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl and (C_{1-6})alkyl-aryl; wherein said (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, aryl and (C_{1-6})alkyl-aryl are optionally substituted with one or more substituents independently selected from halogen, (C_{1-6})alkyl, hydroxy, cyano, O-(C_{1-6})alkyl, -NH_2, -NH(C_{1-4})alkyl, -N((C_{1-4})alkyl)$_2$, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, –COOH, and –COO(C_{1-6})alkyl; or R^{N2} and R^{N1} are linked, together with the nitrogen to which they are bonded, to form a 3- to 7-membered monocyclic saturated or unsaturated heterocycle or a 9- or 10-membered bicyclic saturated or unsaturated heterocycle, each of which optionally containing from one to three further heteroatoms independently selected from N, S and O, and each of which being optionally substituted with one or more substituents independently selected from halogen, (C_{1-6})alkyl, hydroxy, cyano, O-(C_{1-6})alkyl, -NH_2, -NH(C_{1-4})alkyl, -N((C_{1-4})alkyl)$_2$, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, –COOH, and –COO(C_{1-6})alkyl;

or a pharmaceutically acceptable salt or ester thereof.

Included within the scope of this invention is a pharmaceutical composition comprising an anti-hepatitis C virally effective amount of a compound of formula I, or a pharmaceutically acceptable salt or ester thereof, in admixture with at least one pharmaceutically acceptable carrier medium or auxiliary agent.

According to a further aspect of this embodiment the pharmaceutical composition according to this invention further comprises a therapeutically effective amount of at least one other antiviral agent.

Another important aspect of the invention involves a method of treating or preventing a hepatitis C viral infection in a mammal by administering to the mammal

an anti-hepatitis C virally effective amount of a compound of formula I, a pharmaceutically acceptable salt or ester thereof, or a composition as described above, alone or in combination with at least one other antiviral agent, administered together or separately.

Also within the scope of this invention is the use of a compound of formula I, or a pharmaceutically acceptable salt or ester thereof, as described herein, for the manufacture of a medicament for the treatment or prevention of hepatitis C viral infection in mammal.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

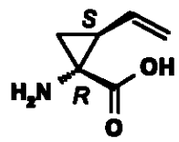
Definitions

As used herein, the following definitions apply unless otherwise noted:

With reference to the instances where *(R)* or *(S)* is used to designate the absolute configuration of a substituent or asymmetric center of a compound of formula I, the designation is done in the context of the whole compound and not in the context of the substituent or asymmetric center alone.

The designation "P1, P2, and P3" as used herein refer to the position of the amino acid residues starting from the C-terminus end of the peptide analogs and extending towards the N-terminus (i.e. P1 refers to position 1 from the C-terminus, P2: second position from the C-terminus, etc.) (see Berger A. & Schechter I., Transactions of the Royal Society London series B257, 249-264 (1970)).

As used herein the term "(1*R*, 2*S*)-vinyl-ACCA" refers to a compound of formula:



namely, (*1R, 2S*) 1-amino-2-ethenylcyclopropanecarboxylic acid.

The term "(C_{1-n})alkyl" as used herein, either alone or in combination with another substituent, means acyclic, straight or branched chain alkyl substituents containing from 1 to n carbon atoms. "(C_{1-6})alkyl" includes, but is not limited to, methyl, ethyl, n-

propyl, n-butyl, 1-methylethyl (i-propyl), 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl (*tert*-butyl), pentyl and hexyl. The abbreviations Me and Pr denote a methyl group and n-propyl respectively.

The term "(C_{3-7})cycloalkyl" as used herein, either alone or in combination with another substituent, means a cycloalkyl substituent containing from 3 to 7 carbon atoms and includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "(C_{1-n})alkyl-(C_{3-7})cycloalkyl" as used herein means an alkylene radical containing 1 to n carbon atoms to which a cycloalkyl radical containing from 3 to 7 carbon atoms is directly linked;and includes, but is not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, 1-cyclopentylethyl, 2-cyclopentylethyl, cyclohexylmethyl, 1-cyclohexylethyl, 2-cyclohexylethyl and cycloheptylpropyl.

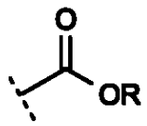
The term aryl or "C_6 or C_{10} aryl" as used herein interchangeably, either alone or in combination with another radical, means either an aromatic monocyclic group containing 6 carbon atoms or an aromatic bicyclic group containing 10 carbon atoms. Aryl includes, but is not limited to, phenyl, 1-naphthyl or 2-naphthyl.

As used herein, the term "(C_{1-n})alkyl-aryl" means an alkyl radical containing from 1 to n carbon atoms to which an aryl is bonded. Examples of (C_{1-3})alkyl-aryl include, but are not limited to, benzyl (phenylmethyl), 1-phenylethyl, 2-phenylethyl and phenylpropyl.

The term "O-(C_{1-n})alkyl" or "(C_{1-n})alkoxy" as used herein, either alone or in combination with another radical, means the radical -O-(C_{1-n})alkyl wherein alkyl is as defined above containing from 1 to n carbon atoms, and includes methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy and 1,1-dimethylethoxy. The latter radical is known commonly as *tert*-butoxy.

The term "halo" or "halogen" as used herein means a halogen substituent selected from fluoro, chloro, bromo or iodo.

The term "pharmaceutically acceptable ester" as used herein, either alone or in combination with another substituent, means esters of the compound of formula I in which any of the carboxyl functions of the molecule, but preferably the carboxy terminus, is replaced by an alkoxycarbonyl function:



in which the R moiety of the ester is selected from alkyl (including, but not limited to,. methyl, ethyl, *n*-propyl, t-butyl, *n*-butyl); alkoxyalkyl (including, but not limited to methoxymethyl); alkoxyacyl (including, but not limited to acetoxymethyl); alkyl-aryl (including, but not limited to benzyl); aryloxyalkyl (including, but not limited to phenoxymethyl); aryl (including, but not limited to phenyl), optionally substituted with halogen, (C_{1-4})alkyl or (C_{1-4})alkoxy. Other suitable prodrug esters can be found in Design of prodrugs, Bundgaard, H. Ed. Elsevier (1985). Such pharmaceutically acceptable esters are usually hydrolyzed *in vivo* when injected in a mammal and transformed into the acid form of the compound of formula I. With regard to the esters described above, unless otherwise specified, any alkyl moiety present advantageously contains 1 to 16 carbon atoms, particularly 1 to 6 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group. In particular the esters may be a C_{1-16} alkyl ester, an unsubstituted benzyl ester or a benzyl ester substituted with at least one halogen, C_{1-6} alkyl, C_{1-6} alkoxy, nitro or trifluoromethyl.

The term "pharmaceutically acceptable salt" means a salt of a compound of formula (I) which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, generally water or oil-soluble or dispersible, and effective for their intended use. The term includes pharmaceutically-acceptable acid addition salts and pharmaceutically-acceptable base addition salts. Lists of suitable salts are found in, e.g., S.M. Birge et al., J. Pharm. Sci., 1977, 66, pp. 1-19.

The term "pharmaceutically-acceptable acid addition salt" means those salts which retain the biological effectiveness and properties of the free bases and which are not

biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, phosphoric acid, and the like, and organic acids such as acetic acid, trifluoroacetic acid, adipic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, butyric acid, camphoric acid, camphorsulfonic acid, cinnamic acid, citric acid, digluconic acid, ethanesulfonic acid, glutamic acid, glycolic acid, glycerophosphoric acid, hemisulfic acid, hexanoic acid, formic acid, fumaric acid, 2-hydroxyethane-sulfonic acid (isethionic acid), lactic acid, hydroxymaleic acid, malic acid, malonic acid, mandelic acid, mesitylenesulfonic acid, methanesulfonic acid, naphthalenesulfonic acid, nicotinic acid, 2-naphthalenesulfonic acid, oxalic acid, pamoic acid, pectinic acid, phenylacetic acid, 3-phenylpropionic acid, pivalic acid, propionic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, sulfanilic acid, tartaric acid, p-toluenesulfonic acid, undecanoic acid, and the like.

The term "pharmaceutically-acceptable base addition salt" means those salts which retain the biological effectiveness and properties of the free acids and which are not biologically or otherwise undesirable, formed with inorganic bases such as ammonia or hydroxide, carbonate, or bicarbonate of ammonium or a metal cation such as sodium, potassium, lithium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Particularly preferred are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically-acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, quaternary amine compounds, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion-exchange resins, such as methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, isopropylamine, tripropylamine, tributylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, tetramethylammonium compounds, tetraethylammonium compounds, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, dibenzylamine, N,N-dibenzylphenethylamine, 1-ephenamine, N,N'-dibenzylethylenediamine, polyamine resins, and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine,

trimethylamine, dicyclohexylamine, choline, and caffeine.

The term "mammal" as it is used herein is meant to encompass humans, as well as non-human mammals which are susceptible to infection by hepatitis C virus including domestic animals, such as cows, pigs, horses, dogs and cats, and non-domestic animals.

The term "antiviral agent" as used herein means an agent (compound or biological) that is effective to inhibit the formation and/or replication of a virus in a mammal. This includes agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a mammal. Such agents can be selected from: another anti-HCV agent, HIV inhibitor, HAV inhibitor and HBV inhibitor. Antiviral agents include, for example, ribavirin, amantadine, VX-497 (merimepodib, Vertex Pharmaceuticals), VX-498 (Vertex Pharmaceuticals), Levovirin, Viramidine, Ceplene (maxamine), XTL-001 and XTL-002 (XTL Biopharmaceuticals).

The term "other anti-HCV agent" as used herein means those agents that are effective for diminishing or preventing the progression of hepatitis C related symptoms of disease. Such agents can be selected from: immunomodulatory agents, inhibitors of HCV NS3 protease, inhibitors of HCV polymerase or inhibitors of another target in the HCV life cycle.

The term "immunomodulatory agent" as used herein means those agents (compounds or biologicals) that are effective to enhance or potentiate the immune system response in a mammal. Immunomodulatory agents include, for example, class I interferons (such as α-, β-, δ- ,ω- and τ-interferons, consensus interferons and asialo-interferons), class II interferons (such as γ-interferons) and pegylated forms thereof.

The term "inhibitor of HCV NS3 protease" as used herein means an agent (compound or biological) that is effective to inhibit the function of HCV NS3 protease in a mammal. Inhibitors of HCV NS3 protease include, for example, those compounds described in WO 99/07733, WO 99/07734, WO 00/09558, WO

00/09543, WO 00/59929, WO 03/064416, WO 03/064455, WO 03/064456, WO 02/060926, WO 03/053349, WO 03/099316 or WO 03/099274, and the Vertex pre-development candidate identified as VX-950.

The term "inhibitor of HCV polymerase" as used herein means an agent (compound or biological) that is effective to inhibit the function of an HCV polymerase in a mammal. This includes, for example, inhibitors of HCV NS5B polymerase. Inhibitors of HCV polymerase include non-nucleosides, for example, those compounds described in:

- US Application No. 60/441,674 filed January 22, 2003, herein incorporated by reference in its entirety (Boehringer Ingelheim),
- US Application No. 60/441,871 filed January 22, 2003, herein incorporated by reference in its entirety (Boehringer Ingelheim),

WO 04/005286 (Gilead), WO 04/002977 (Pharmacia), WO 04/002944 (Pharmacia), WO 04/002940 (Pharmacia), WO 03/101993 (Neogenesis), WO 03/099824 (Wyeth), WO 03/099275 (Wyeth), WO 03/099801 (GSK)), WO 03/097646 (GSK), WO 03/095441 (Pfizer), WO 03/090674 (Viropharma), WO 03/084953 (B&C Biopharm), WO 03/082265 (Fujisawa), WO 03/082848 (Pfizer), WO 03/062211 (Merck), WO 03/059356 (GSK), EP 1321463 (Shire), WO 03/040112 (Rigel), WO 03/037893 (GSK), WO 03/037894 (GSK), WO 03/037262 (GSK), WO 03/037895 (GSK), WO 03/026587 (BMS), WO 03/002518 (Dong Wha), WO 03/000254 (Japan Tobacco), WO 02/100846 A1 (Shire), WO 02/100851 A2 (Shire), WO 02/098424 A1 (GSK), WO 02/079187 (Dong Wha), WO 03/02/20497 (Shionogi), WO 02/06246 (Merck), WO 01/47883 (Japan Tobacco), WO 01/85172 A1 (GSK), WO 01/85720 (GSK), WO 01/77091 (Tularik), WO 00/18231 (Viropharma), WO 00/13708 (Viropharma), WO 01/10573 (Viropharma) WO 00/06529 (Merck), EP 1 256 628 A2 (Agouron), WO 02/04425 (Boehringer Ingelheim) WO 03/007945 (Boehringer Ingelheim), WO 03/010140 (Boehringer Ingelheim) and WO 03/010141 (Boehringer Ingelheim). Furthermore other inhibitors of HCV polymerase also include nucleoside analogs, for example, those compounds described in: WO 04/007512 (Merck/Isis), WO 04/003000 (Idenix), WO 04/002999 (Idenix), WO 04/0002422 (Idenix), WO 04/003138 (Merck), WO 03/105770 (Merck), WO 03/105770 (Merck), WO 03/093290 (Genelabs), WO 03/087298 (Biocryst), WO 03/062256 (Ribapharm), WO 03/062255 (Ribapharm), WO 03/061385 (Ribapharm), WO 03/026675 (Idenix), WO

03/026589 (Idenix), WO 03/020222 (Merck), WO 03/000713 (Glaxo), WO 02/100415 (Hoffmann-La Roche), WO 02/1094289 (Hoffmann-La Roche), WO 02/051425 (Mitsubishi), WO 02/18404 (Hoffmann-La Roche), WO 02/069903 (Biocryst Pharmaceuticals Inc.), WO 02/057287 (Merck/Isis), WO 02/057425 (Merck/Isis), WO 01/90121 (Idenix), WO 01/60315 (Shire) and WO 01/32153 (Shire). Specific examples of inhibitors of an HCV polymerase, include JTK-002, JTK-003 and JTK-109 (Japan Tobacco).

The term "inhibitor of another target in the HCV life cycle" as used herein means an agent (compound or biological) that is effective to inhibit the formation and/or replication of HCV in a mammal other than by inhibiting the function of the HCV NS3 protease. This includes agents that interfere with either host or HCV viral mechanisms necessary for the formation and/or replication of HCV in a mammal. Inhibitors of another target in the HCV life cycle include, for example, agents that inhibit a target selected from helicase, NS2/3 protease and internal ribosome entry site (IRES). Specific examples of inhibitors of another target in the HCV life cycle include ISIS-14803 (ISIS Pharmaceuticals).

The term "HIV inhibitor" as used herein means an agents (compound or biological) that is effective to inhibit the formation and/or replication of HIV in a mammal. This includes agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of HIV in a mammal. HIV inhibitors include, for example, nucleoside inhibitors, non-nucleoside inhibitors, protease inhibitors, fusion inhibitors and integrase inhibitors.

The term "HAV inhibitor" as used herein means an agent (compound or biological) that is effective to inhibit the formation and/or replication of HAV in a mammal. This includes agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of HAV in a mammal. HAV inhibitors include Hepatitis A vaccines, for example, Havrix® (GlaxoSmithKline), VAQTA® (Merck) and Avaxim® (Aventis Pasteur).

The term "HBV inhibitor" as used herein means an agent (compound or biological) that is effective to inhibit the formation and/or replication of HBV in a mammal. This

Includes agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of HBV in a mammal. HBV inhibitors include, for example, agents that inhibit HBV viral DNA polymerase or HBV vaccines. Specific examples of HBV inhibitors include Lamivudine (Epivir-HBV®), Adefovir Dipivoxil, Entecavir, FTC (Coviracil®), DAPD (DXG), L-FMAU (Clevudine®), AM365 (Amrad), Ldt (Telbivudine), monoval-LdC (Valtorcitabine), ACH-126,443 (L-Fd4C) (Achillion), MCC478 (Eli Lilly), Racivir (RCV), Fluoro-L and D nucleosides, Robustaflavone, ICN 2001-3 (ICN), Bam 205 (Novelos), XTL-001 (XTL), Imino-Sugars (Nonyl-DNJ) (Synergy), HepBzyme; and immunomodulator products such as: Interferon alpha 2b, HE2000 (Hollis-Eden), Theradigm (Epimmune), EHT899 (Enzo Biochem), Thymosin alpha-1 (Zadaxin®), HBV DNA vaccine (PowderJect), HBV DNA vaccine (Jefferon Center), HBV antigen (OraGen), BayHep B® (Bayer), Nabi-HB® (Nabi) and Anti-hepatitis B (Cangene); and HBV vaccine products such as the following: Engerix B, Recombivax HB, GenHevac B, Hepacare, Bio-Hep B, TwinRix, Comvax, Hexavac.

The term "class I interferon" as used herein means an interferon selected from a group of interferons that all bind to receptor type I. This includes both naturally and synthetically produced class I interferons. Examples of class I interferons include α-, β-, δ-, ω- and τ-interferons, consensus interferons, asialo-interferons and pegylated forms thereof.

The term "class II interferon" as used herein means an interferon selected from a group of interferons that all bind to receptor type II. Examples of class II interferons include γ-interferons.

Specific preferred examples of some of these agents are listed below:

- antiviral agents: ribavirin or amantadine;
- immunomodulatory agents: class I interferons, class II interferons or pegylated forms thereof;
- HCV polymerase inhibitors: nucleoside analogs or non-nucleosides;
- inhibitor of another target in the HCV life cycle that inhibits a target selected from: NS3 helicase, NS2/3 protease or internal ribosome entry site (IRES);
- HIV inhibitors: nucleosidic inhibitors, non-nucleosidic inhibitors, protease

inhibitors, fusion inhibitors or integrase inhibitors; or

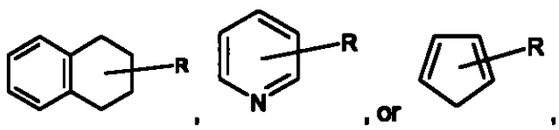
- HBV inhibitors: agents that inhibit viral DNA polymerase or is an HBV vaccine.

As discussed above, combination therapy is contemplated wherein a compound of formula (I), or a pharmaceutically acceptable salt thereof, is co-administered with at least one additional agent selected from: an antiviral agent, an immunomodulatory agent, another inhibitor of HCV NS3 protease, an inhibitor of HCV polymerase, an inhibitor of another target in the HCV life cycle, an HIV inhibitor, an HAV inhibitor and an HBV inhibitor. Examples of such agents are provided in the Definitions section above. These additional agents may be combined with the compounds of this invention to create a single pharmaceutical dosage form. Alternatively these additional agents may be separately administered to the patient as part of a multiple dosage form, for example, using a kit. Such additional agents may be administered to the patient prior to, concurrently with, or following the administration of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

As used herein, the term "treatment" means the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of the hepatitis C disease and/or to reduce viral load in a patient.

As used herein, the term "prevention" means the administration of a compound or composition according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood, to prevent the appearance of symptoms of the disease.

As used herein, the designation whereby a bond to a substituent R is drawn as emanating from the center of a ring, such as, for example,



, , or ,

means that the substituent R may be attached to any free position on the ring that would otherwise be substituted with a hydrogen atom, unless specified otherwise.

The following sign - - - or → are used interchangeably in sub-formulas to indicate the bond which is connected to the rest of the molecule as defined.

Preferred embodiments

In the following preferred embodiments, groups and substituents of the compounds according to this invention are described in detail.

B is preferably selected from (C_{2-8})alkyl, (C_{3-7})cycloalkyl and (C_{1-3})alkyl-(C_{3-7})cycloalkyl,

a) wherein said alkyl, cycloalkyl, and alkyl-cycloalkyl may be mono-, di- or tri-substituted with (C_{1-3})alkyl; and
b) wherein said alkyl, cycloalkyl and alkyl-cycloalkyl may be mono- or di-substituted with substituents selected from hydroxy and O-(C_{1-4})alkyl; and
c) wherein each of said alkyl groups may be mono-, di- or tri-substituted with fluorine or mono-substituted with chlorine or bromine; and
d) wherein in each of said cycloalkyl groups being 5-, 6- or 7-membered, one or two -CH_2-groups not being directly linked to each other may be replaced by -O- such that the O-atom is linked to the group **X** via at least two C-atoms.

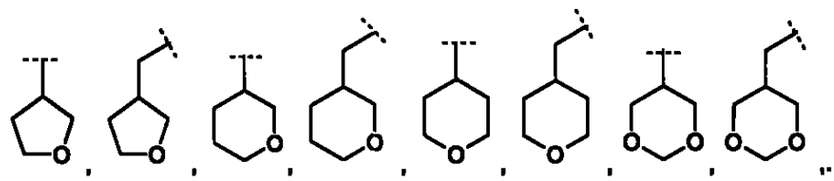
More preferably, B is selected from ethyl, n-propyl, i-propyl, n-butyl, 1-methylpropyl, 2-methylpropyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl,

a) wherein each of said groups is optionally substituted with 1 to 3 substituents selected from methyl and ethyl;
b) wherein each of said groups is optionally mono- or di-substituted with substituents selected from hydroxy, methoxy and ethoxy; and
c) wherein each of said alkyl groups may be mono-, di- or tri-substituted with fluorine or mono-substituted with chlorine or bromine; and
d) wherein in each of said cycloalkyl groups being 5-, 6- or 7-membered, one or two -CH_2-groups not being directly linked to each other may be replaced by -O- such that the O-atom is linked to the group **X** via at least two C-atoms.

B is even more preferably selected from ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethylpropyl, 1-ethyl-2-

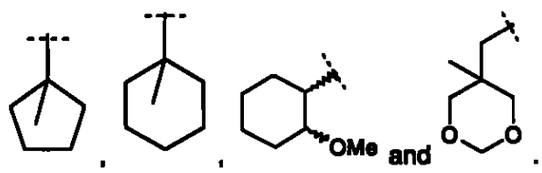
methylpropyl, 1-(1-methylethyl)-2-methylpropyl, 1-ethyl-2,2-dimethylpropyl, butyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,2-dimethylbutyl, 1,1-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1,2,2-trimethylbutyl, 1,2,3-trimethylbutyl, 2,2,3-trimethylbutyl, 2,3,3-trimethylbutyl and 2,2,3-trimethylbutyl, whereby these alkyl-groups may be substituted with chlorine or bromine, or with 1, 2 or 3 fluorine substituents. Examples of preferred fluorinated alkyl groups include, but are not limited to, 2-fluoroethyl, 3-fluoropropyl and 3,3,3-trifluoropropyl.

In addition, even more preferably, B is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl or is selected from the following formulas, wherein one or two CH_2-groups of a cycloalkyl group is replaced by oxygen:

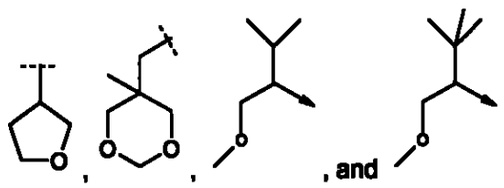


From the above list, cycloalkyl and alkyl-cycloalkyl groups optionally comprising 1 or 2 O-atoms are optionally substituted with 1, 2 or 3 methyl-groups. Especially those cycloalkyl groups, optionally comprising 1 or 2 O-atoms, are preferred, wherein the α-C-atom is substituted with methyl.

Further examples of preferred substituted cyclic groups are



Most preferably B is selected from ethyl, n-propyl, *tert*-butyl, 2-methylpropyl, 1,2-dimethylpropyl, 1,2,2-trimethylpropyl, 2-fluoroethyl, 3-fluoropropyl, 3,3,3-trifluoropropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclopentyl and 1-methylcyclohexyl, and a group selected from:



Still, most preferably B is selected from ethyl, *n*-propyl, *tert*-butyl, cyclopentyl, 1-methylcyclopentyl, 2-fluoroethyl or 3-fluoropropyl.

According to one embodiment of this invention X is O.

According to another embodiment of this invention X is NH.

R^3 is preferably (C_{2-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-3})alkyl-(C_{3-7})cycloalkyl, each of which being optionally substituted with 1 to 3 substituents selected from (C_{1-4})alkyl.

R^3 is more preferably selected from ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, or cyclohexylmethyl, each of which optionally being substituted with 1 or 2 substituents selected from methyl, ethyl and propyl.

Even more preferably R^3 is selected from 1-methylethyl, 1,1-dimethylethyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, cyclopentyl, cyclohexyl, 1-methylcyclopentyl, 1-methylcyclohexyl, cyclopentylmethyl, cyclohexylmethyl, (1-methylcyclopentyl)methyl and (1-methylcyclohexyl)methyl.

R^3 is most preferably selected from 1,1-dimethylethyl, cyclopentyl, cyclohexyl and 1-methylcyclohexyl.

Still, R^3 is most preferably selected from 1,1-dimethylethyl and cyclohexyl.

L^0 is preferably selected from H, halogen, CH_3, -OH, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-OCH(CH_3)_2$, $-NHCH_3$, $-NHC_2H_5$, $-NHC_3H_7$, $-NHCH(CH_3)_2$, $-N(CH_3)_2$, $-N(CH_3)C_2H_5$, $-N(CH_3)C_3H_7$ and $-N(CH_3)CH(CH_3)_2$.

Most preferably L^0 is selected from H, -OH, $-OCH_3$, halogen and $-N(CH_3)_2$.

Even most preferably, L^0 is H, -OH or-OCH_3.

Still, most preferably, L^0 is H or $-OCH_3$.

L^1 and L^2 are preferably each independently selected from: halogen, $-CH_3$, $-C_2H_5$, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-OCH(CH_3)_2$, CF_3, -SMe, -SOMe, and SO_2Me whereby either L^1 or L^2 may be H.

More preferably either one of L^1 and L^2 is $-CH_3$, -F, -Cl, -Br, -OMe, -SMe, or $-SO_2Me$ and the other of L^1 and L^2 is H.

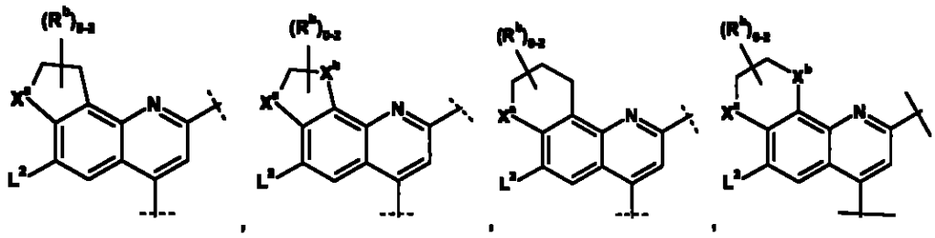
Most preferably L^1 is CH_3, -F, -Cl, -Br, -OMe, -SMe, or $-SO_2Me$ and L^2 is H.

Therefore, preferably L^0 is selected from: H, -OH and $-OCH_3$; and either one of L^1 and L^2 is CH_3, -F, -Cl, -Br, -OMe, -SMe, or $-SO_2Me$ and the other of L^1 and L^2 is H.

More preferably L^0 is selected from H, -OH and $-OCH_3$; L^1 is - CH_3, -F, -Cl, -Br, -OMe, -SMe, or $-SO_2Me$; and L^2 is H.

Most preferably L^0 is H or $-OCH_3$; L^1 is $-CH_3$, Cl or Br; and L^2 is H.

In the case L^0 and L^1 are covalently bonded to form together with the quinoline residue to which they are linked a ring system, this ring system is preferably selected from:



wherein

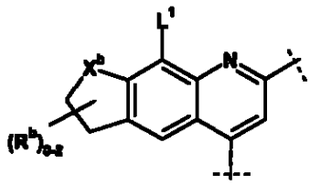
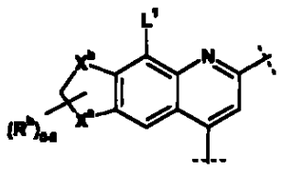
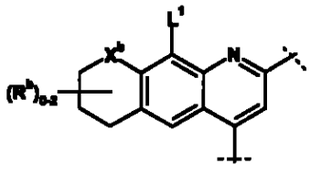
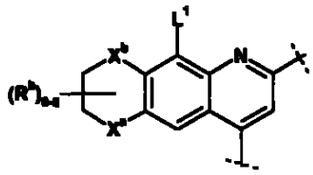
X^a, X^b are independently selected from CH_2, O and NR^a; most preferably O;

R^a is each independently H or (C_{1-4})alkyl;

R^b is each independently (C_{1-4})alkyl;

L^2 is as defined; preferably H or methyl, particularly H.

In the case L^0 and L^2 are covalently bonded to form together with the quinoline residue to which they are linked a ring system, this ring system is preferably selected from:

, and

wherein

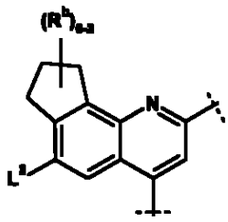
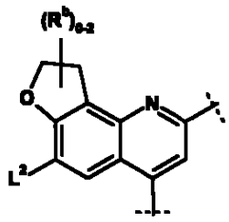
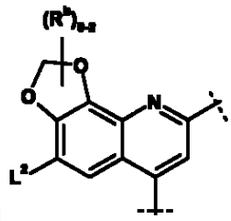
X^a, X^b are independently selected from CH_2, O and NR^a; most preferably O;

R^a is each independently H or (C_{1-4})alkyl;

R^b is each independently (C_{1-4})alkyl;

L^1 is as defined; preferably H or methyl, particularly H.

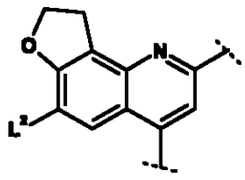
More preferably, L^0 and L^1 are covalently bonded to form, together with the quinoline residue to which they are linked, a ring system which is selected from:

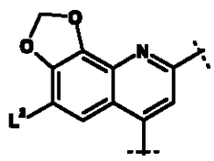
, , and

wherein each R^b is independently (C_{1-4})alkyl and L^2 is as defined; preferably H or methyl, particularly H.

Most preferably, L^0 and L^1 are covalently bonded to form together with the quinoline residue to which they are linked a ring system selected from



, and



wherein L^2 is H or $-CH_3$, preferably H.

R^2 is preferably R^{20}, $-NHCOR^{20}$, $-NHCOOR^{20}$, $-NHR^{21}$ and $-NHCONR^{21}R^{23}$, wherein

R^{20} is selected from (C_{1-8})alkyl, (C_{3-7})cycloalkyl, (C_{1-3})alkyl-(C_{3-7})cycloalkyl, wherein said cycloalkyl and alkyl-cycloalkyl may be mono-, di- or tri-substituted with (C_{1-3})alkyl; and

R^{21} is H or R^{20} as defined above; and

R^{23} is H or methyl; most preferably H.

More preferably, R^2 is R^{20}, $NHCOR^{20}$, $-NHCOOR^{20}$, $-NHR^{21}$ -and $-NHCONR^{21}R^{23}$, wherein

R^{20} is selected from methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, 1-methylpropyl, 2-methylpropyl, *tert*-butyl, 2,2-dimethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1,2,2-trimethylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropyl-methyl, cyclobutylmethyl, cyclopentylmethyl, and cyclohexylmethyl, each of said cycloalkyl and alkyl-cycloalkyl groups being optionally substituted with 1 to 3 substituents selected from methyl and ethyl, in particular methyl; and

R^{21} is H or R^{20} as defined above; and

R^{23} is H or methyl; most preferably H.

Preferably, R^2 is selected from:

a) amino, *N*-methylamino, *N*-ethylamino, *N*-propylamino, *N*-(1-methylethyl)amino, *N*-(1,1-dimethylethyl)amino, *N*-(2-methylpropyl)amino, *N*-(1-methylpropyl)amino, *N*-(2,2-dimethylpropyl)amino, *N*-(1,2-dimethylpropyl)amino, *N*-(1,1-dimethylpropyl)amino, *N*-cyclopropylamino, *N*-cyclobutylamino-,

N-cyclopentylamino-, *N*-cyclohexylamino-, *N*-(cyclopropylmethyl)amino, *N*-(cyclobutylmethyl)amino, *N*-(cyclopentylmethyl)amino, and *N*-(cyclohexylmethyl)amino;

b) methylcarbonylamino, ethylcarbonylamino, 1-methylethylcarbonylamino, propylcarbonylamino, 2-methylpropylcarbonylamino, 1-methylpropylcarbonylamino, 2,2-dimethylpropylcarbonylamino, 1,2-dimethylpropylcarbonylamino, 1,1-dimethylpropylcarbonylamino, cyclopropylcarbonylamino, cyclobutylcarbonylamino, cyclopentylcarbonylamino, cyclohexylcarbonylamino, cyclopropylmethylcarbonylamino, cyclobutylmethylcarbonylamino, cyclopentylmethylcarbonylamino, cyclohexylmethylcarbonylamino; and

c) methoxycarbonylamino, ethoxycarbonylamino, 1-methylethoxycarbonylamino, propoxycarbonylamino, *tert*-butoxycarbonylamino, cyclopropyloxycarbonylamino, cyclobutyloxycarbonylamino, cyclopentyloxycarbonylamino, cyclohexyloxycarbonylamino, cyclopropylmethoxycarbonylamino, cyclobutylmethoxycarbonylamino, cyclopentylmethoxycarbonylamino, cyclohexylmethoxycarbonylamino;

wherein all said cycloalkyl or alkyl-cycloalkyl groups may be mono- or disubstituted with methyl.

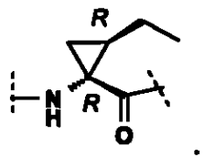
Most preferably R^2 is -NHCOR^{20}, -NHCOOR^{20}, or -NHR^{21}, wherein R^{20} and R^{21} are as defined herein.

Preferably, R^{20} and R^{21} are independently selected from: methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, 1-methylpropyl, 2-methylpropyl, *tert*-butyl, 2,2-dimethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1,2,2-trimethylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, each of said cycloalkyl or alkyl-cycloalkyl groups optionally being mono- or di-substituted with methyl or ethyl.

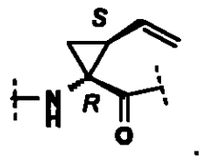
More preferably, R^{20} and R^{21} are independently selected from: methyl, ethyl, *n*-propyl, *i*-propyl, 2,2-dimethylpropyl, cyclopentyl and cyclopentylmethyl.

In the moiety P1 the substituent R^1 and the carbonyl take a *syn* orientation. Therefore, in the case R^1 is ethyl, the asymmetric carbon atoms in the cyclopropyl

group take the *R,R* configuration according to the subformula:



In the case R^1 is vinyl, the asymmetric carbon atoms in the cyclopropyl group take the *R,S* configuration according to the subformula:



R^1 is preferably vinyl.

R^C is preferably selected from hydroxy or $NHSO_2R^S$
wherein R^S is methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, 1-methylpropyl, 2-methylpropyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, phenyl, naphthyl, pyridinyl, phenylmethyl (benzyl), naphthylmethyl or pyridinylmethyl;

a) each of which optionally being mono-, di- or tri-substituted with substituents selected from fluorine and methyl; and
b) each of which optionally being mono- or disubstituted with substituents selected from hydroxy, trifluoromethyl, methoxy and trifluoromethoxy; and
c) each of which optionally being monosubstituted with substituents selected from chlorine, bromine, cyano, nitro, -CO-NH_2, -CO-$NHCH_3$, -CO-$N(CH_3)_2$, -NH_2, -$NH(CH_3)$ and -$N(CH_3)_2$.

Alternatively preferably, R^C is $NHSO_2R^S$, wherein R^S is $-N(R^{N2})R^{N1})$, wherein R^{N1} and R^{N2} are independently selected from H, (C_{1-4})alkyl, (C_{3-7})cycloalkyl, (C_{1-3})alkyl-(C_{3-7})cycloalkyl, phenyl, and (C_{1-3})alkyl-phenyl; wherein said (C_{1-4})alkyl, (C_{3-7})cycloalkyl, (C_{1-3})alkyl-(C_{3-7})cycloalkyl, phenyl and (C_{1-3})alkyl-phenyl are optionally substituted with one, two or three substituents independently selected from halogen, (C_{1-6})alkyl, hydroxy, cyano, O-(C_{1-6})alkyl, -NH_2, -$NH(C_{1-4})$alkyl,

-N((C_{1-4})alkyl)$_2$, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, –COOH, and –COO(C_{1-6})alkyl; or

R^{N2} and R^{N1} are linked, together with the nitrogen to which they are bonded, to form a 5 or 6-membered monocyclic heterocycle which may be saturated or unsaturated, optionally containing from one to three further heteroatoms independently selected from N, S and O, and optionally substituted with one, two or three substituents independently selected from halogen, (C_{1-6})alkyl, hydroxy, cyano, O-(C_{1-6})alkyl, -NH_2, -NH(C_{1-4})alkyl, -N((C_{1-4})alkyl)$_2$, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N((C_{1-4})alkyl)$_2$, –COOH, and –COO(C_{1-6})alkyl.

Preferably, the group R^C is hydroxy, $NHSO_2$-methyl, $NHSO_2$-ethyl, $NHSO_2$-(1-methyl)ethyl, $NHSO_2$-propyl, $NHSO_2$-cyclopropyl, $NHSO_2$-CH_2-cyclopropyl, $NHSO_2$-cyclobutyl, $NHSO_2$-cyclopentyl, or $NHSO_2$-phenyl.

More preferably, R^C is hydroxy, or $NHSO_2$-cyclopropyl.

According to a most preferred embodiment, the group R^C is hydroxy. According to an alternative most preferred embodiment, the group R^C is $NHSO_2$-cyclopropyl. According to another alternative most preferred embodiment, the group R^C is $NHSO_2N(CH_3)_2$.

Also encompassed within the scope of the present invention, are compounds of formula (I) wherein:

B is (C_{1-10})alkyl, (C_{3-7})cycloalkyl, or (C_{1-4})alkyl-(C_{3-7})cycloalkyl,

a) wherein said cycloalkyl, and alkyl-cycloalkyl may be mono-, di- or tri-substituted with (C_{1-3})alkyl; and

b) wherein said alkyl, cycloalkyl, and alkyl-cycloalkyl may be mono- or di-substituted with substituents selected from hydroxy and O-(C_{1-4})alkyl; and

c) wherein all said alkyl-groups may be mono-, di- or tri-substituted with halogen; and

d) wherein all said cycloalkyl-groups being 4-, 5-, 6- or 7-membered having optionally one (for the 4-, 5, 6, or 7-membered) or two (for the 5-, 6- or 7-membered) -CH_2-groups not directly linked to each other replaced by -O- such that the O-atom is linked to the group X via at least two C-atoms;

X is O or NH;

R^3 is (C_{2-8})alkyl, (C_{3-7})cycloalkyl or (C_{1-3})alkyl-(C_{3-7})cycloalkyl, wherein said cycloalkyl groups may be mono-, di- or tri-substituted with (C_{1-4})alkyl;

L^0 is H, –OH, –O-(C_{1-4})alkyl, -NH_2, –NH(C_{1-4})alkyl or –N$((C_{1-4})alkyl)_2$;

L^1, L^2 are each independently halogen, (C_{1-4})alkyl, -O-(C_{1-4})alkyl or -S-(C_{1-4})alkyl (in any oxidized state such as SO or SO_2); and
either L^1 or L^2 (but not both at the same time) may also be H; or

L^0 and L^1 or
L^0 and L^2 may be covalently bonded to form, together with the two C-atoms to which they are linked, a 5- or 6-membered carbocyclic ring wherein one or two -CH_2-groups not being directly linked to each other may be replaced each independently by -O- or NR^a wherein R^a is H or (C_{1-4})alkyl, and wherein said carbo- or heterocyclic ring is optionally mono- or di-substituted with (C_{1-4})alkyl;

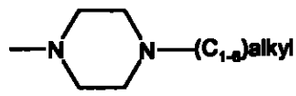
R^2 is R^{20}, -$NR^{22}COR^{20}$, -$NR^{22}COOR^{20}$ -$NR^{22}R^{21}$ and –$NR^{22}CONR^{21}R^{23}$, wherein R^{20} is selected from (C_{1-8})alkyl, (C_{3-7})cycloalkyl and (C_{1-4})alkyl-(C_{3-7})cycloalkyl, wherein said cycloalkyl and alkyl-cycloalkyl may be mono-, di- or tri-substituted with (C_{1-3})alkyl;
R^{21} is H or has one of the meanings of R^{20} as defined above,
R^{22} and R^{23} are independently selected from H and methyl,

R^1 is ethyl or vinyl;

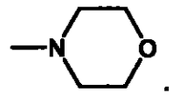
R^C is hydroxy or $NHSO_2R^B$ wherein R^B is (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-6})alkyl-(C_{3-7})cycloalkyl, phenyl, naphthyl, pyridinyl, (C_{1-4})alkyl-phenyl, (C_{1-4})alkyl-naphthyl or (C_{1-4})alkyl-pyridinyl; all of which optionally being mono-, di- or tri-substituted with substituents selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-6})alkyl, -CO-NH_2, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})alkyl)_2$,

$-NH_2$, $-NH(C_{1-4})$alkyl and $-N((C_{1-4})alkyl)_2$; and all of which optionally being monosubstituted with nitro;

or R^8 can be further selected from: $-NH(C_{1-6})$alkyl, $N((C_{1-6})alkyl)_2$, -Het,



or



;

or a pharmaceutically acceptable salt or ester thereof.

Preferably,

B is (C_{2-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-3})alkyl-(C_{3-7})cycloalkyl,

a) wherein said alkyl, cycloalkyl, and alkyl-cycloalkyl may be mono-, di- or tri-substituted with (C_{1-3})alkyl; and

b) wherein said alkyl, cycloalkyl, and alkyl-cycloalkyl may be mono- or di-substituted with substituents selected from hydroxy and O-(C_{1-4})alkyl; and

c) wherein each of said alkyl groups may be mono-, di- or tri-substituted with fluorine or mono-substituted with chlorine or bromine; and

d) wherein in each of said cycloalkyl groups being 5-, 6- or 7-membered, one or two $-CH_2$-groups not being directly linked to each other may be replaced by -O- such that the O-atom is linked to the group **X** via at least two C-atoms;

X is O or NH;

R^3 is (C_{2-6})alkyl or (C_{3-7})cycloalkyl, both of which being optionally substituted with 1 to 3 substituents selected from (C_{1-4})alkyl;

L^0 is H, $-OH$, $-OCH_3$, halogen or $-N(CH_3)_2$;

L^1 and L^2 are each independently selected from: halogen, $-CH_3$, $-C_2H_5$, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-OCH(CH_3)_2$, CF_3, -SMe, -SOMe, and SO_2Me, whereby either L^1 or L^2 may be H;

R^2 is R^{20}, $-NHCOR^{20}$, $-NHCOOR^{20}$, $-NHR^{21}$ and $-NHCONR^{21}R^{23}$,

wherein

R^{20} is selected from (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-3})alkyl-(C_{3-7})cycloalkyl, wherein each of said cycloalkyl and alkyl-cycloalkyl groups may be mono-, di- or tri-substituted with (C_{1-3})alkyl; and

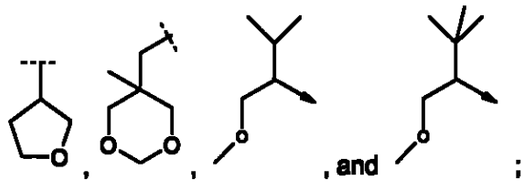
R^{21} is H or R^{20} as defined above; and

R^{23} is H or methyl;

R^1 is ethyl or vinyl; and

R^C is hydroxy, $NHSO_2$-methyl, $NHSO_2$-ethyl, $NHSO_2$-(1-methyl)ethyl, $NHSO_2$-propyl, $NHSO_2$-cyclopropyl, $NHSO_2$-CH_2-cyclopropyl, $NHSO_2$-cyclobutyl, $NHSO_2$-cyclopentyl or $NHSO_2$-phenyl.

More preferably, B is selected from: ethyl, n-propyl, *tert*-butyl, 2-methylpropyl, 1,2-dimethylpropyl, 1,2,2-trimethylpropyl, 2-fluoroethyl, 3-fluoropropyl, 3,3,3-trifluoropropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclopentyl and 1-methylcyclohexyl, and a group selected from:



;

R^3 is selected from 1,1-dimethylethyl, cyclopentyl, cyclohexyl and 1-methylcyclohexyl; L^0 is H, -OH or-OCH_3; L^1 is CH_3, -F, -Cl, -Br, -OMe, -SMe, or -SO_2Me; L^2 is H;

R^2 is -$NHCOR^{20}$, -$NHCOOR^{20}$ or -NHR^{21}, wherein R^{20} and R^{21} are independently selected from methyl, ethyl, *n*-propyl, *i*-propyl, 2,2-dimethylpropyl, cyclopentyl and cyclopentylmethyl;

R^1 is vinyl; and R^C is hydroxy or $NHSO_2$-cyclopropyl.

Most preferably, B is selected from ethyl, *n*-propyl, *tert*-butyl, cyclopentyl, 1-methylcyclopentyl, 2-fluoroethyl and 3-fluoropropyl; R^3 is selected from 1,1-dimethylethyl and cyclohexyl; L^0 is H or -OCH_3; L^1 is -CH_3, -Cl, or -Br; L^2 is H; and R^C is hydroxy.

Examples of preferred embodiments according to this invention is each single compound listed in the following Tables 1, 2, 3, 4, 5 and 6.

According to an alternate embodiment, the pharmaceutical composition of this invention may additionally comprise at least one other anti-HCV agent. Examples of anti-HCV agents include, α- (alpha), β- (beta), δ- (delta), γ- (gamma), ω- (omega) or τ- (tau) interferon, pegylated α-interferon, ribavirin and amantadine.

According to another alternate embodiment, the pharmaceutical composition of this

invention may additionally comprise at least one other inhibitor of HCV NS3 protease.

According to another alternate embodiment, the pharmaceutical composition of this invention may additionally comprise at least one inhibitor of HCV polymerase.

According to yet another alternate embodiment, the pharmaceutical composition of this invention may additionally comprise at least one inhibitor of other targets in the HCV life cycle, including but not limited to, helicase, NS2/3 protease or internal ribosome entry site (IRES).

The pharmaceutical composition of this invention may be administered orally, parenterally or via an implanted reservoir. Oral administration or administration by injection is preferred. The pharmaceutical composition of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, and intralesional injection or infusion techniques.

The pharmaceutical composition may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example Tween 80) and suspending agents.

The pharmaceutical composition of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous

suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

Other suitable vehicles or carriers for the above noted formulations and compositions can be found in standard pharmaceutical texts, e.g. in "Remington's Pharmaceutical Sciences", The Science and Practice of Pharmacy, 19th Ed. Mack Publishing Company, Easton, Penn., (1995).

Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between about 0.1 and about 50 mg/kg body weight per day of the protease inhibitor compound described herein are useful in a monotherapy for the prevention and treatment of HCV mediated disease. Typically, the pharmaceutical composition of this invention will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (*w/w*). Preferably, such preparations contain from about 20% to about 80% active compound.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the infection, the patient's disposition to the infection and the judgment of the treating physician. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the peptide. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

When the composition of this invention comprises a combination of a compound of formula I and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

When these compounds, including their pharmaceutically acceptable salts and esters, are formulated together with a pharmaceutically acceptable carrier, the resulting composition may be administered *in vivo* to mammals, such as man, to inhibit HCV NS3 protease or to treat or prevent HCV virus infection. Such treatment may also be achieved using a compound of this invention in combination with another antiviral agent. Preferred other antiviral agents are described within the Definitions section and the section of preferred pharmaceutical compositions according to this invention and include, but are not limited to: α-, β-, δ-, ω-, γ- or τ-interferon, ribavirin, amantadine; other inhibitors of HCV NS3 protease; inhibitors of HCV polymerase; inhibitors of other targets in the HCV life cycle, which include but are not limited to, helicase, NS2/3 protease, or internal ribosome entry site (IRES); or combinations thereof. The additional agents may be combined with compounds of this invention to create a single dosage form. Alternatively these additional agents may be separately administered to a mammal as part of a multiple dosage form.

Accordingly, another embodiment of this invention provides a method of inhibiting HCV NS3 protease activity in a mammal by administering a compound of the formula I, including a pharmaceutically acceptable salt or ester thereof.

In a preferred embodiment, this method is useful in decreasing the NS3 protease activity of the hepatitis C virus infecting a mammal.

As discussed above, combination therapy is contemplated wherein a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof, is co-administered with at least one additional antiviral agent. Preferred antiviral agents are described hereinbefore and examples of such agents are provided in the Definitions section. These additional agents may be combined with the compounds of this invention to

create a single pharmaceutical dosage form. Alternatively these additional agents may be separately administered to the patient as part of a multiple dosage form, for example, using a kit. Such additional agents may be administered to the patient prior to, concurrently with, or following the administration of a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof.

A compound of formula (I), or a pharmaceutically acceptable salt or ester thereof, set forth herein may also be used as a laboratory reagent. Furthermore a compound of this invention, including a pharmaceutically acceptable salt or ester thereof, may also be used to treat or prevent viral contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials (e.g. blood, tissue, surgical instruments and garments, laboratory instruments and garments, and blood collection apparatuses and materials).

A compound of formula (I), including a pharmaceutically acceptable salt or ester thereof, set forth herein may also be used as a research reagent. A compound of formula (I), including a pharmaceutically acceptable salt or ester thereof, may also be used as positive control to validate surrogate cell-based assays or *in vitro* or *in vivo* viral replication assays.

METHODOLOGY

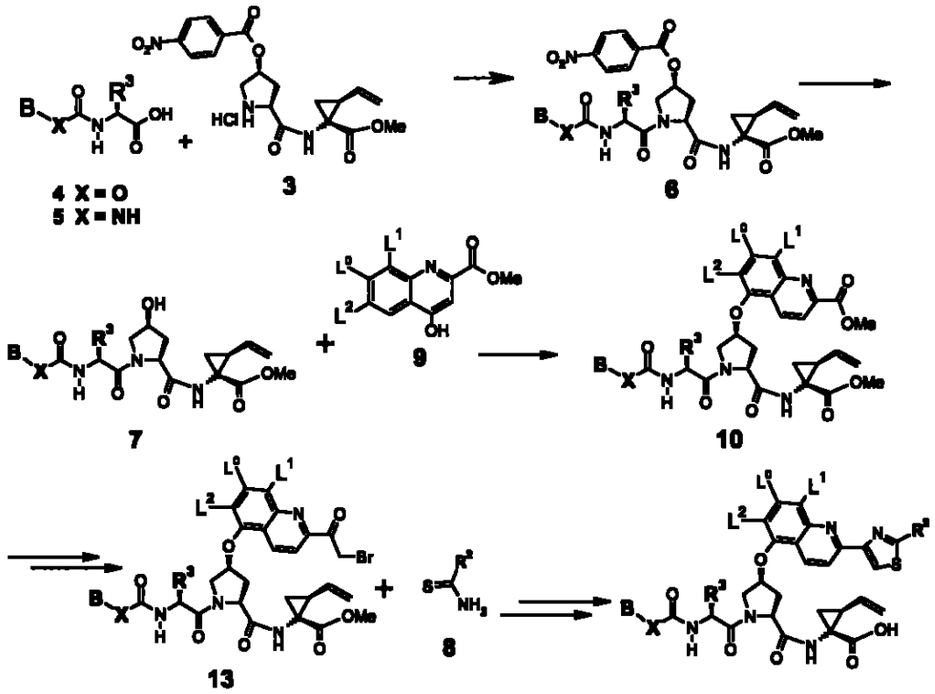
Several ways of carrying out the synthesis of compounds of formula I with different quinoline derivatives are disclosed in WO 00/09558. The dipeptide intermediate 15 (Scheme 2) and 2-carbomethoxy-4-hydroxy-7-methoxyquinoline 9 (Scheme 1) were synthesized according to the general methods described in WO 00/09543.

Compounds of formula I wherein R^C is $NHSO_2R^8$ as defined herein are prepared by coupling the corresponding acid of formula I (i.e. R^C is hydroxy) with an appropriate sulfonamide of formula $R^8SO_2NH_2$ in the presence of a coupling agent under standard conditions. Although several commonly used coupling agents can be employed, TBTU and HATU have been found to be practical. The sulfonamides are available commercially or can be prepared by known methods.

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65

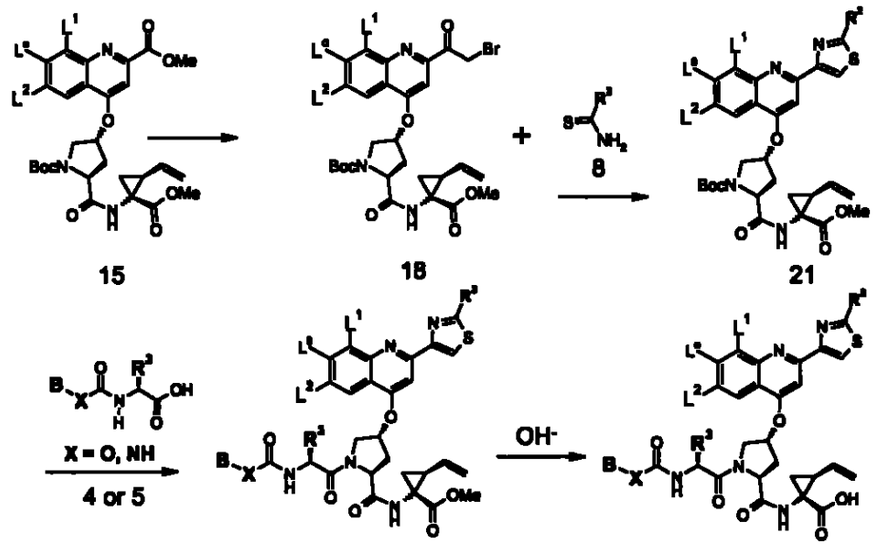
The following schemes illustrate two convenient processes using known methods for preparing the compounds of formula 1 when R^1 is vinyl and R^C is OH.

Scheme 1



Briefly, the synthesis of dipeptide **3** is carried out by coupling the P1 residue to the properly protected *trans*-hydroxy proline under standard conditions. The stereochemistry of the hydroxyl group is inverted by the well known Mitsunobu reaction using *para*-nitrobenzoic acid. Coupling of dipeptide with the P3 moiety (prepared using standard methodology and exemplified in the examples section) yielded tripeptide **6**. Introduction of the quinoline moiety to the hydroxyl group of the tripeptide **7** with inversion of stereochemistry can be carried out using either a Mitsunobu reaction or by converting the free hydroxyl group into a good leaving group (such as a brosylate) and displacing it with the hydroxyl quinoline derivative **9**. For the synthesis of the 2-(2-amino-4-thiazolyl) derivatives, the quinoline used contains a 2-carbomethoxy group as shown in **9**. Conversion of the carboxylate group to the aminothiazole derivative is carried out by well known synthetic methodology and is described and exemplified in WO 00/09543 and WO 00/09598. Finally the C-terminal ester is hydrolyzed under basic aqueous conditions.

Scheme 2



Scheme 2 describes another reaction sequence for making compounds of Formula I. In this case the quinoline moiety is introduced to the dipeptide in a similar way as described in Scheme 1. Finally, the P3 moiety is coupled under standard conditions to the dipeptide **21**. Conversion of the resulting tripeptide to the final compound is carried out as described in Scheme 1.

SYNTHESIS OF P1 FRAGMENTS

P1 moieties of compounds of Formula (I) were prepared using the protocols outlined in WO 00/59929, published October 12, 2000, and WO 00/09543, published on February 24, 2000. In particular, reference is made to pages 33-35, Example 1 of WO00/59929 and Pages 56-69 , Example 9 – 20 of WO00/09543 for the preparation of 1-aminocyclopropanecarboxylic acid P1 moieties.

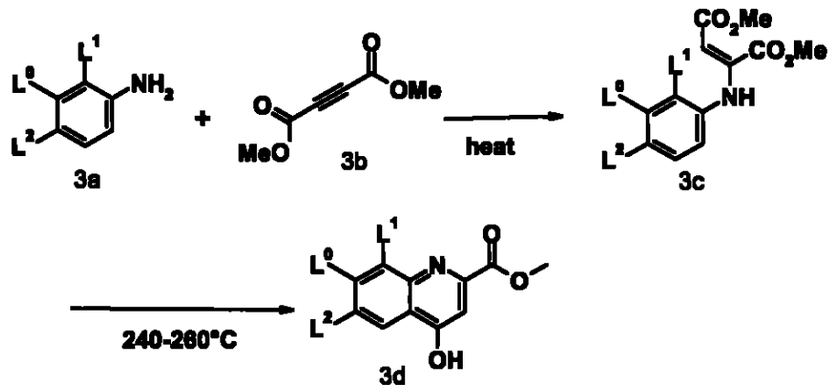
SYNTHESIS OF P2 SUBSTITUENTS

Compounds of formula 9 can be synthesized from commercially available materials using the techniques described in International Patent Applications WO 00/59929, WO 00/09543, WO 00/09558 and U.S. Patent 6,323,180 B1.

Examples of synthesis of different 2-carbomethoxy-4-hydroxyquinoline derivatives were carried out as follows:

Synthesis of 2-carbomethoxy-4-hydroxy-quinoline derivatives was carried out from the corresponding anilines according to the procedure of : Unangst, P.C.; Connor, D.T. *J. Heterocyc. Chem.* **29**, *5*, **1992**, 1097-1100. The procedure is shown in scheme 3 below:

Scheme 3



Briefly, properly substituted anilines at the 2, 3 and/or 4 position are allowed to react with dimethyl acetylene dicarboxylate and the resulting enamine is heated at high temperatures to effect the cyclization.

The corresponding anilines are commercially available or may require some well known chemical transformation. For example it can be that the nitro is commercially available and is then converted to the corresponding amine by using a reducing agent. Also when the carboxylic acid is commercially available, it can be transformed into the corresponding amine via a Curtius rearrangement.

Further details of the invention are illustrated in the following examples which are understood to be non-limiting with respect to the appended claims. Other specific ways of synthesis or resolution of the compounds of this invention can be found in WO 00/09543; WO 00/09558 & WO 00/59929 and in co-pending application 09/368,670, all of which are hereby incorporated by reference.

EXAMPLES

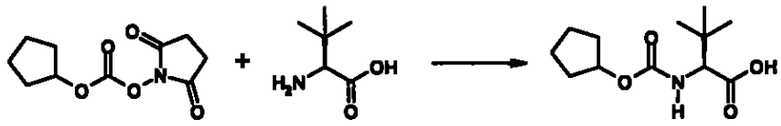
Temperatures are given in degrees Celsius. Solution percentages express a weight to volume relationship, and solution ratios express a volume to volume relationship, unless stated otherwise. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz spectrometer; the chemical shifts (δ) are reported in parts per million. Flash chromatography was carried out on silica gel (SiO_2) according to Still's flash chromatography technique (W.C. Still *et al.*, J. Org. Chem., (1978), 43, 2923).

Abbreviations used in the examples include:
BOC or Boc: *tert*-butyloxycarbonyl; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DCM: dichloromethane; DIAD: diisopropylazodicarboxylate; DIEA: diisopropylethylamine; DIPEA: diisopropylethyl amine; DMF: *N, N*-dimethylformamide; DMAP: 4-(dimethylamino)pyridine; DMSO: dimethylsulfoxide; EtOAc: ethyl acetate; HATU: [O-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate]; HPLC: high performance liquid chromatography; MS: mass spectrometry (MALDI-TOF: Matrix Assisted Laser Desorption Ionization-Time of Flight, FAB: Fast Atom Bombardment); Me: methyl; MeOH: methanol; Ph: phenyl; R.T.: room temperature (18 to 22°); *tert*-butyl or t-butyl: 1,1-dimethylethyl; Tbg: *tert*-butyl glycine: *tert*-leucine; TBTU: 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate; TEA: triethylamine; TFA: trifluoroacetic acid; and THF: tetrahydrofuran.

EXAMPLE 1

Synthesis of P3 derivatives:

Synthesis of carbamate 4a

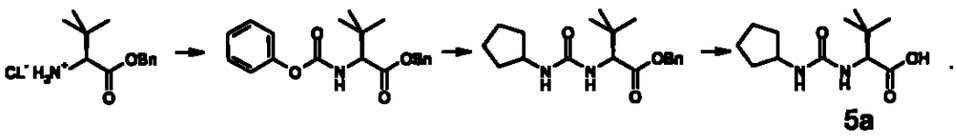


4a

THF (350 mL) was added to a flask containing carbonic acid cyclopentyl ester 2,5-dioxo-pyrrolidin-1-yl ester (9.00 g; 39.6 mmol) and *tert*-butyl glycine (6.24 g; 47.5 mmol) resulting in a suspension. Distilled water (100 mL) was added with vigorous stirring. A small amount of solid remained undissolved. Triethylamine (16.6 mL; 119 mmol) was then added resulting in a homogenous solution which was stirred at

R.T. After 2.5 h, the THF was evaporated and the aqueous residue diluted with water (100 mL). The reaction was rendered basic by the addition of 1 N NaOH (25 mL - final pH >10). The solution was washed with EtOAc (2x 200 mL) and the aqueous phase acidified with 1 N HCl (ca. 70 mL - final pH <2). The turbid solution was extracted with EtOAc (200 + 150 mL). The extract was dried ($MgSO_4$) and evaporated to give carbamate **4a** as a white solid (8.68 g).

Preparation of Ureas **5a**



5a

A solution of *tert*-butyl glycine benzyl ester hydrochloride salt (2.55 g; 9.89 mmol) in THF (20 mL) and pyridine (2.0 mL; 24.73 mmol) was cooled to 0°C. Phenyl chloroformate (1.30 mL; 10.19 mmol) was added dropwise to the cooled solution. The resulting suspension was stirred for 5 min at 0°C, then at R.T. for 1.5 h. The reaction mixture was diluted with EtOAc, washed with 10% citric acid (2x), water (2x), saturated $NaHCO_3$ (2x), water (2x) and brine (1x), dried ($MgSO_4$), filtered and evaporated to obtain the crude compound as a nearly colorless oil (3.73 g; >100%; assume 9.89 mmol). The crude product (1.01 g; 2.97 mmol) was dissolved in DMSO (6.5 mL) and cyclopentylamine was added dropwise. The reaction mixture was stirred at R.T. for 45 min and then diluted with EtOAc. The organic phase was washed with 10% citric acid (2x), water (2x), saturated $NaHCO_3$ (2x), water (2x) and brine (1x), dried ($MgSO_4$), filtered and evaporated to give the crude cyclopentyl urea -Tbg-OBn product as a nearly colorless oil. The crude material was purified by flash column chromatography with silica using hexane:EtOAc 9:1 to remove the less polar impurities and 7:3 to elute the purified product as a thick colorless oil (936 mg; 95%). The benzyl ester product (936 mg; 2.82 mmol) was deprotected under a hydrogen filled balloon at R.T. in absolute ethanol (15 mL) solution by stirring the solution with 10% Pd/C (93.6 mg) for 5.5 h. The reaction mixture was filtered through a 0.45 micron filter and evaporated to dryness to provide urea **5a** as a white solid (669 mg; 98%)

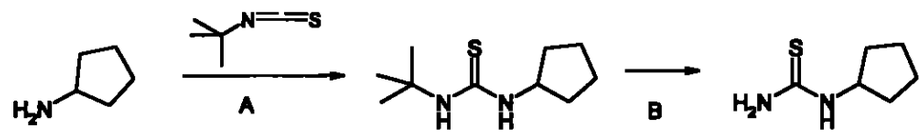
^1H NMR (400 MHz, DMSO-d_6): δ 12.39 (s, 1H), 6.09 (d, J = 7.4 Hz, 1H), 5.93 (d, J = 9.4 Hz, 1H), 3.90 (d, J = 9.4 Hz, 1H), 3.87-3.77 (m, 1H), 1.84-1.72 (m, 2H), 1.63-1.42 (m, 4H), 1.30-1.19 (m, 2H), 0.89 (s, 9H).

M.S.(electrospray) : 241.0 $(M-H)^-$ 243.0 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06% TFA; CH_3CN : H_2O) : 99%.

EXAMPLE 2

Synthesis of Thioureas 8

Synthesis of thiourea 8a:

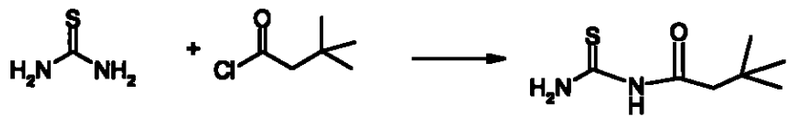


8a

To a solution of *tert*-butyl isothiocyanate (5.0 mL; 39.4 mmoL) in DCM (200 mL) was added cyclopentylamine (4.67 mL; 47.3 mmoL) followed by DIPEA and the reaction mixture was stirred at R.T. for 2 h. The mixture was diluted with EtOAc, and washed with a 10% aqueous solution of citric acid (2x), saturated $NaHCO_3$ (2x), H_2O (2x) and brine (1x). The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to yield *N-tert*-butyl–*N'*-cyclopentylthiourea as a white solid (3.70 g; 47% yield). The *N-tert*-butyl-*N'*-cyclopentylthiourea (3.70 g) was dissolved in concentrated HCl (46 mL). The dark yellow solution was heated at a gentle reflux. After 40 min the reaction mixture was allowed to cool to R.T. and thereafter cooled in ice and rendered basic to pH 9.5 with solid and a saturated aqueous solution of $NaHCO_3$. The product was extracted into EtOAc (3x). The combined EtOAc extracts were washed with H_2O (2x) and brine (1x). The organic layer was dried ($MgSO_4$), filtered and concentrated to yield a beige solid (2.46 g crude). Trituration of the crude material in hexane/ EtOAc 95 / 5 provided, after filtration, the *N*-cyclopentylthiourea 8a as a white solid (2.38 g; 90% yield).

^1H NMR (400 MHz, DMSO-d_6): δ 7.58 (bs, 1H), 7.19 (bs, 1H), 6.76 (bs, 1H), 4.34 (bs, 1H), 1.92-1.79 (m,2H), 1.66-1.55 (m, 2H), 1.55-1.30 (m,4H). MS; es^+ 144.9 $(M + H)^+$, es^-: 142.8 $(M - H)^-$.

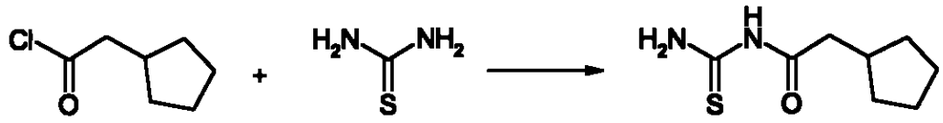
Preparation of Thiourea 8b



8b

Thiourea (5.0 g, 66 mmol) was dissolved in toluene (50 mL) and *tert*-butylacetyl chloride (8.88 g, 66 mmol) was added. The mixture was heated at reflux for 14 h to give a yellow solution. The mixture was concentrated to dryness, and the residue partitioned between EtOAc and sat. $NaHCO_3$. The yellow organic phase was dried over $MgSO_4$, filtered and concentrated to give a yellow solid. The solid was dissolved into a minimum amount of EtOAc and triturated with hexane to give **8b** as a white solid (8.52 g; 75%). M.S. (electrospray): 173 $(M-H)^-$ 175 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 99 %.

Preparation of Thiourea 8c



8c

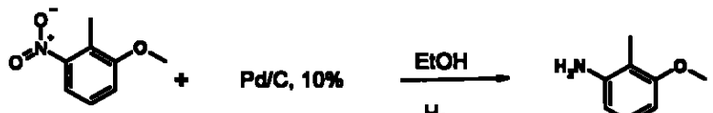
Using the procedure described above but using commercially available cyclopentyl acetyl chloride instead of *tert*-butylacetyl chloride yielded thiourea **8c**.

SYNTHESIS OF 2-CARBOMETHOXY-4-HYDROXY QUINOLINE DERIVATIVES

EXAMPLE 3A

Synthesis of 2-carbomethoxy-4-hydroxy-7-methoxy-8-methylquinoline (A5)

Step A

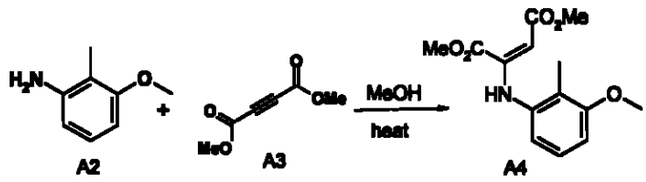


A1 A2

To a solution of 2-methyl-3-nitro anisole **A1** (5.1 g; 30.33 mmol; requires ~30 min to dissolve) in absolute ethanol (85 mL) was added 10% Pd/C catalyst (500 mg) . The solution was hydrogenated under a hydrogen filled balloon at atmospheric pressure and room temperature for 19 h. The reaction mixture was filtered through a Celite pad, rinsed and evaporated to dryness to obtain 2-methyl-3-methoxyaniline **A2** as a deep mauve oil (4.1 g; 29.81 mmol; 98 % yield).

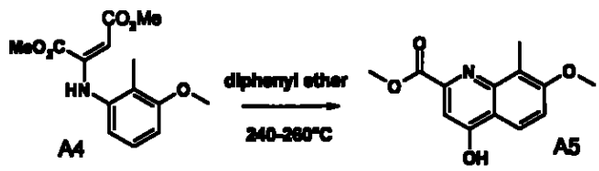
MS 137 $(MH)^+$. Reverse Phase HPLC Homogeneity @ 220 nm (0.06 % TFA; $CH_3CN : H_2O$) : 99%.

Step B



Dimethyl acetylene dicarboxylate **A3** (3.6 mL, 29.28 mmol) was added dropwise to a solution of 2-methyl-3-methoxyaniline **A2** (3.95 g, 28.79 mmol) in MeOH (100 mL) (reaction is exothermic). The mixture was heated at a gentle reflux for 5 hours cooled and concentrated under vacuum. The crude material was purified by flash column chromatography on silica gel with hexane : EtOAc (95 : 5) to provide, after evaporation of the pure fractions, the product **A4** (6.5 g; 23.27 mmol; 81 % yield). Reverse Phase HPLC Homogeneity @ 220 nm (0.06 % TFA; $CH_3CN : H_2O$) : 95%.

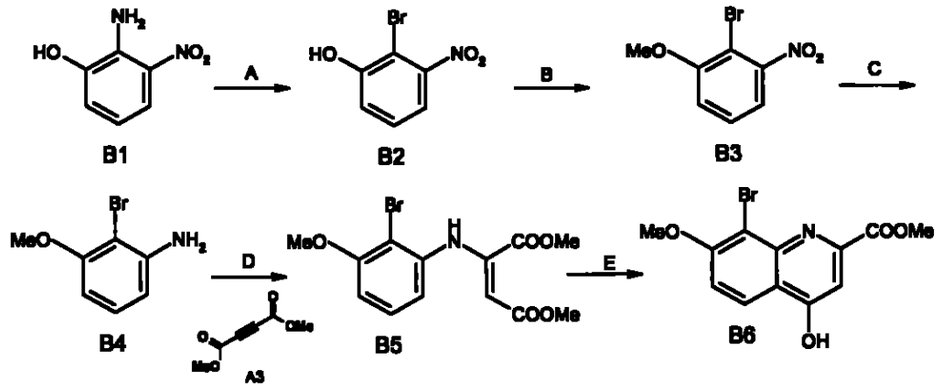
Step C



The diester **A4** (6.5 g, 23.27 mmol) was dissolved in diphenyl ether (12 mL) and the reaction mixture placed into a pre-heated sand bath at a bath temperature of 350-400°C. Once the reaction mixture attained an internal temperature of 240°C (observe MeOH evolution at 230-240°C) a count of six minutes was begun before the bath (temperature end point: 262°C) was removed and the reaction allowed to cool to room temperature. A solid formed upon cooling which was diluted with ether, filtered and dried to give a tan brown solid (3.48 g crude). The crude material was chromatographed on silica gel column with hexane : EtOAc; 5 : 5 to remove impurities, then 2 : 8 and then 100 % EtOAc to complete the elution of the product to provide **A5**, after evaporation, as a pale yellow solid (2.1 g, 37% yield).
MS $(M + H)^+$; 246, and $(M - H)^-$; 248.1. Reverse Phase HPLC Homogeneity @ 220 nm (0.06 % TFA; $CH_3CN : H_2O$): 99 %.

EXAMPLE 3B

Synthesis of 2-carbomethoxy-8-bromo-4-hydroxy-7-methoxyquinoline (B6)



Step A

2-Amino-3-nitrophenol **B1** (5 g; 32.4 mmol) was dissolved in H_2O (29.5 mL) and 1,4-dioxane (14.7 mL). The mixture was heated to reflux and hydrobromic acid (48%; 16.7 mL; 147 mmol) was added dropwise over a period of 20 min. Upon completion of the addition, the reflux was maintained an additional 15 min. The reaction was cooled to 0°C (ice bath), and sodium nitrite (2.23 g; 32.3 mmol) in H_2O (20 mL) was added over a period of 30 min. The stirring was continued for 15 min at 0°C, then the mixture was transferred to a jacketed dropping funnel (0°C) and added dropwise to a stirred mixture of Cu(I)Br (5.34 g; 37.2 mmol) in H_2O (29.5 mL) and HBr (48%; 16.7 mL; 147 mmol) at 0°C. The reaction was stirred for 15 min at 0°C, warmed to 60°C, stirred for an additional 15 min, cooled to room temperature, and left to stir overnight. The reaction mixture was transferred to a separatory funnel and extracted with ether (3x 150 mL). The organic layers were combined, washed with brine (1X), dried (Na_2SO_4), filtered and concentrated to afford the crude product (7.99 g) as a red-brown oil. The crude material was purified by flash column chromatography (1:25 ultra pure silica gel, 230-400 mesh, 40-60 mm, 60 angstroms; CH_2Cl_2 as the solvent) to afford pure 2-bromo-3-nitrophenol **B2** (45%; 3.16 g) as an orange-brown solid.

MS 217.8 $(MH)^-$. Homogeneity by HPLC (TFA) @ 220 nm: 97%.

Step B

The nitrophenol starting material **B2** (3.1 g; 14.2 mmol) was dissolved in DMF (20 mL) and to the solution was added ground cesium carbonate (5.58 g; 17.1

mmol) followed by MeI (2.6 mL; 42.5 mmol). The mixture was stirred at room temperature overnight. The DMF was evaporated, the residue taken up in ether (1x 200 mL), washed with water (1x 200 mL), brine (4x 100 mL), dried ($MgSO_4$), filtered and evaporated to afford the crude 2-bromo-3-nitroanisole **B3** (94%; 3.1 g) as an orange solid.
MS 234 $(M+2H)^+$; Homogeneity by HPLC (TFA) @ 220 nm: 98%.

Step C

2-Bromo-3-nitroanisole **B3** (1.00 g; 4.31 mmol) was dissolved in glacial acetic acid (11.0 mL) and ethanol (11.0 mL). To this solution was added iron powder (0.98 g; 17.5 mmol). The mixture was stirred at reflux for 3.5 h and worked up. The reaction mixture was diluted with water (35 mL), neutralized with solid Na_2CO_3 and the product extracted with CH_2Cl_2(3X 50 mL). The extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude product, 2-bromo-3 methoxyaniline **B4** (91%; 0.79 g) as a pale yellow oil.
MS 201.8 $(MH)^+$; Homogeneity by HPLC (TFA) @ 220 nm: 95%.

Step D

To a solution of 2-bromo-3-methoxyaniline **B4** (0.79 g; 3.9 mmol) in MeOH (7.6 mL) was added dimethyl acetylene dicarboxylate **A3** (0.53 mL; 4.3 mmol) dropwise at 0°C (caution: reaction is exothermic!). The solution was heated overnight at reflux and worked-up. The MeOH was evaporated and the crude product dried under high vacuum to afford a red gum, purified by flash column chromatography (1:30 ultra pure silica gel, 230-400 mesh, 40-60 mm, 60 angstroms; 4:1 hexane/EtOAc) to afford adduct **B5** (86 %; 1.16 g) as a pale yellow solid.
MS 344.0 $(MH)^+$; Homogeneity by HPLC (TFA) @ 220 nm: 72%.

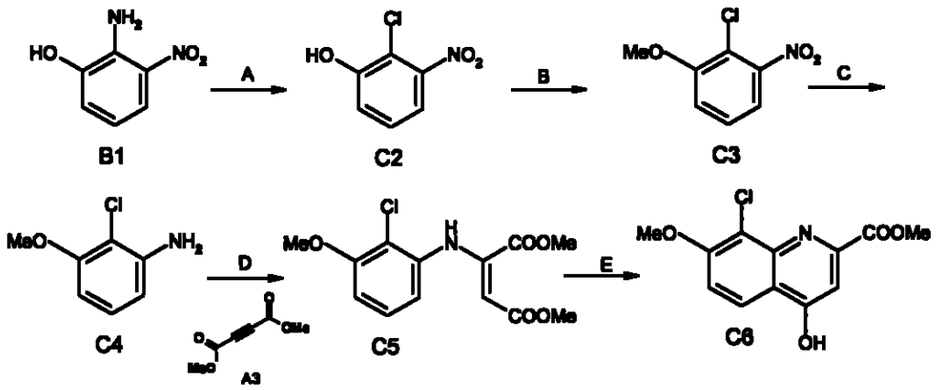
Step E

To a pre-heated sand bath at about 440°C(external temperature) was placed the diester adduct **B5** (1.1 g; 3.16 mmol) in diphenyl ether (3.6 mL). The reaction was stirred between 230°C - 245°C (internal temperature; MeOH started evaporating off at about 215°C) for 7 min and subsequently cooled to room temperature. As the solution cooled the product crystallized from the reaction mixture. The resulting brown solid was filtered, washed with ether and dried under high vacuum to afford

the crude bromoquinoline **B6** product (74%; 0.74 g) as a brown solid. NMR revealed this product to be a mixture of about 1:1 tautomers.
NMR (DMSO; 400 MHz) ok(1:1 mixture of tautomers); MS 311.9 $(MH)^+$;
Homogeneity by HPLC (TFA) @ 220 nm: 96%.

EXAMPLE 3C

Synthesis of 2-carbomethoxy-8-chloro-4-hydroxy-7-methoxyquinoline (C6)



Step A

2-Amino-3-nitrophenol **B1** (5 g; 32.4 mmol) was dissolved in concentrated HCl (75 mL) and 1,4-dioxane (14.7 mL). The mixture was heated to 70°C until most of the solids were in solution. The reaction mixture was cooled to 0°C (ice bath), and sodium nitrite (2.23 g; 32.3 mmol) in H_2O (5.4 mL) was added over a period of 3 hours to the brown solution. The temperature was maintained below 10°C during the addition and the stirring was continued for an additional 15 min at 0°C. This diazonium intermediate was poured into a solution of Cu(I)Cl (3.8 g; 38.9 mmol) in H_2O (18.5 mL) and conc. HCl (18.5 mL) at 0°C. The reaction was stirred for 15 min at 0°C, warmed to 60°C, and stirred for an additional 15 min The reaction mixture was then brought to room temperature, and left to stir overnight. The reaction mixture was transferred to a separatory funnel and extracted with ether (3X 150 mL). The organic layers were combined, washed with brine (1X), dried (Na_2SO_4), filtered and concentrated to afford the crude product (5.83 g) as a red-brown oil. The crude material was purified by flash column chromatography (1:25 ultra pure silica gel, 230-400 mesh, 40-60 mm, 60 angstroms; 3:1 hexane/EtOAc as the solvent) to afford pure 2-chloro-3-nitrophenol **C2** (48%; 2.7 g) as an orange solid. MS 171.8 $(MH)^-$: Homogeneity by HPLC (TFA) @ 220 nm: 96%.

Relevant literature for the Sandmeyer Reaction: *J. Med. Chem*, 1982, 25(4), 446-451.

Step B

The nitrophenol starting material **C2** (1.3 g; 7.49 mmol) was dissolved in DMF (10 mL) and to this solution was added ground cesium carbonate (2.92 g; 8.96 mmol), followed by MeI (1.4 mL; 22.5 mmol). The mixture was stirred at room temperature overnight. The DMF was evaporated in *vacuo* and the residue taken up in ether (150 mL), washed with water (150 mL), brine (4x 100 mL), and then dried over ($MgSO_4$). The organic phase was filtered and evaporated to afford the crude 2-chloro-3-nitroanisole **C3** (98%; 1.38 g) as an orange solid.
Homogeneity by HPLC (TFA) @ 220 nm: 93%.

Step C

2-Chloro-3-nitroanisole **C3** (1.38 g; 7.36 mmol) was dissolved in a mixture of glacial acetic acid (19 mL)/ethanol (19 mL). To this solution was added iron powder (1.64 g; 29.4 mmol). The mixture was stirred at reflux for 3.5 hr and worked up. The reaction mixture was diluted with water (70 mL), neutralized with solid Na_2CO_3 and the product extracted with CH_2Cl_2(3X 150 mL). The extracts were combined and washed with saturated. brine and then dried over (Na_2SO_4), filtered and concentrated in *vacuo* to afford the crude product, 2-chloro-3-methoxyaniline **C4** (100%; 1.2 g) as a yellow oil. This material was used as such in the following steps.
MS 157.9 $(MH)^+$; Homogeneity by HPLC (TFA) @ 220 nm: 86%.

Step D

To a solution of 2-chloro-3-methoxyaniline **C4** (1.2 g; 7.61 mmol) in MeOH (15 mL) was added dimethyl acetylene dicarboxylate **A3** (1.0 mL; 8.4 mmol) dropwise at 0°C (caution: reaction is exothermic!). The solution was heated overnight at reflux and worked-up. The MeOH was evaporated and the crude product dried under high vacuum to afford a red gum which was purified by flash column chromatography (1:30 ultra pure silica gel, 230-400 mesh, 40-60 mm, 60 angstroms; 4:1 hexane/EtOAc) to afford adduct **C5** (74 %; 1.68 g) as a yellow solid.
MS 300 $(MH)^+$; Homogeneity by HPLC (TFA) @ 220 nm: 90%.

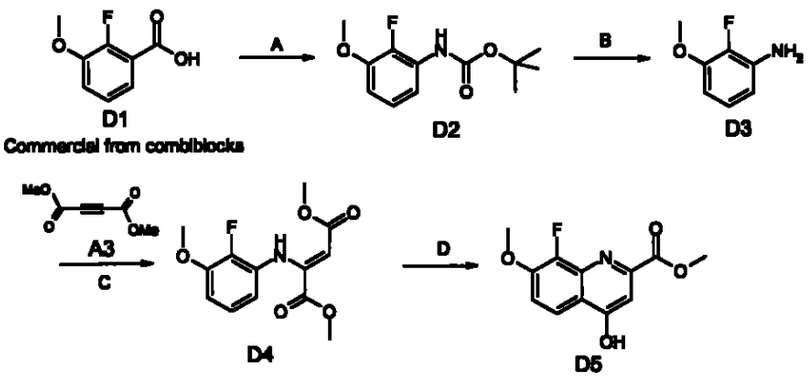
Step E

To a pre-heated sand bath at about 440°C (external temperature) was placed the diester adduct C5 (1.68 g; 5.6 mmol) in diphenyl ether (6.3 mL). The reaction was stirred between 230°C - 245°C (internal temperature; MeOH started evaporating off at about 215°C) for 7 min and subsequently cooled to room temperature. As the solution cooled the product crystallized from the reaction mixture. The resulting brownish solid was filtered, washed with ether and dried under high vacuum to afford the quinoline C6 (83%; 1.25 g) as a beige solid. NMR revealed this product to be a mixture of about 1:1 tautomers (keto/phenol forms).

MS 267.9 $(MH)^+$; Homogeneity by HPLC (TFA) @ 220 nm: 92%.

EXAMPLE 3D

Synthesis of 2-carbomethoxy-8-fluoro-4-hydroxy-7-methoxyquinoline (D5)



Step A

A solution of 2-fluoro-3-methoxy benzoic acid D1 (1.68 g, 9.87 mmol) and DIPEA (2.07 mL, 11.85 mmol, 1.2 equiv.) in a mixture of toluene (8 mL) and t-BuOH (8 mL) were stirred over activated 4A molecular sieves for 1 h followed by addition of diphenyl phosphoryl azide (DPPA, 2.55 mL, 11.85 mmol) and this mixture was refluxed overnight. Reaction mixture was filtered and the filtrate was concentrated *in vacuo*, the residue was taken in EtOAc (50 mL), washed with H_2O (2x 30 mL) and brine(1x 30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product D2 (2.38 g, 96%) was used as is in the following step. MS analysis shows the loss of Boc group: 141.9 $((M+H)\text{-Boc})^+$, 139.9 $((M\text{-}H)\text{-Boc})^-$.

Step B

Compound D2 (2.28 g, 9.45 mmol) was treated with 4N HCl/dioxane solution (from Aldrich) (10 mL, 40 mmol) for 60 min and HPLC analysis showed that the starting material was fully consumed. The reaction mixture was concentrated in *vacuo*, re-dissolved in EtOAc and washed with water, saturated $NaHCO_3$ (aq), and saturated brine. The organic phase was dried ($MgSO_4$), filtered and concentrated to give 1.18 g (88%) of D3 as a brown oil, which was used as is in the following step. MS: 141.9 $(M + H)^+$, 139.9 $(M - H)^-$.

Step C

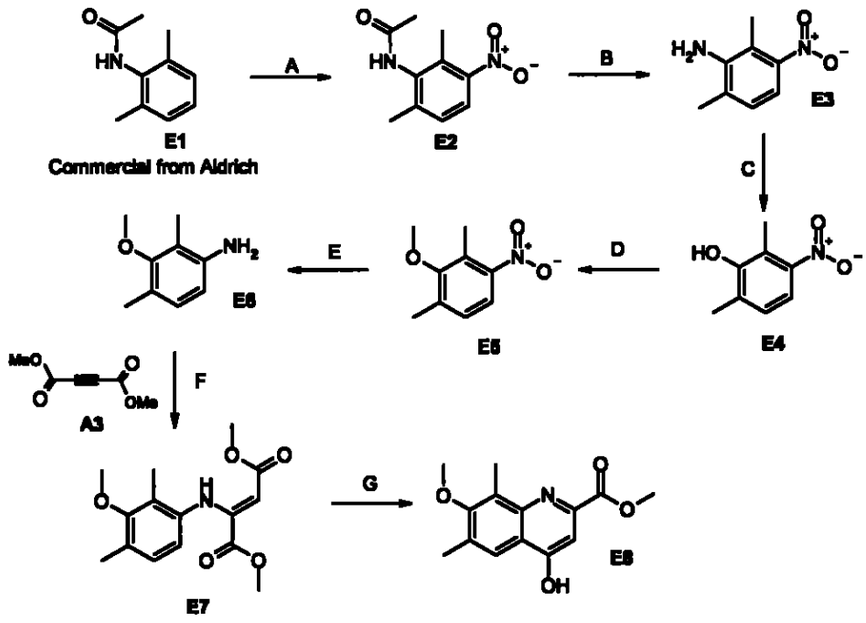
Aniline D3 (1.18 g, 8.36 mmol) was combined with dimethylacetylene dicarboxylate A3 (1.45 mL, 10.0 mmol) in methanol (25 mL). The reaction was refluxed for 2 hours before being concentrated to dryness. The crude material was purified by flash chromatography eluting with 9/1 (hexane/EtOAc) to give the Michael adduct D4 as a yellow oil, (1.27 g, 54%).

Step D

The Michael adduct D4 was dissolved in warm diphenyl ether (6 mL) and placed in a sand bath previously heated to ~350°C. The internal temperature of the reaction was monitored and maintained at ~245°C for about 5 minutes (solution turns brown). After cooling to R.T., the desired 4-hydroxyquinoline crashed out of solution. The brown solid was filtered and washed several times with diethyl ether to give, after drying, quinoline D5 as a brown solid (0.51 g, 45%). MS: 252 $(M + H)^+$, 249.9 $(M - H)^-$. Mixture of 1:1 tautomers, 1H-NMR (DMSO-d6, 400 MHz) 12.04 (s, 1H), 11.02 (s. 1H), 8.0 (d, 1H), 7.88 (d, 1H), 7.65 (m, 1H), 7.39 (s, 1H), 7.32 (m, 1H), 6.5 (s, 1H), 4.0 (s, 3H), 3.98 (s, 3H), 3.95 (s, 3H), 3.91 (s, 3H).

EXAMPLE 3E

Synthesis of 2-carbomethoxy-6,8-dimethyl-4-hydroxy-7-methoxyquinoline (E8)



Step A

The amide **E1** (5.0 g, 30.63 mmol) was dissolved in a mixture of acetic acid (5 mL) and sulfuric acid (10 mL) and cooled to 0°C. A mixture of nitric acid (70%, 3 mL) and sulfuric acid (2 mL) was added dropwise after which the solution was warmed to R.T. and stirred for 1 h. The reaction mixture was then poured onto crushed ice and filtered (after the ice had melted but the solution was still cold) to yield the desired compound **E2** (5.8 g, 91%) which was carried forward to the next reaction without further purification. MS ES^+ = 209.0, ES^- = 206.9. *(Ref: Giumanini, A.G.; Verardo, G.; Polana, M. J. Prak. Chem. 1988, 181).*

Step B

Compound **E2** (5.8 g, 27.86 mmol) was treated with 6M HCl solution (5 mL) in MeOH (10 mL) and heated at reflux for 48 h to yield the desired product **E3** (4.6 g, 99 %). RP-HPLC indicates full consumption of starting material (R_t (**E2**) = 2.6 min.; R_t (**E3**)= 3.9 min.). The mixture was concentrated and employed in subsequent reaction without further purification.

Step C

Sulfuric acid (18 mL) was added to the solution of aniline E3 (4.20 g, 25.27 mmol) in water (36 mL) at 0°C followed by the addition of sodium nitrite (2.3 g, 33.33 mmol in water (6 mL). In a separate flask was placed a mixture of water (14 mL) and sulfuric acid (1.5 mL). This solution was brought to reflux and then the initial solution was added dropwise while maintaining a boil. After the addition was complete, boiling was continued for 5 min and the mixture then poured onto ice/sodium carbonate mixture while cooling in an ice bath. The product was extracted with aq. EtOAc and concentrated to yield a dark brown viscous liquid E4 (2.00 g, 47 %) which was employed in subsequent reaction without further purification. MS ES^- = 210.9.

Step D

MeI (1.42 mL, 22.74 mmol) was added to a solution of the starting phenol E4 (1.9 g, 11.37 mmol) and potassium carbonate (2 g) in DMF (25 mL) at R.T. The mixture was heated at 50°C for 2 h and then cooled to R.T. EtOAc was added and the solution was washed with water (3x) and the aq. layer was then extracted with EtOAc. The combined organic layers were dried, filtered and concentrated to yield the desired methyl ether E5 (2.0 g, 97%). ^{1}H-NMR ($CDCl_3$, 400 MHz) 7.62 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 3.74 (s. 3H), 2.48 (s, 3H), 2.36 (s, 3H).

Step E

Ten percent (10%) Pd/C (200 mg) was added to a solution of nitro starting material E5 (2.0 g, 11.04 mmol) in EtOH and placed on a Parr shaker under 40 psi H_2 atmosphere for 2 h. The solution was filtered through a pad of silica/Celite, rinsed with MeOH and concentrated to yield the desired aniline E6 (1.5 g, 90 %) which was employed without further purification.

Step F

Aniline E6 (1.9 g, 12.65 mmol) was combined with dimethylacetylene dicarboxylate A3 (2.32 mL, 18.85 mmol) in methanol (3 mL). The reaction was heated at reflux for 2 h before being concentrated to dryness. The crude material was purified by flash chromatography (9:1 hexane/EtOAc) to give the Michael adduct E7 as a yellow oil (2.8 g, 76 %). ^{1}H-NMR ($CDCl_3$, 400 MHz) 9.48, (s, br, 1H), 6.89 (d, J = 7.9 Hz, 1H), 6.47 (d, J = 7.9 Hz, 1H), 5.35 (s, 1H), 3.74 (s. 3H), 3.70 (s, 3H), 3.65 (s, 3H) 2.27 (s, 3H), 2.24 (s, 3H).

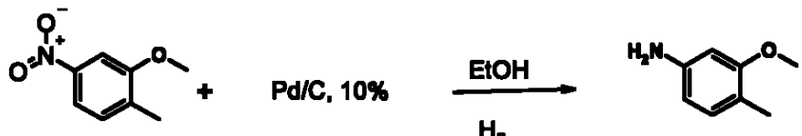
Step G

The Michael adduct E7 was dissolved in warm diphenyl ether (10 mL) and placed in a sand bath previously heated to ~350°C. The internal temperature of the reaction was monitored, maintained at ~245°C for about 5 minutes (solution turns brown) and cooled to R.T. at which time the desired 4-hydroxyquinoline precipitated out of solution. The brown solid was filtered and washed several times with diethyl ether to give quinoline E8 as a yellow-brown solid after drying (1.10 g, 88 %). ^{1}H-NMR ($CHCl_3$, 400 MHz) 8.80, (s, br, 1H), 8.06 (s, 1H), 7.26 (s, 1H), 6.93 (s, 1H), 4.04 (s. 3H), 3.80 (s, 3H), 2.45 (s, 3H) 2.39 (s, 3H).

EXAMPLE 3F

Synthesis of 2-carbomethoxy-4-hydroxy-7-methoxy-8-methyl quinoline (F4):

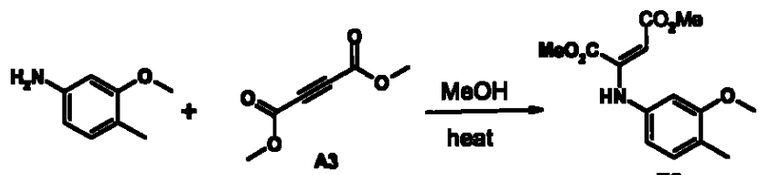
Step A



F1 F2

To a suspension of 2-methyl-5-nitroanisole F1 (1.54 g; 9.21 mmol) in absolute ethanol (15 mL) was added 10% Pd/C catalyst (249 mg). The suspension was hydrogenated under a hydrogen filled balloon at atmospheric pressure and room temperature for 6.5 h. The reaction mixture was filtered through a Millex 0.45 micron filter and evaporated to dryness to provide 4-methyl-*m*-anisidine F2 (1.22 g; 8.89 mmol; 97 % yield)

Step B

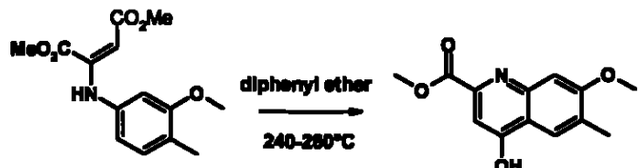


F2 A3 F3

Dimethyl acetylene dicarboxylate A3 (1.1 mL, 8.95 mmol) was added dropwise to a solution of 4-methyl-*m*-anisidine F2 (1.22 g, 8.89 mmol) in MeOH (20 mL). Caution the reaction is exothermic. The mixture was heated at a gentle reflux for 4 hours,

cooled and concentrated under vacuum. The crude material was purified by flash column chromatography on silica gel with hexane : EtOAc (92.5 : 7.5) to provide, after evaporation of the pure fractions, the diester adduct F3 (1.8 g; 6.44 mmol; 73 % yield).

Step C



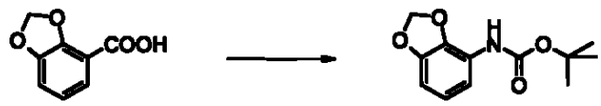
F3 F4

The diester F3 (1.8 g, 6.44 mmol) was dissolved in diphenyl ether (5 mL) and the reaction mixture placed into a pre-heated sand bath at a bath temperature of 350-400°C. Once the reaction mixture attained an internal temperature of 240°C, a count of five minutes was begun before the bath was removed and the reaction allowed to cool to room temperature overnight. A solid formed upon cooling which was diluted with ether, filtered and dried to give a brown solid (0.97 g crude) containing both regioisomers in almost equal proportions. The crude material was triturated with MeOH and EtOAc, filtered and dried to provide the correct regioisomer of the methylquinoline product F4 as a yellow solid (245 mg, 15% yield).
Homogeneity by HPLC (TFA) @ 220 nm: 90%.

EXAMPLE 3G

Synthesis of 2-carbomethoxy-4-hydroxy-[1,3]dioxolo[4,5-h]quinoline (G5):

Step A

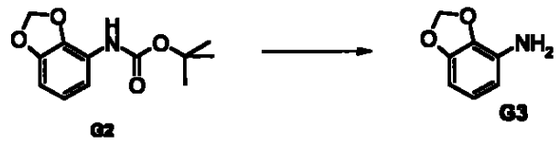


G1 G2

To a refluxing solution of commercially available 2,3-methylenedioxybenzoic acid G1 (485 mg; 2.92 mmol) in 1,4-dioxane (8.0 mL) and t-butanol (2.5 mL) was added TEA (430 µL; 3.08 mmol) and diphenylphosphoryl azide (DPPA, 630 µL; 2.92 mmol) and refluxed for 10 h. The mixture was evaporated, diluted with chloroform, washed with 5 % citric acid (3x), water, saturated sodium bicarbonate and brine, dried ($MgSO_4$), filtered and evaporated to provide the crude product. Flash column purification on

silica gel with hexane : EtOAc (75 : 25) provided the pure Boc-amino compound **G2** (257 mg; 37%).

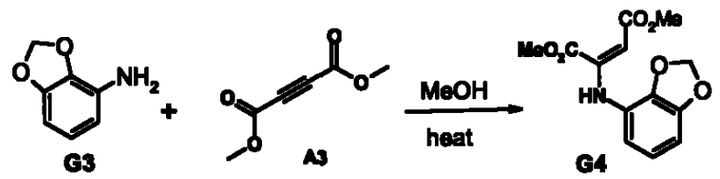
Step B



G2 G3

The Boc starting material **G2** (257 mg; 1.08 mmol) was dissolved in 4M HCl/dioxane (5.0 mL) and stirred at room temperature for 1 hr. The solvent was evaporated and the residue diluted with saturated sodium bicarbonate (few mL) and 1 M NaOH (1 mL), extracted with EtOAc (2x), dried ($MgSO_4$), filtered and evaporated to dryness to provide the crude 2,3-methylene dioxyaniline **G3** (158 mg; 106%).

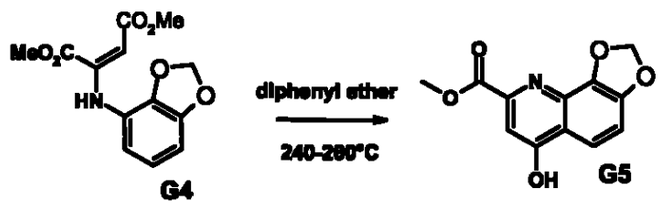
Step C



G3 A3 G4

Dimethyl acetylene dicarboxylate **A3** (130 µL, 1.06 mmol) was added dropwise to a solution of crude 2,3-methylene dioxyaniline **G3** (148 mg, 1.08 mmol) in MeOH (2.5 mL). Caution the reaction is exothermic. The mixture was heated at a gentle reflux for 3 hours, cooled and concentrated under vacuum. The crude material was purified by flash column chromatography on silica gel with hexane : EtOAc (9 : 1) to provide, after evaporation of the pure fractions, the diester adduct **G4** (185 mg; 0.662 mmol; 61% yield).

Step D



G4 G5

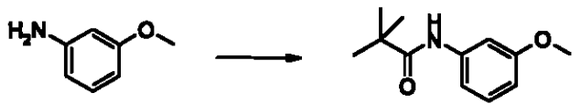
The diester **G4** (180 mg, 0.645 mmol) was dissolved in diphenyl ether (2.5 mL) and

the reaction mixture placed into a pre-heated sand bath at a bath temperature of 350-400°C. Once the reaction mixture attained an internal temperature of 250°C (observe MeOH evolution at 220-230°C) a count of six minutes was begun before the bath (temperature end point :262°C) was removed and the reaction allowed to cool to room temperature. A solid formed upon cooling which was diluted with ether, filtered and dried to give the crude dioxyquinoline **G5** (125 mg; 78 %). Purification was not required and the material was used as such in the following reactions.
MS $(M + H)^+$; 246, and $(M - H)^-$; 248.1.
Homogeneity by HPLC (TFA) @ 220 nm :88%.

EXAMPLE 3H

Synthesis of 2-carbomethoxy-4-hydroxy-8,9-dihydro-furo[2,3-h]quinoline (H7):

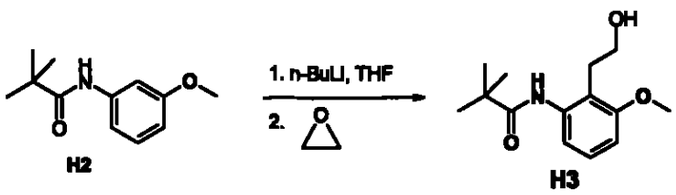
Step A



H1 **H2**

Triethylamine (5.0 mL, 35.6 mmol) was added to a flask containing the amine **H1** (2.0 mL, 17.8 mmol) and dichloromethane (100 mL) under an atmosphere of nitrogen. The contents were cooled in an ice bath and trimethylacetylchloride (3.3 mL, 26.7 mmol) was added dropwise. The reaction was allowed to warm slowly to R.T. and stirred for 14 h. at this temperature. The reaction was quenched with $NaHCO_3$ saturated solution and extracted with EtOAc. The combined organic layers were dried, filtered and concentrated followed by flash column chromatography (4:1 to 1:1 hexane:EtOAc) to yield the desired product **H2** as an off-white solid (3.7 g, 97 % yield).

Step B

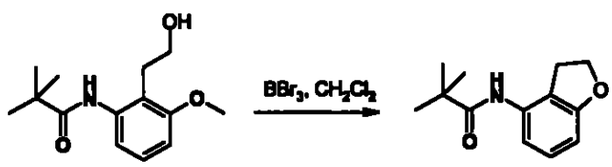


H2 **H3**

n-BuLi (15.9 mL, 1.6M, 25.5 mmol) was added dropwise to a flame dried flask containing a solution of the starting amide **H2** (1.6 g, 7.72 mmol) in THF at 0°C

under argon. Solution turned slight yellow/orange color when n-BuLi was added. The solution was allowed to warm slowly to R.T. and stirred for 24 h. The solution was again cooled to 0°C and ethylene oxide (0.46 mL, 9.26 mmol) was added dropwise. The solution was allowed to slowly warm to 23°C, quenched with $NaHCO_3$ saturated solution, extracted with EtOAc, dried, filtered and concentrated followed by flash column chromatography (4:1 to 1:1 hexane:ethyl acetate) to obtain the desired product H3 (1.94 g, 5.01 mmol, 65 % yield) Homogeneity by HPLC (TFA) @ 220 nm : 99%.

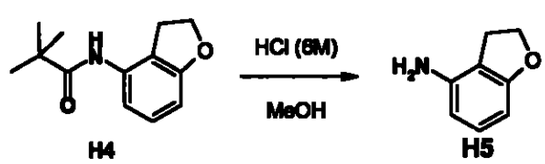
Step C



H3 H4

A BBr_3 solution (26 mL, 1.0 M, 26.0 mmol) was added dropwise to methyl-ether H3 in CH_2Cl_2 at 0°C. The solution was slowly warmed to 23°C and stirred for 14 h at R.T.. The reaction was quenched with 1M NaOH solution and extracted with EtOAc and CH_2Cl_2 to obtain a mixture of desired product H4 and some uncyclized diol. Homogeneity by HPLC (TFA) @ 220 nm : 99%.

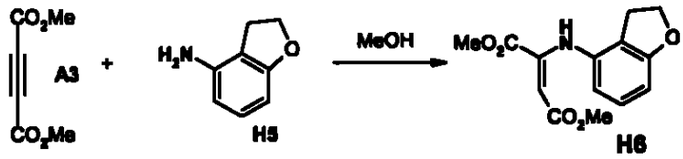
Step D



H4 H5

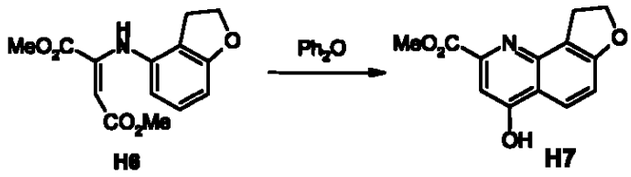
HCl (4.0 mL, 6.0M) was added to a solution of amide H4 (0.27 g, 1.22 mmol) in MeOH (4.0 mL) at 23°C. The reaction was then heated to reflux for 48 h, $NaHCO_3$ (saturated, aq) was added and was extracted with EtOAc. The combined organic layers were dried, filtered and concentrated to obtain the desired aniline H5 which was of sufficient purity to employ in further transformations.

Step E



Dimethyl acetylene dicarboxylate **A3** (0.16 mL, 1.33 mmol) was added to solution of aniline **H5** (0.18 g, 1.33 mmol) in MeOH (3.0 mL) at R.T. The solution was heated at reflux for 3 h., cooled to R.T. and a saturated NaCl solution was added. The mixture was extracted with EtOAc (3x) and the combined organic layers were then dried, filtered and concentrated followed by purification by flash column chromatography (9:1 to 1:1 hex:EtOAc) to afford the desired olefin **H6** (0.29 g, 78%).

Step F

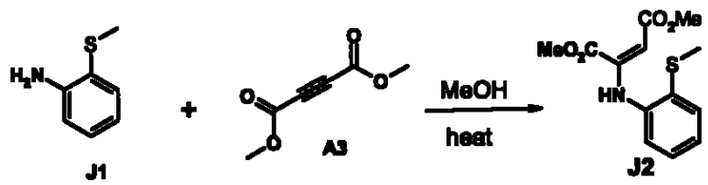


A flask containing starting olefin **H6** (0.29 g, 1.04 mmol) in diphenyl ether (2.0 mL) was lowered into a pre-heated sand bath (350°C). When the internal temperature of the reaction reached 225°C, the flask was heated for 6-7 minutes during which time the internal temperature rose to 240°C. The reaction mixture was then removed from the sand bath and allowed to slowly cool to R.T. A precipitate formed upon standing. Diethyl ether was added and the solution was filtered and rinsed with additional diethyl ether to yield a light-brown solid **H7** (0.20 g, 77%). MS 246.0 $(MH)^+$.

EXAMPLE 3J

Synthesis of 2-carbomethoxy-4-hydroxy-8-methylthioquinoline (J3):

Step A



Dimethyl acetylene dicarboxylate **A3** (5.21 mL, 35.91 mmol) was added dropwise to a solution of 2-methylmercaptoaniline **J1** (5.0 g, 35.91 mmol) in MeOH (100 mL).

Caution the reaction is exothermic. The mixture was heated at a gentle reflux for 2 hours, cooled and concentrated under vacuum. The crude material was purified by flash column chromatography with hexane : EtOAc (90 :10) to provide, after evaporation of the pure fractions, the diester adduct J2 (10.53 g; 37.43 mmol; 99% yield).

Homogeneity by HPLC (TFA) @ 220 nm : 85%.



J2 J3

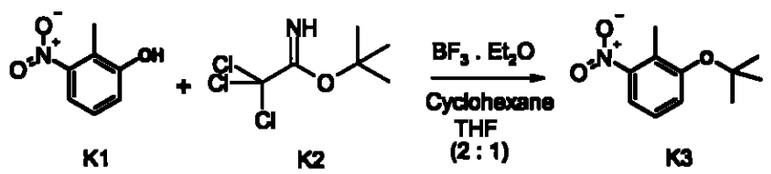
Step B

The diester J2 (10.53 g, 37.43 mmol) was dissolved in diphenyl ether (35 mL) and the reaction mixture placed into a pre-heated sand bath at a bath temperature of 350-400°C. Once the reaction mixture attained an internal temperature of 245°C, a count of six minutes was begun before the bath was removed and the reaction allowed to cool to room temperature. A precipitate formed. which was suspended in ether, filtered and washed again with ether to provide the C8-SMe quinoline product J3 (6.15 g; 66%). MS $(M + H)^+$; 250 Homogeneity by HPLC (TFA) @ 220 nm: 99%.

EXAMPLE 3K

Synthesis of 7-*tert*-butyloxy-2-carbomethoxy-4-hydroxy-8-methylquinoline (K6)

Step 1:

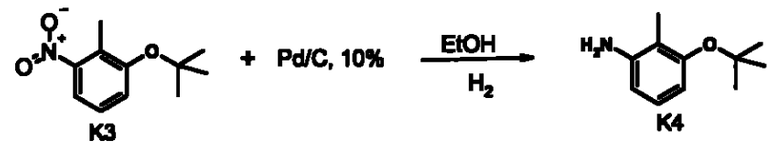


K1 K2 K3

To a solution of 2-methyl-3-nitrophenol K1 (1.1 g ; 7.18 mmol) in THF (13 mL) was added cyclohexane (27 mL; a solution was maintained). *tert*-Butyl

trichloroacetimidate **K2** (5.36 mL ; 28.73 mmol) was added followed by a catalytic amount of boron trifluoride etherate (143.8 µL; 1.14 mmol) and the reaction was stirred at room temperature for 15 h. The reaction was incomplete (by analytical HPLC) and an additional amount of *tert*-butyl trichloroacetimidate (1.4 mL ; 7.51 mmol) was added (reaction remains in solution). The reaction was complete after stirring at room temperature for 5 h. Solid sodium bicarbonate was added, and the mixture was filtered, rinsed with dichloromethane and evaporated to dryness to provide a white solid. The solid was triturated with dichloromethane, the white solid filtered and discarded (= trichloroacetimide). The filtrate was concentrated and loaded onto a flash column for purification (hexane : EtOAc 9 : 1) to provide the pure 2-methyl-3-*tert*-butoxynitrobenzene **K3** (1.17 g ; 78%). Homogeneity by HPLC (TFA) @ 220nm : 96%

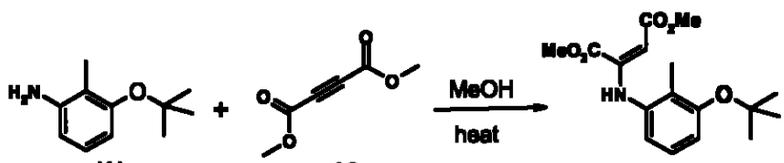
Step 2:



K3 K4

To a solution of 2-methyl-3-*tert*-butoxynitrobenzene **K3** (1.31 g; 6.26 mmol) in absolute ethanol (30 mL) was added 10% Pd/C catalyst (130 mg) . The solution was hydrogenated under a hydrogen filled balloon at atmospheric pressure and room temperature for 63 h. The reaction mixture was filtered through a Celite pad, rinsed with absolute EtOH and evaporated to dryness to provide 2-methyl-3-*tert*-butoxyaniline **K4** (1.1 g ; 6.14 mmol ; 98% yield). M.S. 180 (M+H)+ . Homogeneity by HPLC (TFA) @220nm : 96%

Step 3:

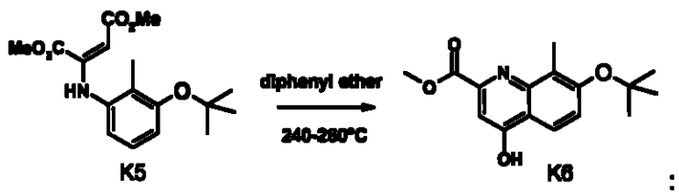


K4 A3 K5

Dimethyl acetylene dicarboxylate **A3** (749 µL, 5.97 mmol) was added dropwise to a

solution of 2-methyl-3-*tert*-butoxyaniline **K4** (1.07, 5.97 mmol) in MeOH (14 mL). The mixture was heated at a gentle reflux for 2 hours, cooled and concentrated under vacuum. The crude material was purified by flash column chromatography with hexane : EtOAc (95 : 5) to provide, after evaporation of the pure fractions, the diester adduct (1.13 g ; 3.52 mmol ; 59% yield). M.S. 320.0 $(M-H)^-$ 322.1 $(M+H)^+$. Homogeneity by HPLC (TFA) @ 220 nm : 92%.

Step 4:



K5 K6 :

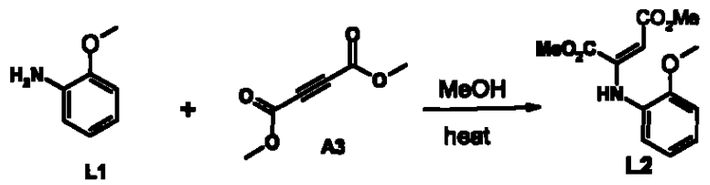
The diester **K5** (1.13 g, 3.52 mmol) was dissolved in diphenyl ether (3.0 mL) and the reaction mixture placed into a pre-heated sand bath at a bath temperature of 400-440°C. Once the reaction mixture attained an internal temperature of 230°C (observe MeOH evolution at 220°C) a count of six minutes was begun before the bath (temperature end point : 242°C) was removed and the reaction allowed to cool to room temperature. No solid formed upon cooling, therefore the crude mixture was flash purified with hexane : EtOAc (8 : 2 to remove the diphenyl ether , then, 4 : 6 to complete elution of the product) to provide the C7-O-*tert*-Bu,C8-Me quinoline **K6** as a beige solid (838 mg ; 82%). MS 288.0 $(M-H)^-$ 290.0 $(M+H)^+$ .Homogeneity by HPLC (TFA) @ 220 nm : 99%.

This quinoline moiety was used for the synthesis of compounds 1032 and 1033 of table 1. For the synthesis of compounds 1034, 1035, 1057 and 1058, also of table 1, quinoline **K6** was used. Conversion of the C7-*tert*-butyl-ether group to an hydroxyl group was done by treatment of the final compound with 50% TFA in dichloromethane for 30 min. at 0°C then for 30 min. at R.T. , evaporated to dryness, diluted with water and lyophilized.

EXAMPLE 3L

Synthesis of 2-carbomethoxy-4-hydroxy-8-methoxyquinoline (L3):

Step A



Dimethyl acetylene dicarboxylate **A3** (5.5 mL, 44.74 mmol) was added dropwise to a solution of *o*-anisidine **L1** (5.0 mL, 44.33 mmol) in MeOH (100 mL). Caution the reaction is exothermic. The mixture was heated at a gentle reflux for 5 hours, cooled and concentrated under vacuum. The crude material was purified by flash column chromatography with hexane : EtOAc (95 : 5 to 90 :10) to provide, after evaporation of the pure fractions, the diester adduct **L2** (10 g; 37.70 mmol; 85% yield). Homogeneity by HPLC (TFA) @ 220 nm : 82%.



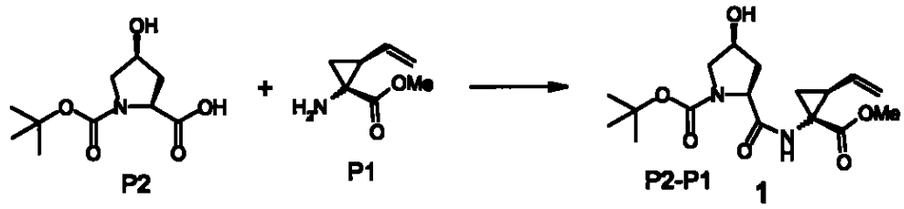
Step B

The diester **L2** (10 g, 37.70 mmol) was dissolved in diphenyl ether (15 mL) and the reaction mixture placed into a pre-heated sand bath at a bath temperature of 350-400°C. Once the reaction mixture attained an internal temperature of 240°C, a count of six minutes was begun before the bath was removed and the reaction allowed to cool to room temperature. No solid formed upon cooling, therefore, the crude mixture was flash column purified with hexane : EtOAc (6 : 4 to 5 : 5 to remove impurities, then, 2 : 8 to complete elution) to provide the C8-OMe quinoline product **L3** (4.56 g; 52 %). MS $(M-H)^-$; 231.9 Homogeneity by HPLC (TFA) @ 220 nm: 99%.

EXAMPLE 4

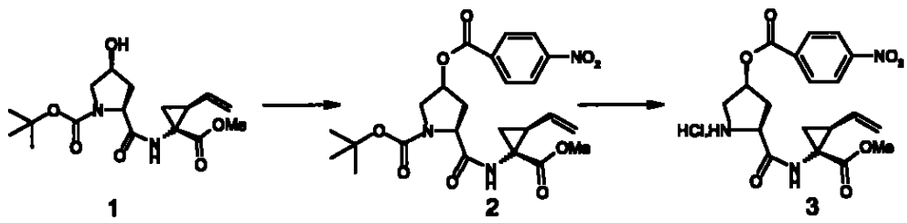
Preparation of Dipeptides

Synthesis of dipeptide 1



A mixture of Boc-hydroxyproline **P2** (50.0 g, 216 mmol), vinyl-ACCA methyl ester **P1** (42.25 g, 238 mmol, 1.1 equiv.), TBTU (76.36 g, 238 mmol, 1.1 equiv.) and DIPEA (113 mL, 649 mmol, 3 equiv.) in DMF (800 mL) was stirred at R.T. under a nitrogen atmosphere. After 3.5 h, the solvent was evaporated and the residue extracted with EtOAc. The extract was washed with hydrochloric acid (10%), saturated sodium bicarbonate and brine. The organic phase was then dried over magnesium sulfate, filtered and evaporated to afford an oil. After drying overnight under high vacuum, dipeptide **1** was obtained as a yellow foam (72.0 g, 94%, purity >95% by HPLC).

Preparation of dipeptide 3



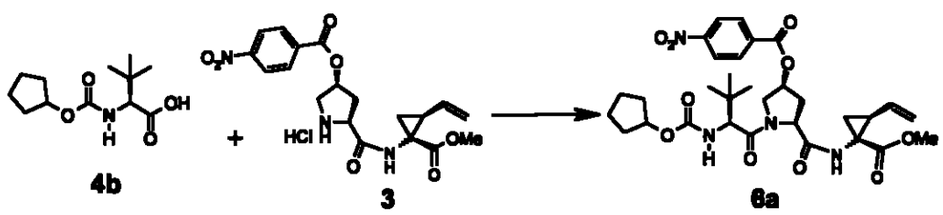
Dipeptide **1** (72.0 g, 203 mmol), triphenylphosphine (63.94 g, 243.8 mmol, 1.2 equiv.) and 4-nitrobenzoic acid (41.08 g, 245.8 mmol, 1.2 equiv) were dissolved in dry THF (1.4 L) The stirred solution was cooled to 0°C under a nitrogen atmosphere. Diethyl azodicarboxylate (38.4 mL, 244 mmol, 1.2 equiv.) was then added dropwise over 45 min and the reaction allowed to warm to R.T. After 4 h, the solvent was evaporated. The residue was divided into four portions. Each of these was purified by chromatography over fine silica gel (10-40 µm mesh, column diameter 12 cm, column length 16 cm) using a gradient of 2 :1 hexane/EtOAc to 1:1 hexane/EtOAc to pure EtOAc. In this manner, the Boc-dipeptide ester **2** was obtained as an amorphous white solid after evaporation of the solvents and drying of the residues under high vacuum at 70°C for 1 h (108.1 g, quantitative). A solution of 4N hydrogen chloride in dioxane was added to the Boc-dipeptide ester **2** (108 g, 243 mmol) resulting in a colorless solution. The solution was stirred at R.T. for 1 h. The solvent was evaporated and the residue placed under high vacuum for 3 h

affording the hydrochloride salt of compound **3** as an amorphous solid. The solid was used as such.

EXAMPLE 5

Preparation of Tripeptides

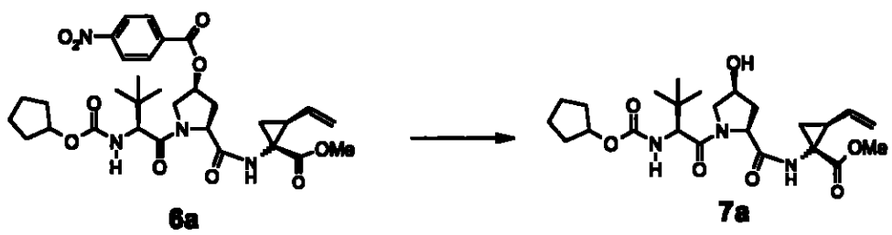
Synthesis of tripeptide 6a



4b **3** **6a**

Carbamate **4b** (6.15 g, 22.5 mmol) and TBTU (7.72 g, 24.7 mmol) were suspended in DCM and the suspension was stirred rapidly. DIPEA (3.92 mL, 22.5 mmol) was added at R.T. and after 10 min, the reaction was nearly homogeneous. A solution of dipeptide **3** (10.39 g, 23.6 mmol) in anhydrous DCM (100 mL) containing DIPEA (4.11 mL, 23.62 mmol) was then poured into the reaction. The resulting yellow solution was allowed to stir for 14 h. The solvent was then evaporated yielding a yellow syrup which was extracted with EtOAc (300 + 150 mL) and washed with 0.05N HCl (2x 200 mL), saturated Na_2CO_3 (300 mL) and brine (150 mL). The combined extracts were dried over $MgSO_4$ and evaporated to yield the tripeptide **6a** as a pale yellow foam (15.68 g, quantitative).

Synthesis of tripeptide 7a:

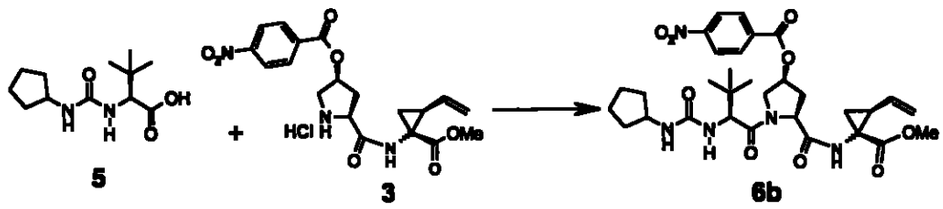


6a **7a**

The tripeptide **6a** (15.68 g) was dissolved in THF (200 mL) and water (30 mL) was added. The resulting solution was cooled to 0°C and a solution of lithium hydroxide monohydrate (1.18 g, 28.12 mmol) was added over 3 min with vigorous stirring. After 3 h at 0°C, the excess base was neutralized with 1N HCl (final pH *ca.* 6) and the THF evaporated, resulting in an aqueous suspension (yellow gum). The mixture

was extracted with EtOAc (2x 200 mL) and washed with saturated $NaHCO_3$ (2x 300 mL). The combined extracts were dried over $MgSO_4$ and evaporated to yield a pale yellow foam. Flash chromatography of the foam over silica gel using EtOAc as eluent afforded **7a** as a white amorphous solid (9.77 g, 91%).

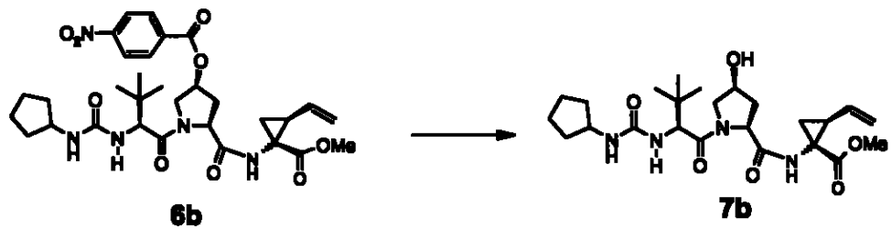
Synthesis of tripeptide 6b



5 + 3 → 6b

The cyclopentylurea-Tbg **5** (2.21 g, 9.10 mmol) and TBTU (3.12 g, 10.0 mmol) were dissolved/suspended in anhydrous dichloromethane (40 mL) and DIPEA (1 equiv.) was added. The reaction was stirred at ambient temperature under a nitrogen atmosphere until the solution became nearly homogeneous (ca. 10 min). A solution of P1-P2 dipeptide (4.20 g, 9.56 mmol) in anhydrous dichloromethane (35 mL containing 1 equiv. DIPEA) was then added to the reaction and the resulting yellow solution allowed to stir for 14 h after the reaction was rendered basic by the addition of DIPEA (*ca.* 1.5 mL). The solvent was evaporated yielding a yellow syrup which was extracted with ethyl acetate (150 + 50 mL) and washed with 0.1N HCl (150 mL), water (100 mL, emulsion broken with brine), saturated Na_2CO_3 (150 mL) and brine (100 mL). The combined extracts were then dried over $MgSO_4$ and evaporated to a pale yellow solid **6b** (6.21 g, HPLC purity 95%).

Synthesis of tripeptide 7b

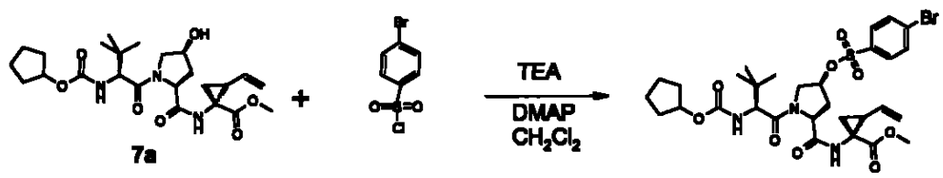


6b → 7b

The crude pNBz ester **6b** prepared above was dissolved in THF (90 mL) and methanol (40 mL) added. 1.0N sodium hydroxide solution (12.0 mL; 12.0 mmol) was then added with vigorous stirring over 10 min (dropping funnel) and the

hydrolysis allowed to proceed at ambient temperature. After 2 h, the excess base was neutralized by the careful addition of 1 N HCl (ca. 1.5 mL, added dropwise until the yellow color faded; final pH ca. 6). The organic solvents were evaporated and the aqueous residue was extracted with ethyl acetate (150 + 50 mL) and washed with saturated sodium bicarbonate (3x 150 mL) and brine (100 mL). The combined extracts were dried over $MgSO_4$ and evaporated to a pale yellow, amorphous solid which was dried under high vacuum **7b** (4.11 g, 87% from the P3-urea, HPLC purity 93%).

Synthesis of Brosylate derivative 7aBrs

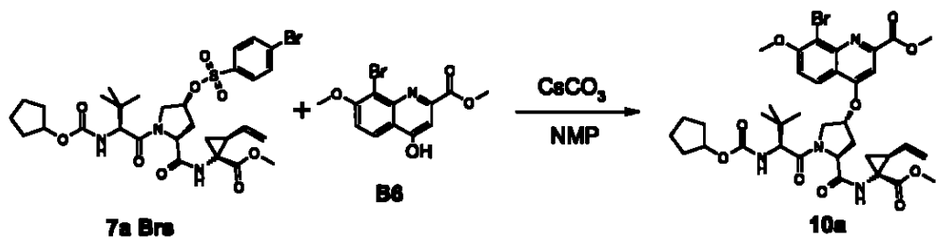


7a **7a Brs**

To a cooled solution (0°C) of the tripeptide (10 g; 20.85 mmol), brosyl chloride (11.19 g; 43.79 mmol) and dimethylaminopyridine (254 mg; 2.09 mmol) dissolved in dichloromethane (75 mL), triethylamine (10.2 mL; 72.98 mmol) was added dropwise. The yellow solution was stirred 1 hour at 0°C, then was slowly allowed to warm to room temperature and stirred 60 hours at room temperature. The reaction mixture was concentrated to dryness, diluted with EtOAc, washed with saturated sodium bicarbonate solution, water and brine, dried ($MgSO_4$), filtered and evaporated to dryness to obtain the crude product The crude material was purified by flash column chromatography with hexane : EtOAc; 60 : 40 to 50 : 50 to provide the pure product **7aBrs** as a white foam (11.66 g; 80%).
M.S. 698 $(M+H)^+$; 700.2 $(MH+2)^+$. Homogeneity by HPLC (TFA) @ 220 nm: 99%.

EXAMPLE 6

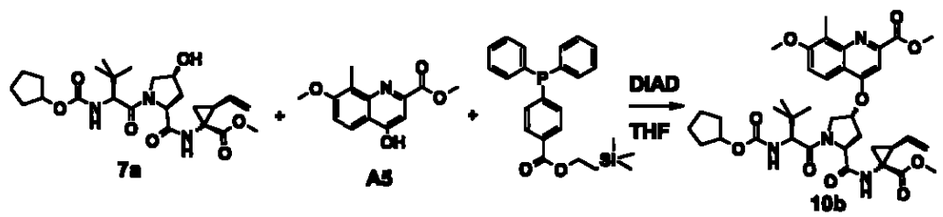
Introduction of quinoline moieties into the tripeptides:
Synthesis of intermediate 10a *via* brosylate displacement:



7a Brs B6 10a

The brosylate **7aBrs** (0.5 g; 0.71 mmol), bromoquinoline **B6** (234 mg; 0.75 mmol) and ground cesium carbonate (56 mg; 0.78 mmol) were all dissolved in 1-methyl-2-pyrrolidinone (7.6 mL), and the solution was heated to 70°C and stirred for 7 h. The solution was subsequently cooled to room temperature and worked-up. The reaction mixture was poured into EtOAc, washed with H_2O (1X), $NaHCO_3$ (saturated; 2X), brine (5X), dried, filtered and concentrated to afford the crude product (0.565 g) as an off white solid. Purification by flash column chromatography (1:30 silica gel; 7:3 EtOAc/hexane) afforded pure product **10a** (77%; 0.429 g) as a white solid.
MS 775.2 $(M+2H)^+$. Homogeneity by HPLC (TFA) @ 220 nm : 96%.

<u>Synthesis of Intermediate 10b *via* Mitsunobu reaction:</u>



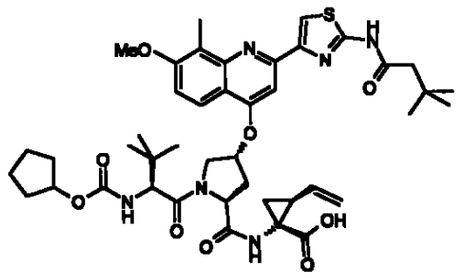
7a A5 10b

To the tripeptide **7a** (1.55 g; 3.23 mmol) dissolved in THF (30 mL), the hydroxyquinoline **A5** (1.08 g; 4.37 mmol) was added followed by 0.5 m triphenylphosphine silyl ester in THF (13 mL; 6.46 mmol). To the yellow suspension, was added dropwise the DIAD reagent (1.27 mL; 6.46 mmol) and stirred at room temperature for 2 hours, worked-up by dropwise addition of 1M TBAF/THF solution (11.3 mL; 11.31 mmol) and stirred at room temperature overnight. By analytical HPLC, it is evident that the cleavage of the formed phosphine oxide by-product (to a water soluble moiety) is complete. The reaction was diluted with EtOAc, washed with saturated sodium bicarbonate solution (2x), water (2x), cold 1N NaOH (2x; removes excess quinoline), water (2x) and brine (1x), dried ($MgSO_4$), filtered and evaporated to obtain a beige solid . The crude material was flash column purified

with hexane : EtOAc (8 : 2) to obtain the product **10b** as an ivory solid (1.92 g; 84%). M.S. 707.4 $(M-H)^-$ 709.4 $(M+H)^+$. Homogeneity by HPLC (TFA) @ 220 nm : 94%.

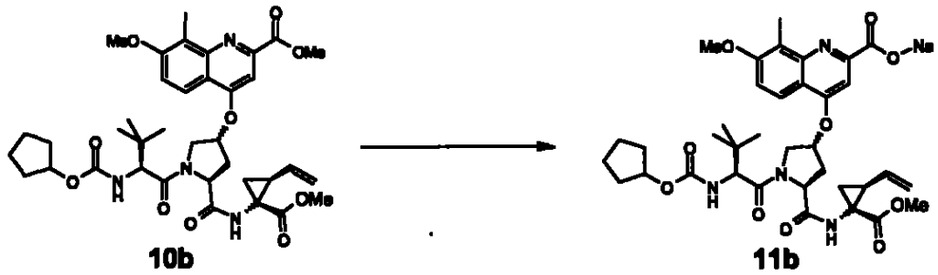
EXAMPLE 7

Synthesis of Compound 1007:



Compound 1007

Step 1 : Selective monohydrolysis of ester 10b:



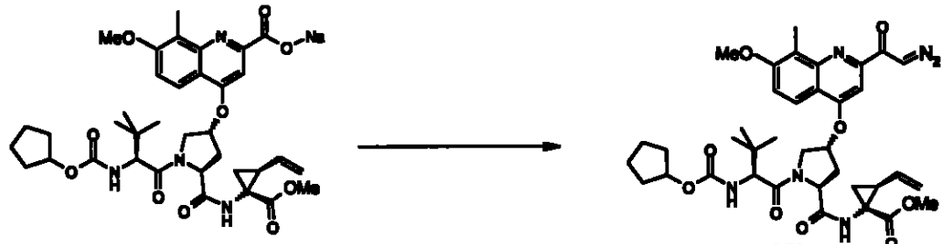
10b **11b**

Tripeptide **10b** (149 mg, 0.210 mmol), in 5 mL of a 1:1 mixture of THF-MeOH, was cooled to 0°C for the addition of a 1N NaOH aqueous solution (0.24 mL, 0.240 mmol). The resulting solution was stirred 15 min at 0°C, 1.5 h at R.T. and found to be incomplete by analytical HPLC. Additional 1N NaOH (0.05 mL, 0.05 mmol) was added and the reaction stirred for an additional hour. The mixture was quenched with 1 M HCl, evaporated to near dryness, diluted with water, frozen and lyophilized to provide the acid **11b** (crude material used for next step; assume 0.210 mmol).

Reverse Phase HPLC Homogeneity (0.06% TFA; CH_3CN : H_2O) : 89%.

97

Step 2 : Synthesis of diazoketone 12b:



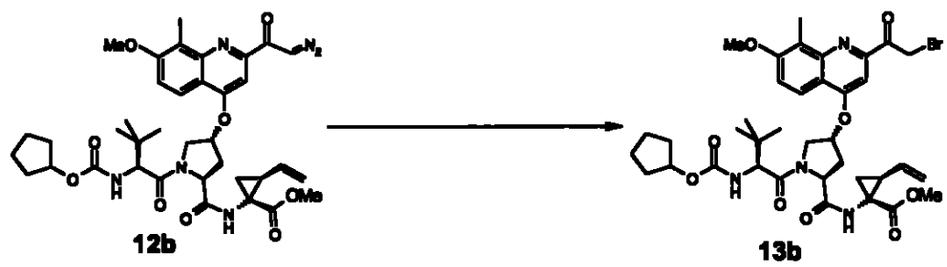
11b 12b

Sodium salt **11b** (assume 0.210 mmol) was dissolved in THF (5 mL), triethylamine (75 µL; 0.538 mmol) was added and the solution cooled to 0°C.

Isobutylchloroformate (45 µL; 0.346 mmol) was added dropwise and the white suspension was stirred at 0°C for 1 hour, followed by the addition of a solution of diazomethane (1M in diethyl ether; 1 mL; 0.999 mmol). The reaction mixture was stirred 15 min at 0°C, 1 hour at R.T. and evaporated to provide a thick suspension. This suspension was dissolved in EtOAc, washed with saturated $NaHCO_3$ (2x), brine (1x), dried ($MgSO_4$), filtered and evaporated to give the crude diazoketone product **12b** (145 mg, 95%).

M.S.(electrospray) : 717.4 $(M-H)^-$ 719.4 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06% TFA; CH_3CN : H_2O) : 85%.

Step 3: Synthesis of bromoketone 13b:

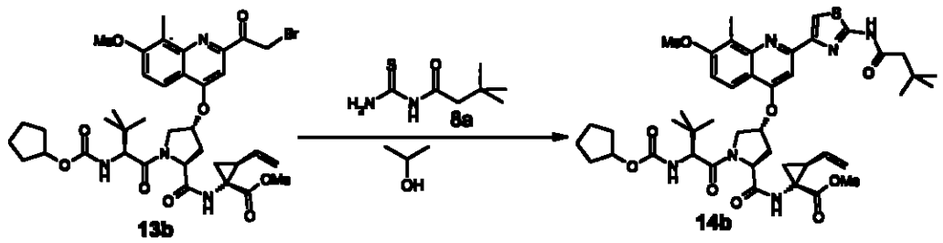


12b 13b

At 0°C, to a solution of diazoketone **12b** (145 mg, 0.201 mmol) in THF (4 mL) was added dropwise an HBr solution (48% aq., 0.1 mL) and the mixture was stirred for 1.25 h. The mixture was quenched with a saturated $NaHCO_3$ solution, then the THF was evaporated. The residue was diluted with EtOAc, washed with a saturated $NaHCO_3$ solution(2x), brine (1x), dried ($MgSO_4$), filtered and evaporated to provide the crude bromoketone **13b** (139 mg, 89%).

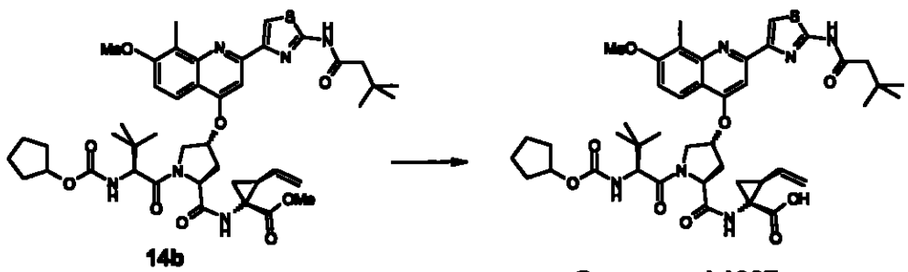
M.S.(electrospray) : 773.3 $(MH+2)^+$ 771.3 $(M+H)^+$ 769 $(M-H)^-$.

Step 4: Synthesis of thiazolyl tripeptide 14b:



α-Bromoketone **13b** (49 mg, 0.0635 mmol) and *N*-neopentylthiourea **8a** (12 mg; 0.0688 mmol) were dissolved in isopropanol (3 mL) and the yellow solution was heated at 75°C for 1 hour. The solution was allowed to cool to R.T. and evaporated to dryness. This crude material **14b** was used for next step (assume 0.0635 mmol).
M.S.(electrospray) : 845.5 $(M-H)^-$ 847.5 $(M+H)^+$.
Reverse Phase HPLC Homogeneity (0.06% TFA; CH_3CN : H_2O) : 69% (contain 16% of starting thiourea).

Step 5: Hydrolysis of ester 14b:

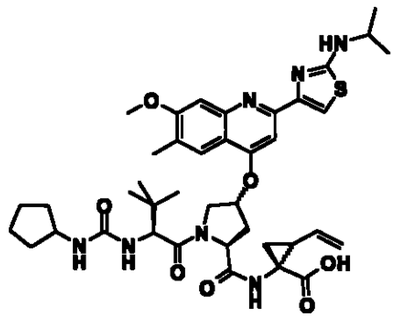


To a solution of methyl ester **14b** (53 mg, 0.0626 mmol), in a 3.5 mL mixture of THF:H_2O (2.5:1), was added solid LIOH-monohydrate (27 mg, 0.643 mmol). 0.5 mL of MeOH was required to obtain an homogeneous solution. The resulting reaction was stirred at room temperature overnight. The organic solution was quenched with acetic acid and concentrated to provide an off white suspension. The crude material was purified by preparatory HPLC (YMC Combiscreen ODS-AQ, 50 x 20 mm ID S-5 micron,120 A; λ= 220 nm) using a linear gradient and 0.06% TFA CH_3CN / H_2O . The pure fractions were combined, concentrated and lyophilized to provide the product **1007** as the TF salt (21 mg; 40% yield).
^1H NMR (400 MHz, DMSO-d_6): ca. 85:15 mixture of rotamers, major rotamer

description: δ 12.31 (br s, 1H), 8.56 (s, 1H), 8.20-8.08 (m, 1H), 8.05 (d, J = 9.2 Hz, 1H), 7.46 (br s, 1H), 7.30 (d, J = 9.0 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 5.79-5.66 (m, 1H), 5.50-5.40 (m, 1H), 5.23-5.14 (m, 1H), 5.10-5.02 (m, 1H), 4.70-4.61 (m, 1H), 4.48-4.33 (m, 2H), 4.16-4.08 (m, 1H), 4.04-3.93 (m, 1H), 3.95 (s, 3H), 2.60 (s, 3H), 2.58-2.49 (m, 1H), 2.40 (br s, 2H), 2.32-2.21 (m, 1H), 2.08-1.98 (m, 1H), 1.80-1.22 (m, 10H), 1.04 (m, 9H), 0.97 (s, 9H).
M.S.(electrospray) : 831.5 $(M-H)^-$ 833.5 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 99 %.

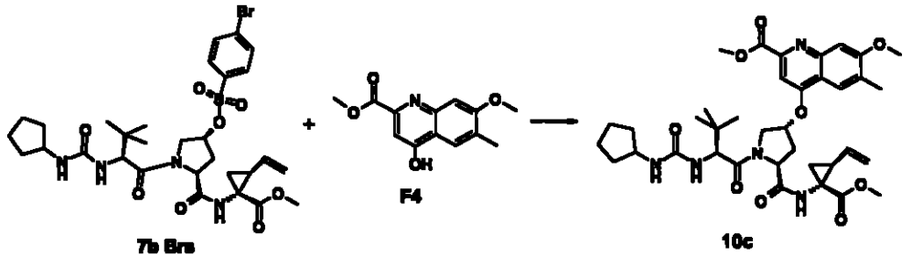
EXAMPLE 8

Synthesis of Compound 5005



Compound 5005

Step 1:



7b Brs **F4** **10c**

To a solution of the brosylate **7b Brs** (1.89 g, 2.71 mmol) and quinoline **F4** (670 mg, 2.71 mmol) in 1-methyl-2-pyrrolidinone (26 mL) was added cesium carbonate (971 mg, 2.98 mmol) at ambient temperature. The reaction mixture was heated at 70°C for 12 hours, cooled to ambient temperature and diluted with EtOAc (100 mL), washed with water (2x 50 mL), saturated $NaHCO_3$ solution containing 1M NaOH (1/5 of the volume) (50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated to afford the crude product as a yellow oil, which was purified by flash chromatography over silica gel column (250-400 Mesh), eluting

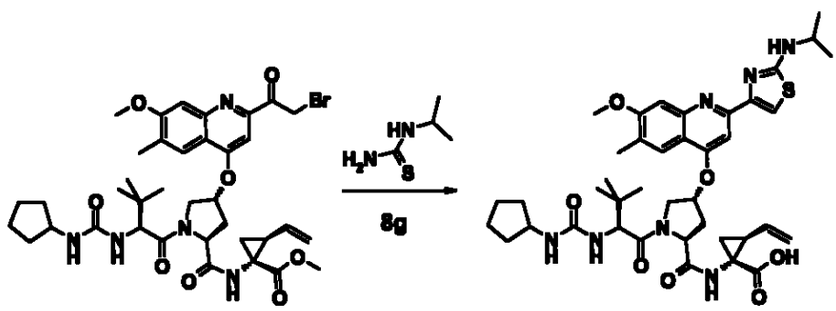
with EtOAc/hexanes (13:7), to afford 1.27 g of a pale yellow solid (contaminated with 20% of starting quinoline). The solid was dissolved in THF (15 mL) and the suspension was treated with CH_2N_2 (5 mL) at R.T. for 12 hours, then concentrated. The residue was purified by flash chromatography over silica gel column (250-400 mesh) eluting with EtOAc/$CHCl_3$ (12:6) to afford 0.9 g of pure **10c** as a pale yellow foam (48%).

Step 2:

The conversion of the 2-carbomethoxy group of **10c** into the 2-(1-oxo-2-bromo)ethyl group of **13c** was done using the reaction sequence described in example 7, steps 1, 2 and 3.

Step 3:

Reaction with thiourea derivative and final hydrolysis:



13c **Compound 5005**

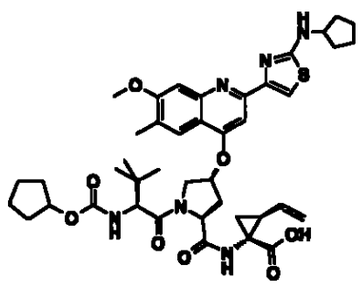
To the solution of **13c** (50 mg, 0.065 mmol) in isopropanol (3 mL) was added isopropylthiourea **8g** (10 mg, 0.085 mmol). The reaction mixture was stirred at 70°C for 45 minutes. HPLC revealed complete consumption of the starting material. Cooled to ambient temperature and diluted with THF (2 mL) and 1.0N sodium hydroxide solution (0.325 mL). Stirred at ambient temperature for 12 hours, the reaction mixture was concentrated to dryness. The residue was dissolved in DMSO (2 mL) and the solution was injected onto a Combi-Prep HPLC column. The pure fractions were pooled and lyophilized to yield 26.1 mg of Compound **5005** as an amorphous yellow solid (trifluoroacetate salt) (50%yield).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.60 and 8.82 (two s, 1H), 8.01-8.11 (m, 1H), 7.98 (s, 1H), 7.86 (s, 1H), 7.72 and 7.75 (two s, 1H), 5.90-6.03 (m, 1H), 5.80-5.90 (d, J= 16Hz, 1H), 5.62-5.79 (m, 2H), 5.15-5.26 (m, 1H), 4.96-5.13 (m, 1H), 4.44-4.61 (m,

2H), 4.16-4.23 (m, 2H), 4.08-4.13 (m, 2H), 3.98-4.01 (two s, 6H), 3.27 -3.38 (m, 1H), 2.53-2.70 (m, 1H), 2.32 and 2.36 (two s, 3H), 1.96-2.09 (q, J = 9 Hz, 17 Hz, 1H), 1.31-1.67 (m, 7H), 1.23-1.30 (m, 7H), 1.02-1.13 (m, 1H), 0.87 and 0.94 (two s, 9H).

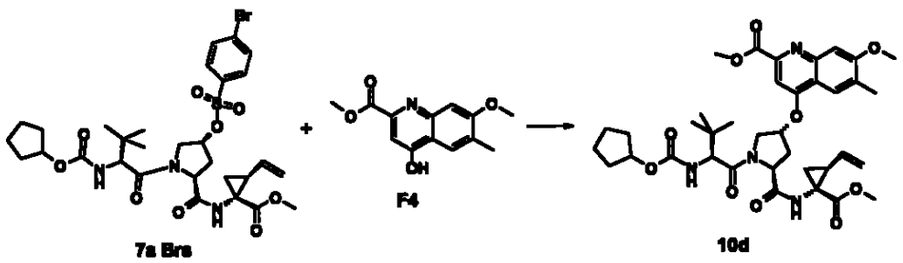
EXAMPLE 9

Synthesis of Compound 4004



Compound 4004

Step 1:



7a Brs **F4** **10d**

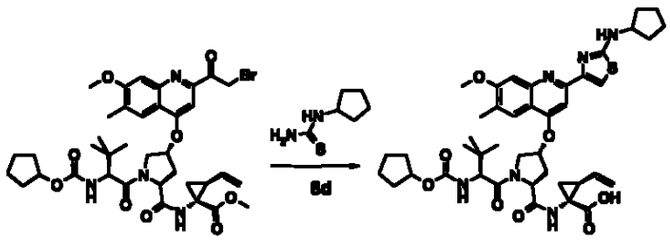
To a solution of brosylate **7a Brs** (0.14 g, 0.20 mmol) and **F4** (0.06 g, 0.24 mmol) in 1-methyl-2-pyrrolidinone (4 mL) was added cesium carbonate (0.08 g, 0.26 mmol). The mixture was heated to 70°C and stirred for 7 hr. The reaction mixture was cooled, poured into EtOAc (30 mL), washed with H_2O (2X 50 mL), sat. $NaHCO_3$ (2X 50 mL), and brine (3X 50 mL). The organic phase was dried, filtered and concentrated to a yellow oil. This material was purified by flash chromatography on a silica gel column (250-400 mesh) eluting with EtOAc/hexane (2:8), to afford 56 mg (40% yield) of the product **10d** as a pale yellow semi-solid.

Step 2:

The conversion of the 2-carbomethoxy group of **10d** into the 2-(1-oxo-2-bromo)ethyl group of **13d** was done using the reaction sequence described in Example 7, steps 1, 2 and 3.

Step 3:

Reaction with thiourea derivative and final hydrolysis:



13d Compound 4004

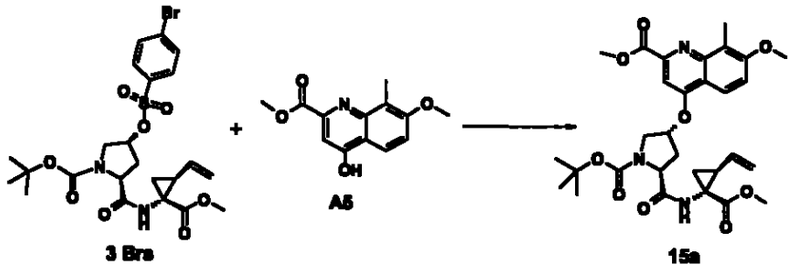
To a solution of bromoketone **13d** (34 mg, 0.045 mmol) in isopropanol (2 mL) was added cyclopentylthiourea **8d** (8.4 mg, 0.06 mmol). The reaction mixture was stirred at 70°C for 45 min, then concentrated to dryness and the residue was dissolved in a mixture of THF (1.5 mL) and methanol (0.3 mL). Water (0.45 mL) was added to this solution slowly with stirring, followed by LiOH (10.3 mg, 0.24 mmol). The reaction mixture was stirred at R.T. for 16 h. HPLC revealed that the reaction has proceeded to completion. The reaction mixture was concentrated, the residue was dissolved in DMSO and the solution was injected on to a Combi-prep HPLC column. The pure fractions were pooled and lyophilized to yield 16.5 mg (42% yield) of compound **4004** as an amorphous white solid (trifluoroacetic acid salt).

^{1}H NMR (400 MHz, DMSO-d_6) (mixture of rotamers;8:2): δ 8.59 and 8.71 (2s,1H), 8.13 (m,2H), 7.83-7.69 (m,2H), 7.1 (d, J=8.2Hz,0.8H), 6.46 (d, J=8.2Hz,0.2H), 5.76-5.67 (m,2H), 5.21 and 5.17 (2s,1H). 5.05 (d, J=11Hz,1H), 4.53-4.49 (m,2H), 4.25 (br.s,1H), 4.04-3.99 (m,5H), 2.66-2.53 (m,1H), 2.34 (s,4H), 2.07-1.98 (m,3H), 1.76-1.25 (m,16H), 0.95 and 0.87 (2s,9H).

EXAMPLE 10

Preparation of Dipeptides:

Synthesis of Dipeptide 3:



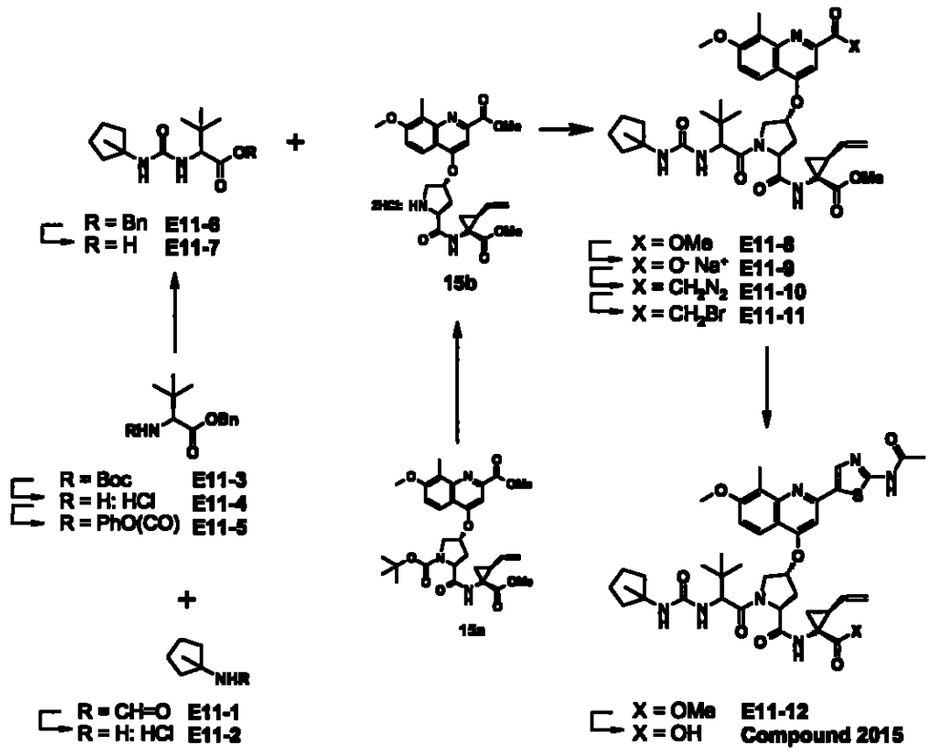
3 Bra A5 15a

To a solution of the brosylate **3 Brs**(4.2 g, 7.32 mmol) and the quinoline **A5** (1.45 g, 5.86 mmol) in 1-methyl-2-pyrrolidinone (25 mL) was added cesium carbonate (3.1 g, 9.5 mmol). The mixture was heated to 70°C for 12 h. The reaction mixture was poured into EtOAc (150 mL), washed with H_2O (2X 150 mL), saturated solution of $NaHCO_3$ (2X 150 mL) and brine (2X 150 mL). The organic phase was separated, dried over Na_2SO_4, filtered and concentrated to afford the crude product as a yellow oil. This material was purified by flash chromatography over silica gel column (250-400 Mesh) eluting with 65% EtOAc in hexane to afford **15a** (1.8 g, 42%) as a white solid.

EXAMPLE 11

Synthesis of Compound 2015

The synthesis was done according to the following sequence:



E11-1: Potassium cyanide (1.43 g, 22.0 mmol) was added to a stirred solution of methylcyclopentanol (2.00 g, 20.0 mmol) in glacial acetic acid (1.00 mL) resulting in a thick slurry. To this was added, dropwise, sulfuric acid (3 mL, caution: exothermic) at a rate at which the temperature was maintained at ca. 30-35°C. Additional acetic

acid (1 mL) was added to facilitate stirring of the thick paste. The mixture was then heated to 55-60°C for 30 min followed by stirring at ambient temperature for 16 h. Ice cold water (35 mL) was then added, the mixture extracted with ethyl ether (2x 40 mL) and the combined organic phases washed with 5% $NaHCO_3$ (5x 30 mL), dried over $MgSO_4$ and the solvent evaporated to yield a pale brown oil (1.16 g). The pH of the combined aqueous washings was then raised to pH 11 by the addition of solid K_2CO_3 and the resulting solids filtered and washed with ethyl ether (3x 40 mL). The filtrate was extracted with ethyl ether (2x 40 mL), the combined extracts dried over $MgSO_4$ and the solvent evaporated to yield additional product (0.355 g) which was combined with the above obtained oil (1.52 g, 60 %).

E11-2: 5N Hydrochloric acid (8 mL) was added to a solution of E11-1 (1.50 g, 11.8 mmol) in dioxane (8.0 mL) resulting in some precipitation. Ethanol (4 mL) was then added and the solution heated to reflux for 4 h. The reaction was then cooled, the organic solvents evaporated and the aqueous residue washed with hexane (40 mL). The aqueous layer was then evaporated to dryness (ethanol was used to azeotrope the last traces of water) and the resulting solid was dried under high vacuum to yield the methylcyclopentylamine hydrochloride as a beige solid (1.38 g, 86%).

E11-3: To a stirred, ice cold solution of Boc-Tbg-OH (5.00 g, 21.6 mmol) in acetonitrile (75 mL) was added benzyl bromide (2.83 mL, 23.8 mmol) under an argon atmosphere. DBU (3.88 mL, 25.9 mmol) was then added in small portions over ca. 5 min. The resulting suspension was stirred at 0°C for a further 30 min then allowed to warm to ambient temperature. After 3 h, the solvent was evaporated and the residue extracted with ethyl acetate (50 mL), washed with 1N HCl (2x 25 mL), 5% aq $NaHCO_3$ (3x 25 mL) and brine (25 mL), and then dried over $MgSO_4$ and the solvent evaporated to yield the benzyl ester as a colorless oil (6.83 g, 98 %).

E11-4: The E11-3 (6.80 g, 21.2 mmol) was dissolved in dioxane (4 mL) and a solution of 4N HCl in dioxane (30 mL, 120 mmol) added. After stirring at ambient temperature for 2 h, the solvent was evaporated and the residue allowed to stand under a stream of nitrogen resulting in slow solidification. This material was then triturated with hexane (2x 50 mL), filtered, air dried for 30 min then placed under

high vacuum for 5 days to afford the hydrochloride salt as a white solid (4.86 g, 89%).

E11-5: To a stirred, ice cold solution of E11-4 (4.85 g, 18.8 mmol) in tetrahydrofuran (75 mL) was added diisopropylethylamine (8.20 mL, 47.0 mmol) followed by the dropwise addition of phenylchloroformate (2.60 mL, 20.7 mmol) under an argon atmosphere. A thick precipitate formed which, upon vigorous stirring, became a fine suspension. After 4.5 h, the mixture was concentrated to a third of its original volume and then extracted with ethyl acetate (50 mL) and washed with water (40 mL), 0.5 M $KHSO_4$ (40 mL), 5 % $NaHCO_3$ (2x 40 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$ and evaporated to yield the phenyl carbamate as a colorless oil which slowly crystallized over a period of days (6.63 g, quantitative).

E11-6: To a solution of E11-5 (1.00 g, 2.93 mmol) in DMSO (2.00 mL) containing acetonitrile (1.00 mL) was added diisopropylethylamine (817 µL) followed by the amine E11-2 (477 mg, 3.52 mmol). The reaction was stirred at ambient temperature for 2 h and then heated to 70°C for 45 min The solution was then diluted with ethyl acetate (30 mL), washed with 5% aq K_2CO_3 (4x 50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$, the solvent evaporated and the residue purified by flash chromatography over TLC grade silica gel using 10:1 to 5:1 (gradient) hexane / ethyl acetate as eluent which afforded the urea E11-6 as a white crystalline solid (798 mg, 79%).

E11-7: To solution of urea E11-6 (780 mg, 2.25 mmol) in absolute ethanol (10 mL) under an argon atmosphere was added 10% Pd-C catalyst (100 mg). The system was purged three times with H_2 and then stirred vigorously under a hydrogen-balloon. After 3 h, the catalyst was filtered over Celite and the filtrate evaporated. The residue was then dissolved in methanol (ca. 10 mL), filtered through a Millipore Millex 0.45 uM filter and then evaporated to yield the acid E11-7 as a white solid (539 mg, 93%).

15b: The Boc-dipeptide 15a (1.23 g, 2.11 mmol) was dissolved in dry dioxane (2 mL) and a solution of 4N HCl in dioxane (10 mL, 40 mmol) added, resulting in a

bright yellow solution which was allowed to stand at ambient temperature. After 3 h, the solvent was evaporated resulting in a gummy yellow solid which was triturated with dichloromethane (ca. 10 mL) and evaporated to a canary yellow powder which was dried under high vacuum (1.23 g, quantitative).

E11-8: The urea E11-7 (239 mg, 0.932 mmol) and TBTU (3.06 mg, 0.979 mmol) were dissolved/suspended in anhydrous dichloromethane (4 mL) and diisopropylethylamine (157 µL, 0.900 mmol) added. The reaction was stirred at ambient temperature under a nitrogen atmosphere until the solution became nearly homogeneous (ca. 5 min). A solution of dipeptide 15b (494 mg, 0.888 mmol) in dichloromethane containing diisopropylethylamine (314 µL, 1.8 mmol) was then added and the resulting solution allowed to stir for 3 h after the reaction was rendered basic by the addition of additional diisopropylethylamine (ca. 0.15 mL). The solvent was evaporated yielding a yellow syrup which was extracted with ethyl acetate (2x 50 mL) and washed with saturated $NaHCO_3$ (2x 50 mL) and brine (30 mL). The combined extracts were then dried over $MgSO_4$ and evaporated to afford the tripeptide E11-8 as a fibrous white solid (650 mg, 97 %).

E11-9: The ester E11-8 (645 mg, 0.894 mmol) was dissolved in tetrahydrofuran (16 mL) containing methanol (8 mL) and 1.0N aqueous sodium hydroxide solution (900 mL, 0.900 mmol) then added dropwise with vigorous stirring at ambient temperature. After 5 h, the solution was evaporated (keeping the bath temperature below 30°C) and then placed under high vacuum overnight to afford the carboxylate salt as a pale yellow solid (725 mg, quantitative) which was used without further purification (ca. 10 % of diacid present).

E11-10: To a stirred, ice cold suspension of sodium salt E11-9 (0.894 mmol) in tetrahydrofuran (10 mL) under an argon atmosphere was added triethylamine (240 µL, 1.72 mmol) followed by the dropwise addition of isobutyl chloroformate (174 µL, 1.34 mmol). The resulting suspension was stirred at 0°C for 3 h and a solution of diazomethane in ethyl ether (0.7M, 10 mL, 7 mmol) then added. The yellow suspension was stirred for 30 min at 0°C and then allowed to warm to ambient temperature. After 1 h, nitrogen was bubbled through the suspension for 15 min. to remove the excess diazomethane and the solvent evaporated. The residue was

extracted with ethyl acetate (20 mL) and washed with 5% aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$ and evaporated to yield the diazoketone E11-10 as a yellow solid (626 mg (96%).

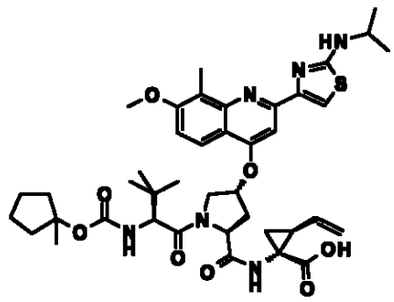
E11-11: To a stirred, ice cold solution of diazoketone E11-10 (620 mg, 0.850 mmol) in tetrahydrofuran (2 mL) was added dropwise 48 % aqueous hydrobromic acid (144 µL, 0.850 mmol) and the reaction stirred for 30 min The solution was then diluted and extracted with ethyl acetate (30 mL) and washed with 5% aqueous $NaHCO_3$ (2x 20 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$ and evaporated to afford the bromoketone E11-11 as a yellow solid (611 mg, 92 %).

E11-12: To a solution of bromoketone E11-11 (75 mg, 0.10 mmol) in isopropanol (0.30 mL) was added diisopropylethylamine (87 µL, 0.50 mmol) and *N*-acetylthiourea (18 mg, 0.15 mmol). The stirred mixture was heated to 70°C for 1 h and then extracted with ethyl acetate (30 mL) and washed with 5% aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$ and evaporated to yield the crude aminothiazole as a yellow solid which was used without further purification.

Compound 2015: The ester E11-12 (0.10 mmol) was dissolved in tetrahydrofuran (0.80 mL) and methanol (0.25 mL) and 1.0 N lithium hydroxide (800 µL, 0.80 mmol) added. After stirring at ambient temperature for 2.5, the organic solvents were evaporated and the resulting aqueous residue was diluted with DMSO (1 mL) and acetic acid (0.7 mL) and the solution injected onto a Combi-Prep HPLC column. The pure fractions were pooled and lyophilized to yield the final inhibitor 2015 as an amorphous yellow solid (trifluoroacetate salt, 16 mg, 20 %): ^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.87 and 0.96 (two s, 9H), 1.19 and 1.28 (two s, 3H), 1.24-1.90 (m, 9H), 2.03 (app q4, Japp = 8.8 Hz, 1H), 2.20 (s, 3H), 2.2-2.28 (m, 1H), 2.60 (s, 3H), 3.83-4.05 (m, 2H), 3.93 (s, 3H), 4.19-4.23 (m, 2H), 4.36-4.46 (m, 3H), 4.81 (app t, Japp = 7 Hz, 0.2H), 5.03-5.07 (two sets of overlapping dd, 1H), 5.16-5.24 (two sets of overlapping dd, 1H), 5.38 and 5.42 (two br. s, 1H), 5.67-5.83 (m, 1H), 5.95-6.04 (m, 2H), 7.26 (d, J = 9.4 Hz, 0.8H), 7.40 (d, J = 9.4 Hz, 0.2H), 7.43-7.55 (br. m, 1H), 7.89 (d, J = 9.2 Hz, 0.2 H), 8.04 (d, J = 9.2 Hz, 0.8H), 8.08 (br. s, 1H), 8.54 (s, 0.8H), 8.87 (s, 0.2H), 12.37 and 12.42 (two br. s, 1H).

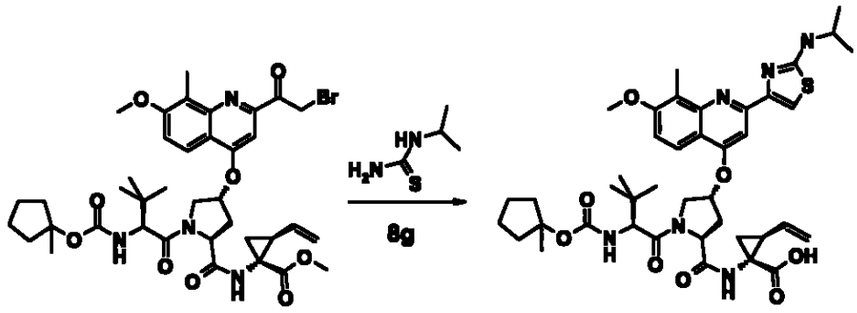
EXAMPLE 12

Synthesis of Compound 1038



Compound 1038

Using a reaction sequence similar to the one described in the last six steps of Example 11, but using carbamate 4c (Example 15) instead of urea 11-7, the following carbamate bromoketone E12-1 was prepared:



E12-1 **Compound 1038**

Conversion of the bromoketone to final compound was done as follows:

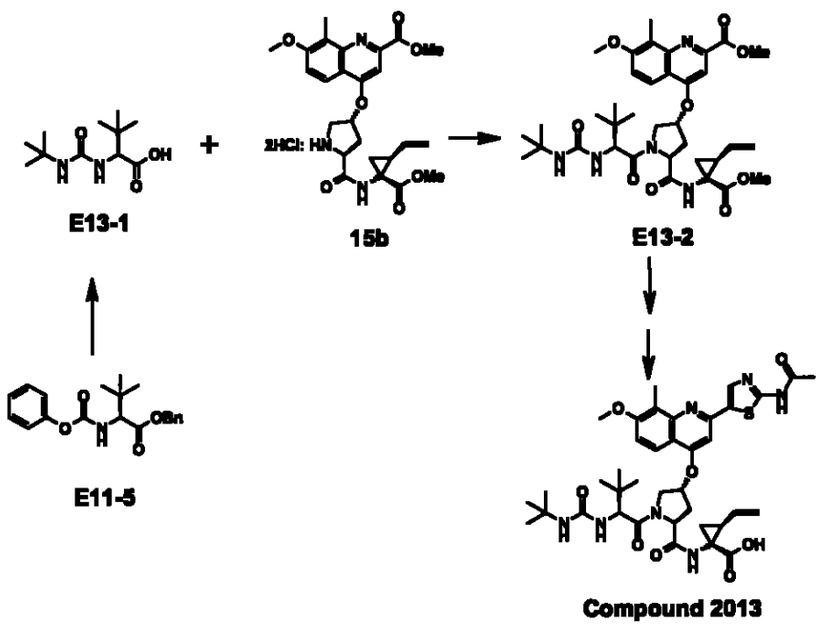
To a solution of the bromoketone **E12-1** (60 mg, 0.076 mmol) in isopropanol (3 mL) was added isopropylthiourea **8g** (11.7 mg, 0.99 mmol). The reaction mixture was heated at 70°C for 45 minutes. HPLC revealed complete consumption of the starting material. The reaction mixture was cooled to ambient temperature, diluted with THF (3 mL) and 1.0N sodium hydroxide solution (1 mL) was added. After stirring at ambient temperature for 12 hours, the reaction mixture was concentrated to dryness. The residue was dissolved in DMSO (2 mL) and the solution was injected onto a Combi-Prep HPLC column. The pure fractions were pooled and lyophilized to yield 9 mg of **Compound 1038** as an amorphous yellow solid (trifluoroacetate salt) (15% yield).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 12.35 (br s, 1H), 8.56 and 8.76 (two s, 1H), 7.72-

8.27 (m, 2H), 7.23-7.68 (m, 2H), 6.68-6.95 (d, J= 9Hz, 0.8H), 6.18-6.34 (d, J= 9Hz, 0.2H), 5.61-5.81 (m, 1H), 5.52 (broad s, 1H), 5.13-5.27 (m, 1H), 4.96-5.13 (m, 1H), 4.31-4.50 (m, 3H), 3.74-4.17 (m, 8H), 2.53-2.60 (m, 3H), 2.20-2.36 (m, 1H), 1.95-2.09 (m, 1H), 1.70-1.91 (m, 2H), 1.95-2.09 (m, 1H), 1.37-1.61, (m, 6H), 1.18-1.32 (m, 9H), 0.87 and 0.96 (two s, 9H).

EXAMPLE 13

Synthesis of Compound 2013



Urea Acid E13-1: The urea-P3 acid was prepared from tert-butylamine and E11-5 by the same sequence of reactions as described in Example 11.

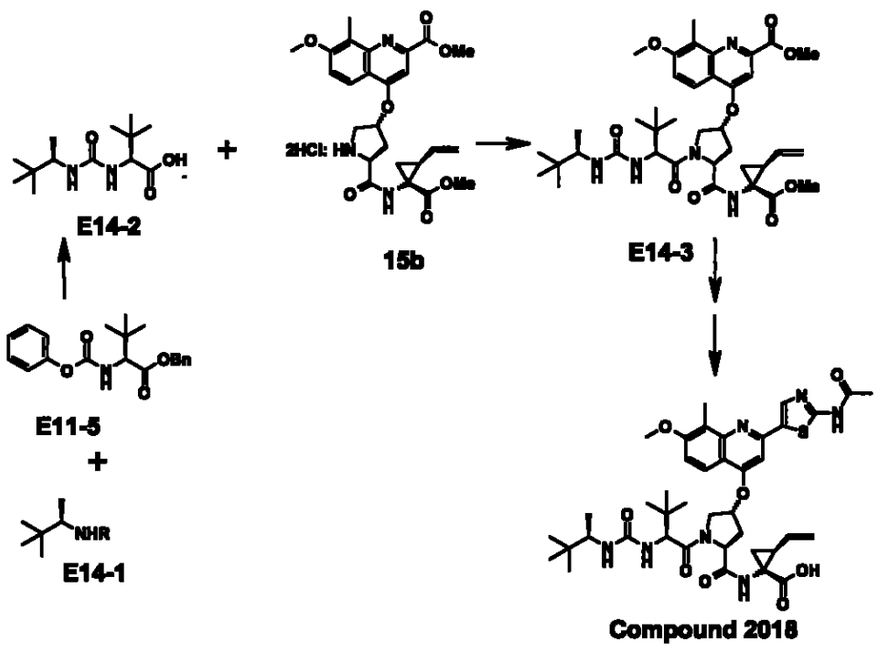
Tripeptide ester E13-2: The urea-P3 acid was coupled with the P1-P2 fragment 15b as described in Example 11.

Compound 2013: The final inhibitor was prepared from E13-2 by a sequence of steps identical to that described in Example 11. The product of the final saponification was isolated as an amorphous yellow powder (trifluoroacetate salt, 21 mg, 28 %). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.91 and 0.96 (two s, 9H), 1.15 and 1.21 (two s, 9H), 1.26 (dd, J = 5.0, 9.4 Hz, 0.8H), 1.53 (dd, J = 5.0, 7.8 Hz, 0.8H), 1.58 (dd, J = 4.3, 9.2 Hz, 0.2H), 2.03 (app q4, Japp = 8.8 Hz, 1H), 2.20 (s, 3H), 2.2-

2.28 (m, 1H), 2.58 (s, 3H), 3.80-4.04 (m, 2H), 3.93 and 3.96 (two s, 3H), 4.18-4.20 (m, 2H), 4.35-4.45 (m, 3H), 4.83 (app t, Japp = 7 Hz, 0.2H), 5.03-5.07 (two sets of overlapping dd, 1H), 5.17-5.24 (two sets of overlapping dd, 1H), 5.36 and 5.42 (two br. s, 1H), 5.66-5.80 (m, 1H), 5.86-6.04 (br. m, 2H), 7.25 (d, J = 9.2 Hz, 0.8H), 7.40 (d, J = 9.2 Hz, 0.2H), 7.4-7.50 (br. m, 1H), 7.88 (d, J = 9.0 Hz, 0.2 H), 8.03-8.15 (br. m, 1.8H), 8.54 (s, 0.8H), 8.89 (s, 0.2H), 12.38 and 12.42 (two br. s, 1H).

EXAMPLE 14

Synthesis of compound 2018



E14-2: The urea-P3 acid E14-2 was prepared from E11-5 and amine E14-1 by the same sequence of reactions as described in Example 11.

E14-3: The urea-P3 acid was coupled with the P1-P2 fragment 15b as described in Example 11.

The final inhibitor was prepared from E14-3 by a sequence of steps identical to that described on Example 11. The product of the final saponification was isolated as an amorphous yellow powder (trifluoroacetate salt, 10 mg, 21 %).

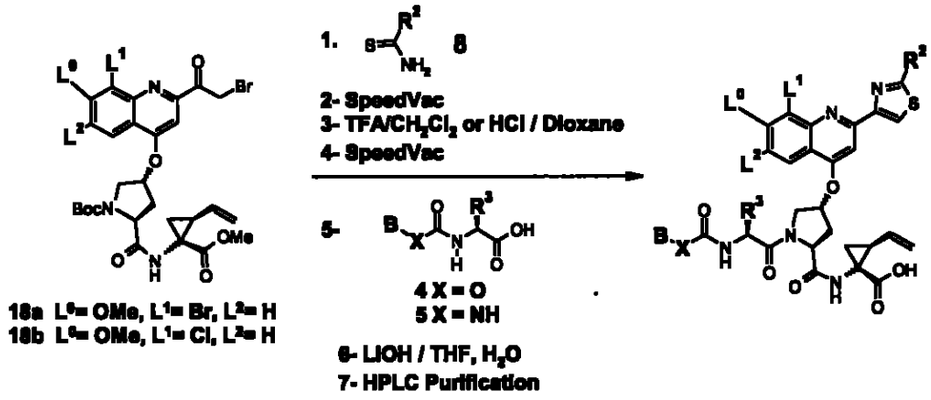
^{1}H-NMR (400 MHz, DMSO-d_6): δ 0.74-0.97 (m, 21H), 1.25 (dd, J=5, 9Hz, 1H), 1.47

(dd, J=8, 4Hz, 0.2H), 1.53 (dd, J=8, 5Hz, 0.8H), 2.02 (app q[4], J_{app}=8Hz, 0.8H), 2.19 (s, 3H), 2.2-2.27 (m, 1H), 2.59 (s, 3H), 3.31-3.43 (m, 1H), 3.93 and 3.95 (two s, 3H), 3.98-4.02* (m), 4.22-4.26* (m), 4.35-4.39* (m), 4.82 (app t, J_{app}=7Hz, 0.2H), 5.01-5.06 (two sets of overlapping dd, 1H), 5.16-5.23 (two sets of overlapping dd, 1H), 5.35 and 5.41 (two br. s, 1H), 5.67-5.79 (m, 1H), 5.87 (d, J=9.4Hz, 0.8H), 5.91 (d, J=9.4Hz, 0.2H), 6.07 (d, J=8.6Hz, 0.8H), 6.14 (d, J=9.2Hz, 0.2H), 7.24-7.5 (m, 2H), 7.89 (d, J=9.2Hz, 0.2H), 8.04-8.12 (m, 1.8H), 8.54 (s, 0.8H), 8.87 (s, 0.2H), 12.37 and 12.41 (two s, 1H). * obscured by HOD signal.

EXAMPLE 15

Permutation library:

Both bromo ketones **18a** and **18b** were used in a permutation library for the parallel synthesis of compounds as shown in the following scheme:



Step 1: Formation of the aminothiazole ring

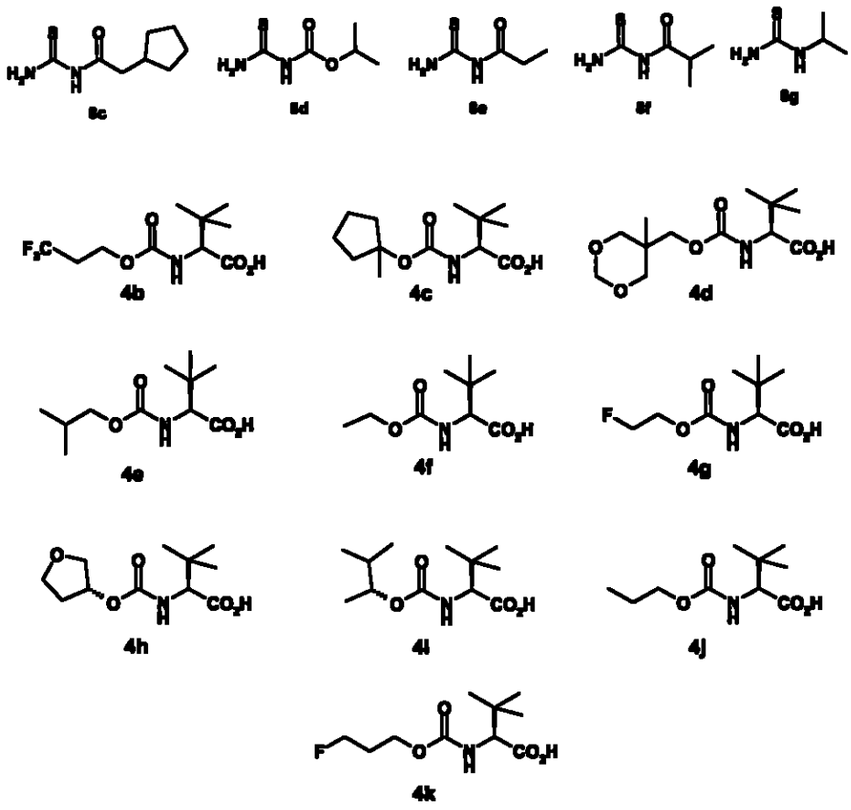
A series of 8-mL vials were disposed in a reaction block from an ACT496 synthesizer (from Advanced Chemtech). In each vial was added the thio-derivative (**8**) of interest (0.0688 mmole), the bromoketone (0.0625 mmole) and isopropanol (500 µL). The closed vials were heated at 70°C for 1 h. The solvent was then evaporated using a vacuum centrifuge (SpeedVac) and was co-evaporated with 1,2-dichloroethane. The crude products were dried under high vacuum overnight.

Step 2: Removal of the Boc protecting group

All the vials were treated with 30% TFA in DCM (500 µL) for 1 h. All vials were transferred on a vacuum centrifuge to remove the volatile material.

Step 3: Coupling

In each vial was added the corresponding carbamate (21c to 21g) and carbamate acid (4b to 4k) (0.0875 mmole), HATU (0.0875 mmole, 33.27 mg) and DIPEA (0.313 mmole, 55 µL) in 500 µL of DMSO and the reaction mixture was allowed to proceed overnight.



Step 4: Saponification and Purification

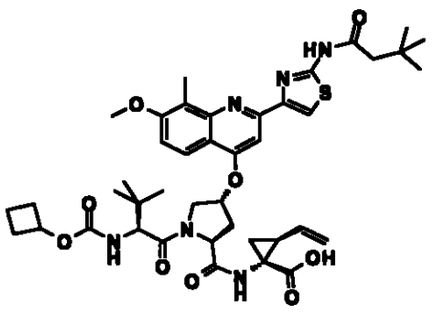
All reactions were diluted with 400 µL of DMSO and 200 µL THF. A solution of 500 µL of 2N aq LiOH (1 mmol) was added to each vial and allowed to proceed overnight after which time, the mixture was neutralized by the addition of 400 µL of AcOH. All compounds were purified by semi-prep reversed-phase HPLC (Symmetry column 5 cm x 19 cm, CH_3CN / H_2O 0.06% TFA gradient).

EXAMPLE 16

The following compounds were prepared using reaction sequences and methodologies as described in the above examples:

113

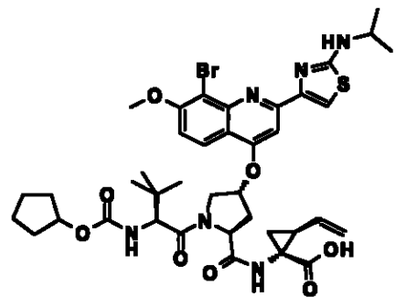
Compounds from Table 1



Compound 1006

Compound 1006:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 12.31 (br s, 1H), 8.56 (s, 1H), 8.14 (br s, 1H), 8.06 (d, J = 9.0 Hz, 1H), 7.47 (br s, 1H), 7.34 (d, J = 9.0 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 5.79-5.66 (m, 1H), 5.51-5.41 (m, 1H), 5.24-5.15 (m, 1H), 5.11-5.03 (m, 1H), 4.53-4.40 (m, 2H), 4.40-4.32 (m, 1H), 4.07 (d, J = 8.6 Hz, 1H), 4.04-3.92 (m, 1H), 3.96 (s, 3H), 2.61 (s, 3H), 2.58-2.50 (m, 1H), 2.40 (br s, 2H), 2.31-2.17 (m, 1H), 2.12-1.95 (m, 3H), 1.91-1.76 (m, 2H), 1.71-1.39 (m, 3H), 1.31-1.23 (m, 1H), 1.04 (m, 9H), 0.97 (s, 9H).
M.S.(electrospray) : 817.4 $(M-H)^-$ 819.5 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 99 %



Compound 1030

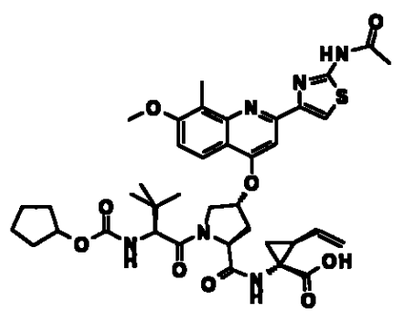
Compound 1030:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 8.56 (s, 1H), 8.14 (d, J = 9.0 Hz, 1H), 8.00-7.78 (m, 1H), 7.73-7.56 (m, 1H), 7.52 (s, 1H), 7.37 (d, J = 9.2 Hz, 1H), 6.97 (d, J = 8.6 Hz, 1H), 5.78-5.65 (m, 1H), 5.52-5.45 (m, 1H), 5.23-5.15 (m, 1H), 5.13-5.03 (m, 1H), 4.58-4.50 (m, 1H), 4.50-4.42 (m, 1H), 4.39-4.31 (m, 1H), 4.10-4.03 (m, 1H), 4.01 (s, 3H), 3.99-3.70 (m,

under H2O, 2H), 2.34-2.23 (m, 1H), 2.07-1.98 (m, 1H), 1.70-1.37 (m, 9H), 1.34-1.23 (m, 2H), 1.26 (br d, J = 6.4 Hz, 6H), 0.96 (s, 9H).

M.S.(electrospray) : 839 $(M-H)^-$ 841.3 $(M-H+2)^-$ 841.3 $(M+H)^+$ 843.3 $(MH+2)^+$.

Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 98 %

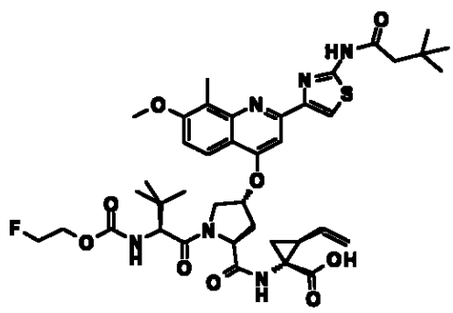


Compound 1015

Compound 1015:

^1H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, <u>major rotamer description</u>; δ 12.32 (br s, 1H), 8.57 (s, 1H), 8.15-8.03 (m, 1H), 8.04 (d, J = 9.2 Hz, 1H), 7.47-7.37 (m, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 8.6 Hz, 1H), 5.78-5.65 (m, 1H), 5.45-5.38 (m, 1H), 5.23-5.14 (m, 1H), 5.09-5.02 (m, 1H), 4.72-4.62 (m, 1H), 4.46-4.32 (m, 2H), 4.16-4.08 (m, 1H), 4.03-3.90 (m, 1H), 3.94 (s, 3H), 2.60 (s, 3H), 2.30-2.19 (m, 1H), 2.20 (s, 3H), 2.06-1.97 (m, 1H), 1.81-1.21 (m, 11H), 0.97 (s, 9H).

M.S.(electrospray) : 775.4 $(M-H)^-$ 777.5 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 99 %

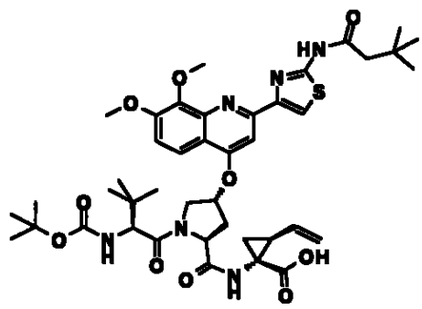


Compound 1024

Compound 1024:

^1H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, <u>major rotamer description</u>; δ 12.31 (s, 1H), 8.55 (s, 1H), 8.20-8.05 (m, 1H), 8.03 (d, J = 9.2 Hz, 1H),

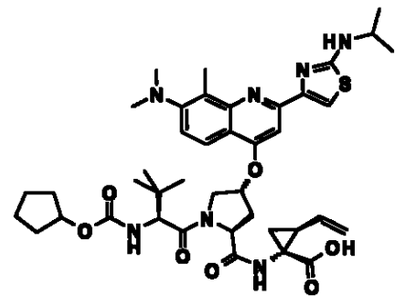
7.54-7.40 (m, 1H), 7.38 (d, J = 8.6 Hz, 1H), 7.33 (d, J = 9.4 Hz, 1H), 5.79-5.66 (m, 1H), 5.49-5.41 (m, 1H), 5.23-5.15 (m, 1H), 5.09-5.02 (m, 1H), 4.77-3.85 (m, 8H), 3.95 (s, 3H), 2.60 (s, 3H), 2.58-2.47 (m, 1H), 2.43-2.36 (m, 2H), 2.31-2.20 (m, 1H), 2.07-1.98 (m, 1H), 1.57-1.51 (m, 1H), 1.31-1.23 (m, 1H), 1.04 (s, 9H), 1.00 (s, 9H).
M.S.(electrospray) : 809.4 $(M-H)^-$ 811.4 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 98 %



Compound 1001

Compound 1001:

^1H NMR (400 MHz, DMSO-d_6): ca, 7:3 mixture of rotamers, major rotamer description; δ 8.01 (br s, 1H), 7.92 (s, 1H), 7.90-7.77 (m, 2H), 7.70 (br s, 1H), 7.31 (d, J = 9.4 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 6.28-6.10 (m, 1H), 5.53-5.33 (m, 1H), 5.03-5.92 (m, 1H), 4.85-4.71 (m, 1H), 4.49-4.40 (m, 1H), 4.19-4.02 (m, 3H), 4.03 (s, 3H), 3.93 (s, 3H), 2.82-2.45 (m, 3H), 2.36-2.23 (m, 1H), 1.90-1.79 (m, 1H), 1.34 (m, 9H), 1.37-1.14 (m, 2H), 1.03 (s, 9H), 0.98 (s, 9H).
M.S.(electrospray) : 835.4 $(M-H)^-$ 837.3 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 99 %

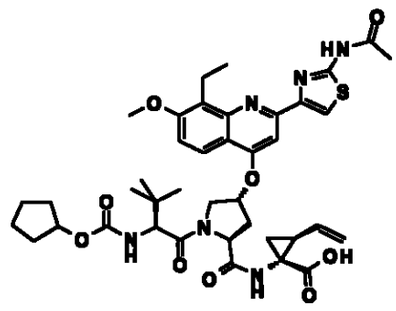


Compound 1011

Compound 1011:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 8.53 (s, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.69 (d, J = 7.4 Hz, 1H), 7.46 (s, 1H), 7.39 (s, 1H), 7.25 (d, J = 9.0 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 5.79-5.64 (m, 1H), 5.44-5.33 (m, 1H), 5.23-5.13 (m, 1H), 5.10-5.00 (m, 1H), 4.81-4.70 (m, 1H), 4.45-4.27 (m, 2H), 4.19-4.11 (m, 1H), 4.04-3.91 (m, 1H), 3.87-3.72 (m, 1H), 2.75 (s, 6H), 2.66 (s, 3H), 2.56-2.42 (m, 1H), 2.29-2.17 (m, 1H), 2.07-1.97 (m, 1H), 1.80-1.21 (m, 10H), 1.25 (br d, J = 6.5 Hz, 6H), 0.97 (s, 9H).

M.S.(electrospray) : 788.4 $(M-H)^-$ 790.5 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 95 %



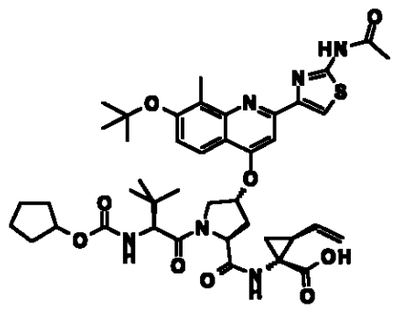
Compound 1023

Compound 1023:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 12.36 (s, 1H), 8.55 (s, 1H), 8.09-7.97 (m, 2H), 7.42 (br s, 1H), 7.29 (d, J = 9.2 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 5.79-5.66 (m, 1H), 5.45-5.38 (m, 1H), 5.23-5.15 (m, 1H), 5.09-5.02 (m, 1H), 4.75-4.66 (m, 1H), 4.47-4.31 (m, 2H), 4.16-4.09 (m, 1H), 4.03-3.91 (m, 1H), 3.94 (s, 3H), 3.29-3.18 (m, 2H), 2.60-2.43 (m, 1H), 2.30-2.18 (m, 1H), 2.20 (s, 3H), 2.07-1.97 (m, 1H), 1.81-1.33 (m, 9H), 1.31-1.23 (m, 1H), 1.18 (t, J = 7.3 Hz, 3H), 0.97 (s, 9H).

M.S.(electrospray) : 789.3 $(M-H)^-$ 791.4 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 98 %

117

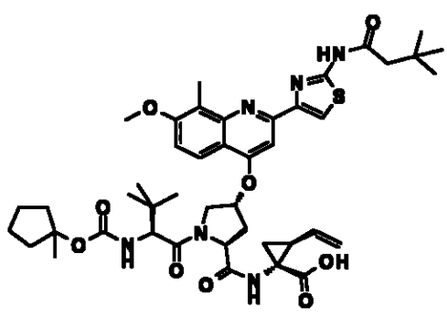


Compound 1033

Compound 1033:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 12.36 (s, 1H), 8.53 (s, 1H), 8.05 (s, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.46 (s, 1H), 7.20 (d, J = 9.0 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 5.80-5.65 (m, 1H), 5.44-5.37 (m, 1H), 5.24-5.14 (m, 1H), 5.10-5.01 (m, 1H), 4.85-4.76 (m, 1H), 4.45-4.34 (m, 2H), 4.21-4.10 (m, 1H), 4.04-3.89 (m, 1H), 2.62 (s, 3H), 2.58-2.47 (m, 1H), 2.28-2.18 (m, 1H), 2.20 (s, 3H), 2.06-1.96 (m, 1H), 1.81-1.38 (m, 9H), 1.39 (s, 9H), 1.29-1.22 (m, 1H), 0.99 (s, 9H).

M.S.(electrospray) : 817.4 $(M-H)^-$ 819.4 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 98 %

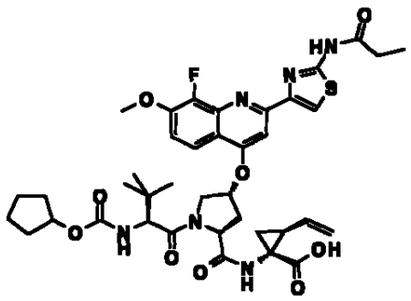


Compound 1037

Compound 1037:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 12.29 (s, 1H), 8.54 (s, 1H), 8.19-8.01 (m, 1H), 8.04 (d, J = 9.0 Hz, 1H), 7.44 (s, 1H), 7.25 (d, J = 9.2 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 5.78-5.65 (m, 1H), 5.47-5.37 (m, 1H), 5.22-5.13 (m, 1H), 5.08-5.02 (m, 1H), 4.45-4.33 (m, 2H), 4.13-4.06 (m, 1H), 3.98-3.90 (m, 1H), 3.92 (s, 3H), 2.59 (s, 3H), 2.56-2.46 (m, 1H), 2.41-2.36 (m, 2H), 2.28-2.18 (m, 1H), 2.05-1.96 (m, 1H), 1.93-1.43 (m, 9H), 1.33 (br s,

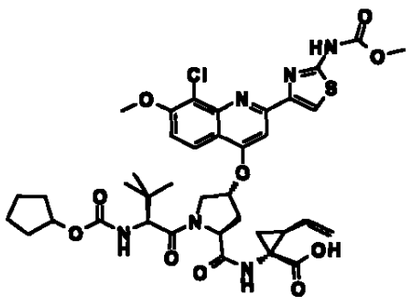
3H), 1.29-1.22 (m, 1H), 1.03 (s, 9H), 0.97 (s, 9H).
M.S.(electrospray) : 845.5 $(M-H)^-$ 847.5 $(M+H)^+$. Reverse Phase HPLC
Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 96 %



Compound 1051

Compound 1051:

^1H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 12.35 (s, 1H), 8.54 (s, 1H), 8.03 (s, 1H), 7.92 (d, J = 9.2 Hz, 1H), 7.47 (s, 1H), 7.38 (t, J = 8.3 Hz, 1H), 6.98 (d, J = 8.7 Hz, 1H), 5.78-5.65 (m, 1H), 5.47-5.38 (m, 1H), 5.23-5.13 (m, 1H), 5.09-5.00 (m, 1H), 4.69-4.60 (m, 1H), 4.48-4.30 (m, 2H), 4.14-3.90 (m, 2H), 3.98 (s, 3H), 2.60-2.39 (m, 3H), 2.30-2.20 (m, 1H), 2.06-1.97 (m, 1H), 1.80-1.37 (m, 8H), 1.37-1.20 (m, 2H), 1.12 (t, J = 7.5 Hz, 3H),.0.96 (s, 9H).
M.S.(electrospray) : 793.3 $(M-H)^-$ 795.3 $(M+H)^+$. Reverse Phase HPLC
Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 98 %



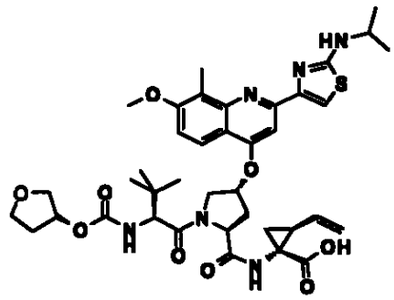
Compound 1053

Compound 1053:

^1H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 12.06 (br s, 1H), 8.55 (s, 1H), 8.12 (d, J = 9.2 Hz, 1H), 8.05 (s, 1H), 7.46 (m, 1H), 7.39 (d, J = 9.3 Hz, 1H), 6.96 (d, J = 8.6 Hz, 1H), 5.78-5.66 (m, 1H),

5.44-5.38 (m, 1H), 5.23-5.15 (m, 1H), 5.09-5.02 (m, 1H), 4.65-4.52 (m, 1H), 4.49-4.32 (m, 2H), 4.12-4.05 (m, 1H), 4.01 (s, 3H), 3.99-3.91 (m, 1H), 3.78 (s, 3H), 2.60-2.45 (m, 1H), 2.31-2.20 (m, 1H), 2.07-1.97 (m, 1H), 1.81-1.37 (m, 8H), 1.37-1.22 (m, 2H), 0.96 (s, 9H).

M.S.(electrospray) : 811.1 $(M-H)^-$ 813.2 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 96 %



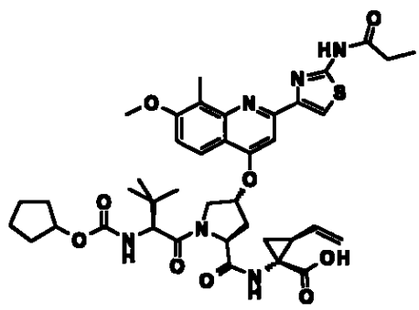
Compound 1027

Compound 1027:

^{1}HNMR(400MHz, DMSO-d_6): δ 8.58 (s, 1H), 8.06 (d, J= 9Hz, 1H), 7.91, 7.89 (2s, 1H), 7.57 (brs, 1H), 7.40,7.38 (2s, 1H), 7.25 (d, J=9Hz, 1H), 5.57-5.68 (m, 1H), 5.55 (brs, 1H), 5.20 (d, J=16Hz, 1H), 5.06 (d, J= 11Hz, 1H)), 4.69 (brs, 1H), 4.47 (t, J= 9Hz, 1H), 4.30-4.35 (m, 1H), 4.08 (d, J= 9Hz, 2H), 4.05-3.96 (m, 2H), 3.97 (s,3H), 3.66-3.40 (m, 8H), 2.56 (s, 3H), 2.35-2.25 (m, 1H), 2.08-1.98 (m, 1H), 1.60-1.50 (m, 2H), 1.28,1.26 (2s, 6H), 0.97 (s, 9H).

EIMS: (M+H) = 779.3, (M-H) = 777.3

Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 99%.



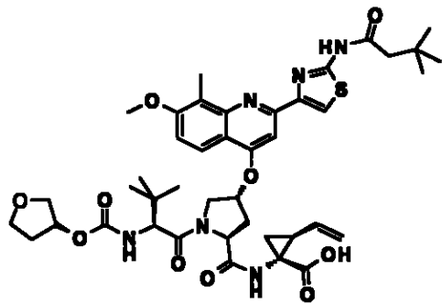
Compound 1041

120

Compound 1041:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 12.33 (br s, 1H), 8.55 (s, 1H), 8.15-8.02 (m, 1H), 8.04 (d, J = 9.0 Hz, 1H), 7.49-7.38 (m, 1H), 7.29 (d, J = 9.2 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 5.78-5.66 (m, 1H), 5.46-5.39 (m, 1H), 5.23-5.14 (m, 1H), 5.09-5.02 (m, 1H), 4.71-4.62 (m, 1H), 4.47-4.32 (m, 2H), 4.15-4.09 (m, 1H), 4.03-3.92 (m, 1H), 3.94 (s, 3H), 2.60 (s, 3H), 2.58-2.40 (m, 2H), 2.30-2.20 (m, 1H), 2.07-1.97 (m, 1H), 1.80-1.21 (m, 11H), 1.13 (t, J = 7.5 Hz, 3H), 0.97 (s, 9H).

M.S.(electrospray) : 789.4 $(M-H)^-$ 791.4 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 98 %.

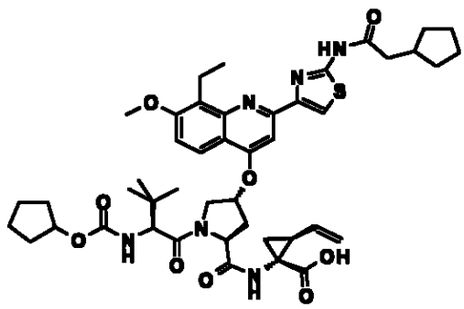


Compound 1026

Compound 1026:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 12.30 (s, 1H), 8.56 (s, 1H), 8.09 (br s, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.44 (br s, 1H), 7.32 (d, J = 9.2 Hz, 1H), 7.24 (d, J = 8.6 Hz, 1H), 5.78-5.66 (m, 1H), 5.47-5.39 (m, 1H), 5.23-5.15 (m, 1H), 5.10-5.03 (m, 1H), 4.80-4.72 (m, 1H), 4.49-4.41 (m, 1H), 4.37-4.29 (m, 1H), 4.15-4.08 (m, 1H), 4.05-3.95 (m, 1H), 3.95 (s, 3H), 3.80-3.51 (m, under H2O, 4H), 2.60 (s, 3H), 2.57-2.48 (m, 1H), 2.41-2.37 (m, 2H), 2.31-2.21 (m, 1H), 2.07-1.98 (m, 1H), 1.95-1.83 (m, 1H), 1.62-1.46 (m, 2H), 1.31-1.22 (m, 1H), 1.04 (s, 9H), 0.97 (s, 9H). M.S.(electrospray) : 833.3 $(M-H)^-$ 835.4 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 99 %

121

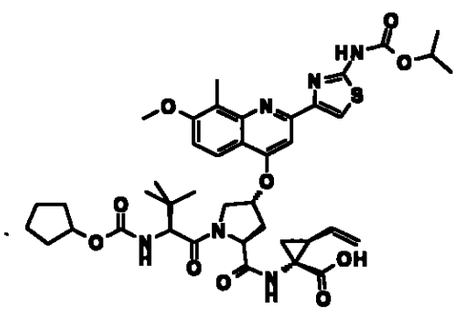


Compound 1022

Compound 1022:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 12.32 (s, 1H), 8.55 (s, 1H), 8.08-7.97 (m, 2H), 7.42 (br s, 1H), 7.29 (d, J = 9.2 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 5.79-5.66 (m, 1H), 5.44-5.37 (m, 1H), 5.24-5.15 (m, 1H), 5.09-5.02 (m, 1H), 4.75-4.67 (m, 1H), 4.43-4.32 (m, 2H), 4.16-3.95 (m, 2H), 3.94 (s, 3H), 3.29-3.18 (m, 2H), 2.59-2.48 (m, 1H), 2.34-2.20 (m, 3H), 2.06-1.98 (m, 1H), 1.81-1.16 (m, 19H), 1.18 (t, J = 7.2 Hz, 3H), 0.97 (s, 9H).

M.S.(electrospray) : 857.4 $(M-H)^-$ 859.5 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 98 %

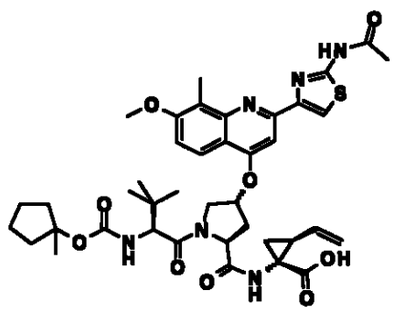


Compound 1046

Compound 1046:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 11.91 (br s, 1H), 8.56 (s, 1H), 8.08 (br s, 1H), 8.04 (d, J = 9.2 Hz, 1H), 7.43 (s, 1H), 7.30 (d, J = 9.0 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 5.78-5.66 (m, 1H), 5.46-5.38 (m, 1H), 5.23-5.15 (m, 1H), 5.09-5.03 (m, 1H), 5.03-4.93 (m, 1H), 4.71-4.62 (m, 1H), 4.47-4.32 (m, 2H), 4.15-4.08 (m, 1H), 4.05-3.95 (m, 1H), 3.94 (s, 3H), 2.59 (s, 3H), 2.58-2.47 (m, 1H), 2.31-2.20 (m, 1H), 2.07-1.97 (m, 1H), 1.81-1.22 (m, 10H), 1.29 (d, J = 6.3 Hz, 6H), 0.97 (s, 9H).

M.S.(electrospray) : 819.4 $(M-H)^-$ 821.4 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 99 %

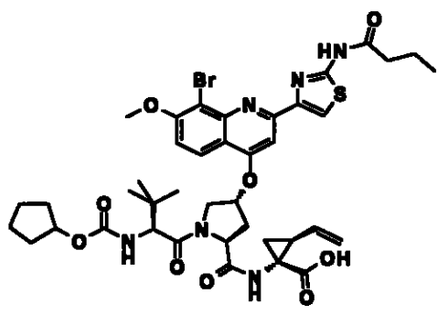


Compound 1036

Compound 1036:

^1H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 12.35 (s, 1H), 8.53 (s, 1H), 8.12-7.98 (m, 2H), 7.41 (s, 1H), 7.24 (d, J = 9.2 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 5.78-5.64 (m, 1H), 5.44-5.34 (m, 1H), 5.22-5.13 (m, 1H), 5.08-5.01 (m, 1H), 4.46-4.33 (m, 2H), 4.15-4.06 (m, 1H), 4.04-3.95 (m, 1H), 3.92 (s, 3H), 2.59 (s, 3H), 2.57-2.47 (m, 1H), 2.28-2.17 (m, 1H), 2.19 (s, 3H), 2.06-1.96 (m, 1H), 1.94-1.77 (m, 2H), 1.72-1.43 (m, 7H), 1.34 (s, 3H), 1.29-1.21 (m, 1H), 0.97 (s, 9H).

M.S.(electrospray) : 789.4 $(M-H)^-$ 791.4 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 95 %



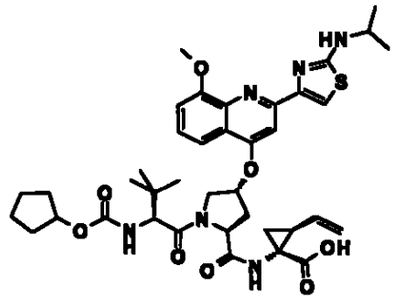
Compound 1056

Compound 1056:

^1H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 12.35 (s, 1H), 8.55 (s, 1H), 8.17 (d, J = 9.2 Hz, 1H), 8.05 (s, 1H), 7.47 (s, 1H), 7.35 (d, J = 9.4 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 5.78-5.66 (m, 1H), 5.46-

5.40 (m, 1H), 5.23-5.15 (m, 1H), 5.09-5.03 (m, 1H), 4.63-4.56 (m, 1H), 4.49-4.34 (m, 2H), 4.13-3.90 (m, under H2O, 2H), 4.01 (s, 3H), 2.60-2.51 (m, 1H), 2.49-2.43 (m, 2H), 2.32-2.21 (m, 1H), 2.07-1.98 (m, 1H), 1.81-1.37 (m, 9H), 1.36-1.16 (m, 3H), 0.96 (s, 9H), 0.93 (t, J = 7.4 Hz, 3H).

M.S.(electrospray) : 869.1 $(M-H)^-$ 871.1 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 98 %

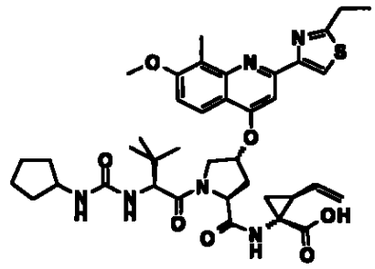


Compound 1181

Compound 1181:

^1H NMR (400 MHz, DMSO-d_6): δ 8.57 (s, 1H), 8.2-7.96 (m, 1H), 7.88-7.70 (m, 2H), 7.62-7.35 (m, 2H), 7.02 (d, J = 7.2 Hz, 1H), 5.78-5.65 (m, 1H), 5.65-5.55 (m, 1H), 5.19 (d, *J* = 17.2 Hz, 1H), 5.065 (d, *J* = 11.9 Hz, 1H), 4.63-4.52 (m, 1H), 4.50-4.40 (m, 1H), 4.13-4.08 (m, 2H), 4.06 (s, 3H), 3.98 (bd, J = 10 Hz, 1H), 3.92-3.80 (m, 1H), 2.62-2.53 (m, 1H), 2.38-2.27 (m, 1H), 2.02 (dd, *J* = 8.6, 8.6 Hz, 1H), 1.69-1.52 (m, 6H), 1.51-1.41 (m, 3H), 1.40-1.31 (m, 1H), 1.27 (d, J = 6.5 Hz, 6H), 0.97 (s, 9H).
MS (electrospray): $(M+H)^+$; 763.4 and $(M-H)^-$ 761.3.
Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 99%.

Compounds from Table 2

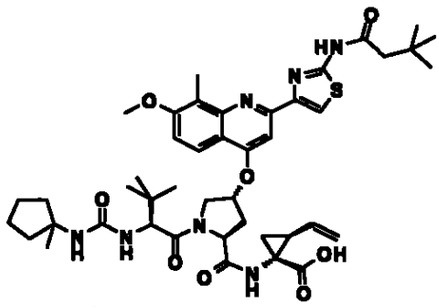


Compound 2010

Compound 2010:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 8:2 mixture of rotamers, major rotamer description; δ 8.56 (s, 1H), 8.41 (br s, 1H), 8.04 (d, J = 9.2 Hz, 1H), 7.55 (s, 1H), 7.29 (d, J = 9.2 Hz, 1H), 6.09-5.99 (m, 1H), 5.97-5.88 (m, 1H), 5.78-5.65 (m, 1H), 5.54-5.48 (m, 1H), 5.23-5.15 (m, 1H), 5.09-5.02 (m, 1H), 4.47-4.33 (m, 2H), 4.27-4.20 (m, 1H), 4.19-3.85 (m, under H2O, 2H), 3.94 (s, 3H), 3.13 (q, J = 7.5 Hz, 2H), 2.60 (s, 3H), 2.55-2.42 (m, 1H), 2.34-2.23 (m, 1H), 2.09-2.00 (m, 1H), 1.80-1.37 (m, 7H), 1.40 (t, J = 7.5 Hz, 3H), 1.31-1.05 (m, 3H), 0.96 (s, 9H).

M.S.(electrospray) : 745.4 $(M-H)^-$ 747.4 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 96 %

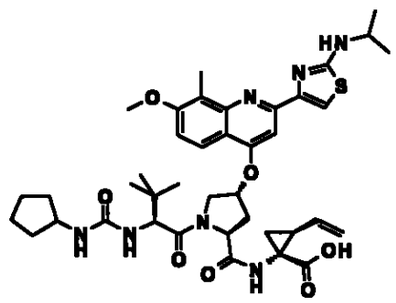


Compound 2012

Compound 2012:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 8:2 mixture of rotamers, major rotamer description; δ 12.29 (s, 1H), 8.54 (s, 1H), 8.08 (br s, 1H), 8.04 (d, J = 9.0 Hz, 1H), 7.44 (br s, 1H), 7.25 (d, J = 9.2 Hz, 1H), 6.08-5.90 (m, 2H), 5.80-5.65 (m, 1H), 5.45-5.37 (m, 1H), 5.22-5.13 (m, 1H), 5.09-5.02 (m, 1H), 4.48-4.34 (m, 2H), 4.26-4.19 (m, 1H), 4.04-3.90 (m, 1H), 3.93 (s, 3H), 2.60 (s, 3H), 2.68-2.57 (m, 1H), 2.42-2.35 (m, 2H), 2.28-2.18 (m, 1H), 2.08-1.98 (m, 1H), 1.81-1.21 (m, 10H), 1.19 (s, 3H), 1.04 (s, 9H), 0.96 (s, 9H).

M.S.(electrospray) : 844.5 $(M-H)^-$ 846.5 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 99 %

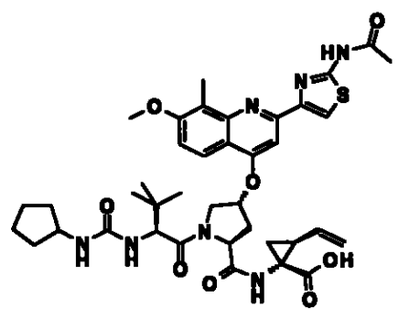


Compound 2002

Compound 2002:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 8:2 mixture of rotamers, major rotamer description; δ 8.57 (s, 1H), 8.28-7.77 (m, 3H), 7.66-7.30 (m, 2H), 6.09-5.98 (m, 1H), 5.96-5.86 (m, 1H), 5.78-5.66 (m, 1H), 5.61-5.48 (m, 1H), 5.26-5.15 (m, 1H), 5.11-5.03 (m, 1H), 4.53-4.39 (m, 2H), 4.25-4.15 (m, 1H), 4.05-3.93 (m, 1H), 3.97 (s, 3H), 3.92-3.50 (m, under H2O, 2H), 2.55 (s, 3H), 2.59-2.42 (m, 1H), 2.36-2.26 (m, 1H), 2.18-1.99 (m, 1H), 1.80-1.36 (m, 7H), 1.27 (d, J = 6.3 Hz, 6H), 1.31-1.05 (m, 3H), 0.95 (s, 9H).

M.S.(electrospray) : 774.4 $(M-H)^-$ 776.5 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 94 %

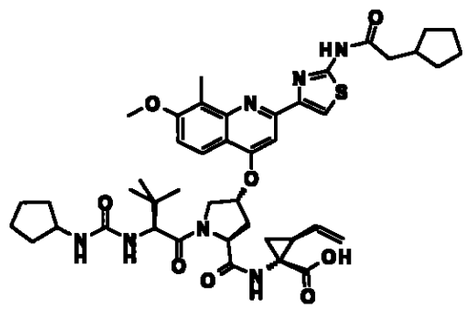


Compound 2007

Compound 2007:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 8:2 mixture of rotamers, major rotamer description; δ 12.38 (s, 1H), 8.55 (s, 1H), 8.09 (br s, 1H), 8.06 (d, J = 9.2 Hz, 1H), 7.44 (s, 1H), 7.28 (d, J = 9.2 Hz, 1H), 6.12-6.01 (m, 1H), 5.98-5.89 (m, 1H), 5.78-5.66 (m, 1H), 5.46-5.38 (m, 1H), 5.23-5.15 (m, 1H), 5.10-5.01 (m, 1H), 4.47-4.36 (m, 2H), 4.28-4.20 (m, 1H), 4.04-3.92 (m, 1H), 3.94 (s, 3H), 3.90-3.50 (m, under H2O, 1H), 2.60 (s, 3H), 2.55-2.47 (m, 1H), 2.31-2.22 (m, 1H), 2.20 (s, 3H), 2.08-1.99 (m,

1H), 1.81-1.38 (m, 7H), 1.31-1.09 (m, 3H), 0.96 (s, 9H).
M.S.(electrospray) : 774.4 $(M-H)^-$ 776.4 $(M+H)^+$. Reverse Phase HPLC
Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 94 %

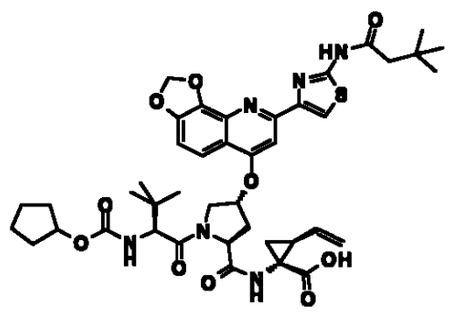


Compound 2008

Compound 2008:

^1H NMR (400 MHz, DMSO-d_6): ca, 8:2 mixture of rotamers, major rotamer description; δ 12.34 (br s, 1H), 8.55 (s, 1H), 8.17-8.05 (m, 1H), 8.07 (d, J = 9.2 Hz, 1H), 7.50-7.42 (m, 1H), 7.28 (d, J = 9.2 Hz, 1H), 6.11-6.01 (m, 1H), 5.98-5.88 (m, 1H), 5.78-5.66 (m, 1H), 5.46-5.38 (m, 1H), 5.24-5.14 (m, 1H), 5.10-5.01 (m, 1H), 4.48-4.36 (m, 2H), 4.28-4.20 (m, 1H), 4.07-3.95 (m, 1H), 3.94 (s, 3H), 3.80-3.65 (m, under H2O, 1H), 2.60 (s, 3H), 2.60-2.50 (m, 1H), 2.31-2.20 (m, 2H), 2.08-1.98 (m, 1H), 1.82-1.37 (m, 15H), 1.31-1.07 (m, 5H), 0.96 (s, 9H).
M.S.(electrospray) : 842.5 $(M-H)^-$ 844.5 $(M+H)^+$. Reverse Phase HPLC
Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 97 %

Compounds from Table 3



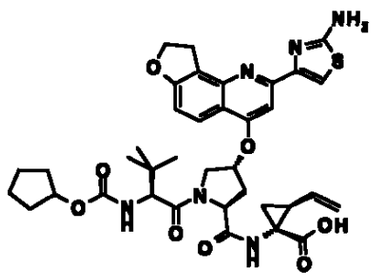
Compound 3002

Compound 3002:

^1H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer

127

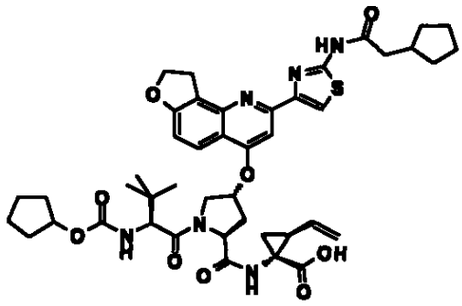
description; δ 12.33 (s, 1H), 8.55 (s, 1H), 7.98 (s, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.40 (s, 1H), 7.19 (d, J = 8.8 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 6.26 (s, 2H), 5.79-5.66 (m, 1H), 5.46-5.38 (m, 1H), 5.23-5.14 (m, 1H), 5.10-5.01 (m, 1H), 4.76-4.67 (m, 1H), 4.47-4.30 (m, 2H), 4.11 (d, J = 8.8 Hz, 1H), 4.00-3.91 (m, 1H), 2.41-2.36 (m, 2H), 2.29-2.19 (m, 1H), 2.08-1.97 (m, 1H), 1.82-1.22 (m, 11H), 1.03 (s, 9H), 0.96 (s, 9H). M.S.(electrospray) : 831.5 $(M-H)^-$ 833.6 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 99 %



Compound 3007

Compound 3007:

^1H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 8.56 (s, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.94-7.64 (m, 3H), 7.49-7.37 (m, 1H), 7.09 (d, J = 8.4 Hz, 1H), 7.00 (d, J = 8.6 Hz, 1H), 5.80-5.66 (m, 1H), 5.58-5.46 (m, 1H), 5.24-5.14 (m, 1H), 5.11-5.01 (m, 1H), 4.85-4.70 (m, 2H), 4.69-4.58 (m, 1H), 4.49-4.81 (m, 2H), 4.09 (d, J = 8.6 Hz, 1H), 4.00-3.88 (m, 1H), 3.75-3.30 (m, under H2O, 2H), 2.35-2.22 (m, 1H), 2.07-1.97 (m, 1H), 1.81-1.20 (m, 11H), 0.97 (s, 9H). M.S.(electrospray) : 731.3 $(M-H)^-$ 733.3 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 94 %



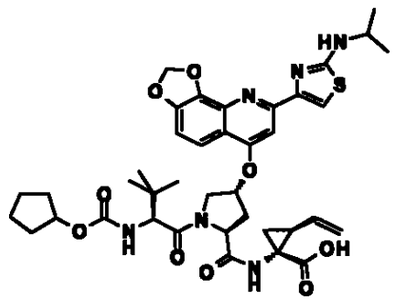
Compound 3010

425
128

Compound 3010:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 12.37 (s, 1H), 8.56 (s, 1H), 8.13-7.96 (m, 2H), 7.43 (s, 1H), 7.05 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 8.6 Hz, 1H), 5.80-5.64 (m, 1H), 5.50-5.37 (m, 1H), 5.24-5.11 (m, 1H), 5.10-4.98 (m, 1H), 4.83-4.63 (m, 3H), 4.47-4.30 (m, 2H), 4.19-4.05 (m, 1H), 4.04-3.86 (m, 1H), 3.75-3.30 (m, under H2O, 2H), 2.34-2.19 (m, 3H), 2.07-1.97 (m, 1H), 1.82-1.13 (m, 20H), 0.97 (s, 9H).

M.S.(electrospray) : 841.3 $(M-H)^-$ 843.4 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 99 %

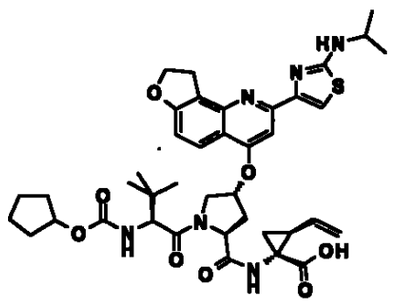


Compound 3001

Compound 3001:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 8.55 (s, 1H), 7.95-7.76 (m, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.49 (s, 1H), 7.41 (s, 1H), 7.18 (d, J = 8.6 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 6.25 (s, 2H), 5.80-5.65 (m, 1H), 5.52-5.46 (m, 1H), 5.24-5.14 (m, 1H), 5.10-5.01 (m, 1H), 4.75-4.66 (m, 1H), 4.48-4.39 (m, 1H), 4.37-4.27 (m, 1H), 4.17-4.07 (m, 1H), 4.01-3.92 (m, 1H), 3.90-3.75 (m, 1H), 2.62-2.44 (m, 1H), 2.31-2.20 (m, 1H), 2.09-1.97 (m, 1H), 1.81-1.20 (m, 10H), 1.25 (br d, J = 6.4 Hz, 6H), 0.96 (s, 9H).

M.S.(electrospray) : 775.5 $(M-H)^-$ 777.6 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 99 %



Compound 3004

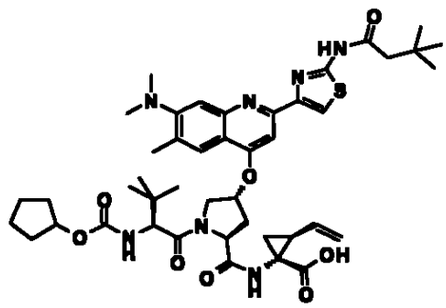
Compound 3004:

Mixture of rotamers (approx. 85:15), ^{1}H NMR of major rotamer given (400 MHz, DMSO-d_6): δ 8.57 (s, 1H); 8.10 – 8.13 (m, 1H); 8.08 (d, J = 8.8 Hz, 1H) 7.86 – 7.88 (m, 2H); 7.53 (s, 1H); 7.14 (d, J = 8.5 Hz, 1H); 7.00 (d, J = 8.5, 1H); 5.68 – 5.78 (m, 1H); 5.57 (s, 1H); 5.19 (d, J = 17.0 Hz, 1H); 5.07 (d, J = 11.9 Hz, 1H); 4.78 – 4.82 (m , 2H); 4.58 – 4.63 (m, 1H); 4.35 – 4.47 (m, 2H); 3.87 – 4.08 (m, 8H); 3.58 – 3.62 (m, 2H); 2.53 – 2.56 (m, 1H); 2.27 – 2.33 (m, 1H); 1.99 – 2.04 (m, 1H); 1.43 – 1.65 (m, 4H); 1.28 – 1.30 (m, 1H); 1.26 (d, J = 6.2 Hz, 6H); 0.96 (s, 9H).

M.S.(electrospray) : 775.4 $(M+H)^+$, 773.4 $(M-H)^-$.

Homogenelty (0.06 % TFA; CH_3CN : H_2O) : 98.8 %

Compounds from Table 4

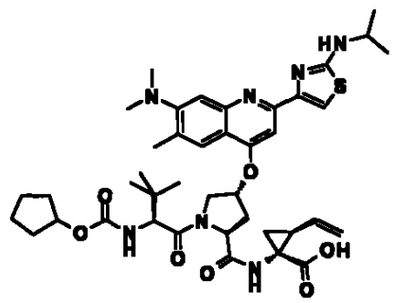


Compound 4005

Compound 4005:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 12.36 (br s, 1H), 8.57 (s, 1H), 8.60-8.20 (m, 1H), 7.90 (s, 1H), 7.68-7.45 (m, 2H), 6.99 (d, J = 8.3 Hz, 1H), 5.78-5.66 (m, 1H), 5.66-5.83 (m, 1H), 5.80-5.50 (m, 1H), 5.23-5.14 (m, 1H), 5.10-5.01 (m, 1H), 4.62-4.36 (m, 3H), 4.11-3.92 (m, 1H), 2.88 (s, 6H), 2.62-2.51 (m, 1H), 2.47 (s, 3H), 2.44-2.38 (m, 2H), 2.36-2.19 (m,

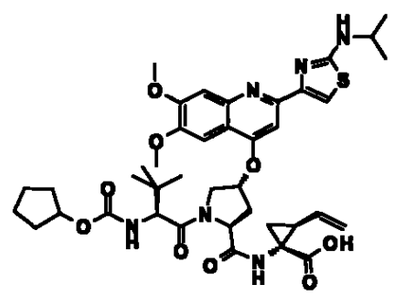
1H), 2.08-1.96 (m, 1H), 1.81-1.20 (m, 10H), 1.03 (s, 9H), 0.96 (s, 9H).
M.S.(electrospray) : 844.4 $(M-H)^-$ 846.5 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 99 %



Compound 4007

Compound 4007:

^1H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 8.59 (s, 1H), 8.27-8.12 (m, 1H), 8.06-7.97 (m, 1H), 7.89 (s, 1H), 7.73 (s, 1H), 7.64 (s, 1H), 6.99 (d, J = 8.5 Hz, 1H), 5.79-5.64 (m, 2H), 5.24-5.14 (m, 1H), 5.10-5.01 (m, 1H), 4.54-4.38 (m, 2H), 4.23-4.08 (m, 1H), 4.02 (d, J = 8.4 Hz, 1H), 4.00-3.91 (m, 1H), 3.70-3.30 (m, under H2O, 1H), 2.90 (s, 6H), 2.64-2.52 (m, 1H), 2.46 (s, 3H), 2.38-2.26 (m, 1H), 2.07-1.96 (m, 1H), 1.81-1.20 (m, 10H), 1.24 (br d, J = 6.5 Hz, 6H), 0.95 (s, 9H).
M.S.(electrospray) : 788.4 $(M-H)^-$ 790.5 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 98 %



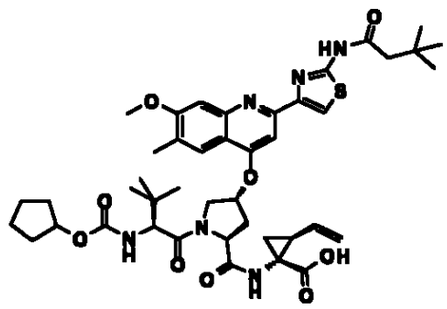
Compound 4014

Compound 4014:

^1H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 8.61 (s, 1H), 8.33-7.60 (m, 4H), 7.33 (s, 1H), 6.95 (d, J = 8.4 Hz, 1H),

5.79-5.67 (m, 2H), 5.24-5.16 (m, 1H), 5.10-5.03 (m, 1H), 4.57-4.32 (m, 2H), 4.20-3.88 (m, 3H), 3.99 (s, 3H), 3.93 (s, 3H), 3.65-3.30 (m, under H2O, 1H), 2.65-2.55 (m, 1H), 2.40-2.28 (m, 1H), 2.08-1.98 (m, 1H), 1.81-1.21 (m, 10H), 1.25 (br d, J = 6.5 Hz, 6H), 0.95 (s, 9H).

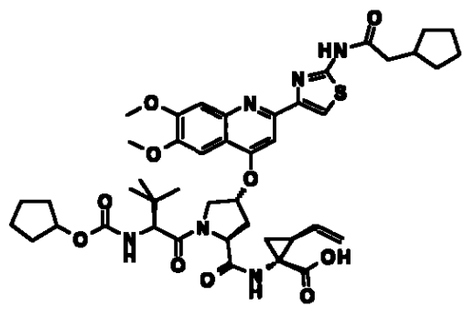
M.S.(electrospray) : 791.3 $(M-H)^-$ 793.4 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 86 %



Compound 4001

Compound 4001:

^1H NMR (400 MHz, DMSO-d_6): ca. 85:15 mixture of rotamers, major rotamer description; δ 12.40 (s, 1H), 8.58 (s, 1H), 8.50-8.20 (m, 1H), 7.95 (br s, 1H), 7.72-7.44 (m, 2H), 7.00 (d, J = 8.2 Hz, 1H), 5.80-5.67 (m, 1H), 5.67-5.51 (m, 1H), 5.24-5.14 (m, 1H), 5.12-5.02 (m, 1H), 4.63-4.45 (m, 2H), 4.45-4.36 (m, 1H), 4.14-3.93 (m, 2H), 3.99 (s, 3H), 2.64-2.46 (m, 1H), 2.45-2.39 (m, 2H), 2.35 (s, 3H), 2.39-2.28 (m, 1H), 2.08-1.98 (m, 1H), 1.82-1.23 (m, 10H), 1.04 (s, 9H), 0.97 (s, 9H).
M.S.(electrospray) : 831.4 $(M-H)^-$ 833.5 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 99 %



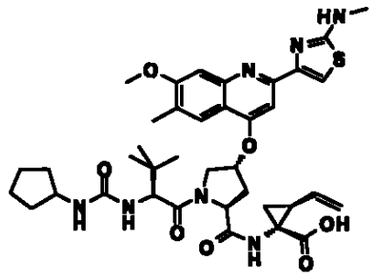
Compound 4013

Compound 4013:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 12.36 (s, 1H), 8.59 (s, 1H), 8.36-7.96 (m, 1H), 7.70-7.42 (m, 2H), 7.32 (s, 1H), 6.94 (d, J = 8.2 Hz, 1H), 5.79-5.66 (m, 1H), 5.63-5.50 (m, 1H), 5.23-5.15 (m, 1H), 5.10-5.02 (m, 1H), 4.58-4.45 (m, 2H), 4.38-4.28 (m, 1H), 4.12-3.90 (m, 2H), 3.97 (s, 3H), 3.91 (s, 3H), 2.62-2.52 (m, 1H), 2.37-2.21 (m, 3H), 2.08-1.98 (m, 1H), 1.77-1.14 (m, 19H), 0.97 (s, 9H).

M.S.(electrospray) : 859.4 $(M-H)^-$ 861.4 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 92 %

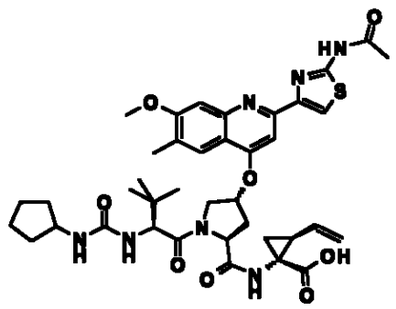
Compounds from Table 5



Compound 5001

Compound 5001:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 8.60 (s, 1H), 8.34-8.19 (m, 1H), 8.04-7.98 (m, 1H), 7.97 (s, 1H), 7.91-7.81 (m, 1H), 7.73 (s, 1H), 5.99-5.91 (m, 1H), 5.90-5.83 (m, 1H), 5.78-5.66 (m, 2H), 5.25-5.15 (m, 1H), 5.11-5.04 (m, 1H), 4.58-4.46 (m, 2H), 4.15-4.07 (m, 1H), 4.00 (s, 3H), 4.03-3.94 (m, 1H), 3.60-3.15 (m, under H2O, 1H), 3.05 (d, J = 4.3 Hz, 3H), 2.63-2.55 (m, 1H), 2.42-2.30 (m, 1H), 2.35 (m, 3H), 2.08-1.99 (m, 1H), 1.80-1.22 (m, 9H), 1.13-1.03 (m, 1H), 0.94 (s, 9H). M.S.(electrospray) : 746.3 $(M-H)^-$ 748.4 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 99 %

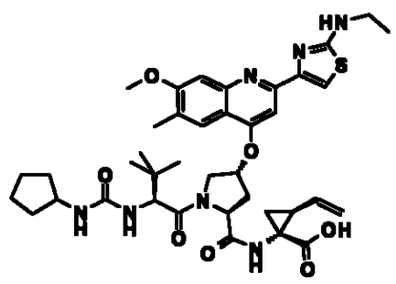


Compound 5002

Compound 5002:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 8:2 mixture of rotamers, major rotamer description; δ 12.44 (s, 1H), 8.59 (s, 1H), 8.52-8.25 (m, 1H), 7.97 (s, 1H), 7.70-7.46 (m, 2H), 6.03-5.96 (m, 1H), 5.90 (d, J = 9.2 Hz, 1H), 5.79-5.66 (m, 1H), 5.64-5.54 (m, 1H), 5.24-5.16 (m, 1H), 5.11-5.04 (m, 1H), 4.55-4.43 (m, 2H), 4.19-4.12 (m, 1H), 4.05-3.94 (m, 1H), 3.99 (s, 3H), 3.80-3.30 (m, under H2O, 1H), 2.68-2.54 (m, 1H), 2.39-2.28 (m, 1H), 2.35 (s, 3H), 2.23 (s, 3H), 2.08-1.99 (m, 1H), 1.80-1.21 (m, 8H), 1.17-1.07 (m, 1H), 1.06-0.95 (m, 1H), 0.95 (s, 9H).

M.S.(electrospray) : 774.4 $(M-H)^-$ 776.4 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 99 %



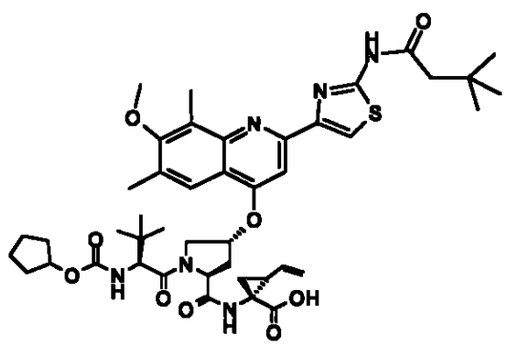
Compound 5004

Compound 5004:

^{1}H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 8.60 (s, 1H), 8.31-8.16 (m, 1H), 8.11-8.02 (m, 1H), 7.97 (s, 1H), 7.89-7.78 (m, 1H), 7.75-7.67 (m, 1H), 6.00-5.92 (m, 1H), 5.90-5.83 (m, 1H), 5.80-5.65 (m, 2H), 5.26-5.16 (m, 1H), 5.11-5.04 (m, 1H), 4.58-4.46 (m, 2H), 4.11 (d, J = 9.2 Hz, 1H), 4.05-3.94 (m, 1H), 4.00 (s, 3H), 3.65-3.15 (m, under H2O, 3H), 2.69-2.54 (m, 1H), 2.42-2.30 (m, 1H), 2.35 (s, 3H), 2.08-1.99 (m, 1H), 1.80-1.21 (m, 8H), 1.24 (t, J

= 7.0 Hz, 3H), 1.14-1.02 (m, 1H), 1.00-0.87 (m, 1H), 0.94 (s, 9H).
M.S.(electrospray) : 760.4 $(M-H)^-$ 762.4 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 96 %

Compounds from Table 6



Compound 6016

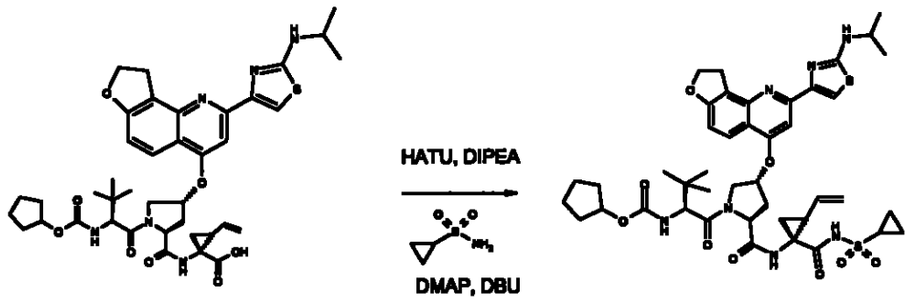
Compound 6016:

^1H NMR (400 MHz, DMSO-d_6): ca, 85:15 mixture of rotamers, major rotamer description; δ 12.28 (s, 2H); 8.56 (s, 1H); 8.04 (s, 1H) 7.79 (s, 1H); 7.46 (s, 1H); 6.96 – 7.00 (m, 1H); 5.68 – 5.75 (m, 1H); 5.40 (s, br, 1H); 5.19 (d, J = 17.0 Hz, 1H); 5.06 (d, J = 10.1 Hz, 1H); 4.71 – 4.76 (m , 2H); 4.43 (t, J = 8.3, 1H); 4.32 – 4.34 (m, 1H); 4.13 (d, J = 8.3 Hz, 1H); 3.96 – 4.03 (m, 1H); 3.77 (s, 3H); 2.67 (s, 3H); 2.40 (d, J = 4.1 Hz, 3H); 2.24 – 2.36 (m, 3H); 2.03 (q, J = 8.6 Hz, 1H); 1.17 - 1.75 (m, 10H); 1.04 (s, 9H); 0.98 (s, 9H).
M.S.(electrospray) : 845.4 $(M-H)^-$ 847.5 $(M+H)^+$. Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O) : 96.7 %

Synthesis of compounds of formula I wherein R^C is $NHSO_2R^B$:

EXAMPLE 17A

Synthesis of Compound 7001:



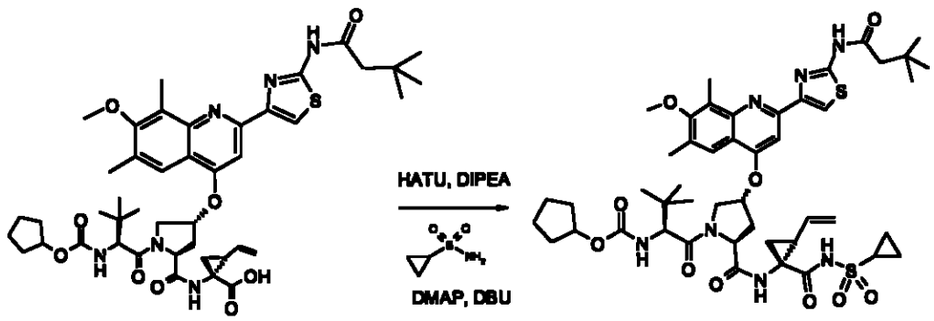
17A1 17A2

HATU (20 mg, 0.05 mmol) was added to a solution of compound **17A1** (Compound 3004, Table 3; 20 mg, 0.03 mmol) and DIPEA (0.03 mL, 0.16 mmol) in DMF (1.5 mL) at RT. The solution was stirred for 1h followed by the addition of DMAP (16 mg, 0.13 mmol) and cyclopropanesulfonamide (7.0 mg, 0.06 mmol). After addition was complete, the mixture was allowed to stir for 15 min and DBU (0.02 mL, 0.14 mmol) was added dropwise. The resulting solution was stirred for 16 h at 23°C, then diluted with DMSO to 2.5 mL total volume and purified by prep HPLC (H_2O/CH_3CN + 0.06% TFA). The fractions containing the pure product were combined and the solvents removed by lyophilization to yield **17A2** as a yellow solid (Compound 7001, table 7, 5.4 mg, 23 %).

Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O): 98.9% (220 nm). MS: 878.8 $(M+H)^+$, 876.4 $(M-H)^-$. ^1H NMR (400 MHz, DMSO-d_6): δ 10.47 (s, 1H); 8.82 (s, 1H); 8.06 (s, br, 1H); 7.52 (s, br, 1H); 7.15 (m, 1H); 7.03 (d, J = 8.0 Hz, 1H); 5.58 (m, 2H); 5.20 (d, J = 17.0 Hz, 1H); 5.09 (d, J = 11.5, 1H); 4.79 (m, 2H); 4.64 (m, 1H); 4.36 – 4.52 (m, 2H); 4.06 (d, J = 8.0 Hz, 1H); 4.00 – 4.03 (m, 1H); 2.88 – 2.96 (m, 1H); 2.54 – 2.57 (m, 1H); 2.10 – 2.20 (m, 2H); 1.32 – 1.71 (m, 11H); 1.24 (dd, J = 6.3, 1.2 Hz, 6H); 1.00 – 1.08 (m, 8 H); 0.97 (s, 9H).

EXAMPLE 17B

Synthesis of Compound 7002:



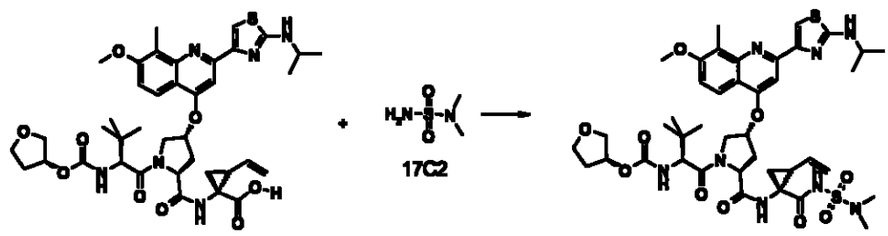
17B1 17B2

Using the procedure of Example 17A but starting with compound 17B1 (Compound 6016, Table 6), compound **17B2** (Compound 7002, Table 7) was prepared as a light yellow solid (5.4 mg, 16% yield).

Reverse Phase HPLC Homogeneity (0.06 % TFA; CH_3CN : H_2O): 93.1 % (220 nm). MS: 950.4 $(M+H)^+$, 948.4 $(M-H)^-$. ^1H NMR (400 MHz, DMSO-d_6): δ 12.26 (s, 1H); 10.48 (s, 1H); 8.83 (s, 1H); 8.02 (s, 1H); 7.79 (s, 1H); 7.45 (s, 1H); 6.94 – 7.00 (m, 1H); 5.56 – 5.65 (m, 1H); 5.40 (s, 1H); 5.19 (d, J = 16.9, 1H); 5.07 (d, J = 11.4, 1H); 4.77 (s, 1H); 4.33 – 4.42 (m, 2H); 4.11 (d, J = 8.0 Hz, 1H); 3.97 (d, J = 9.6, 1H); 3.76 (s, 3H); 3.76 (s, 3H); 2.88 – 2.96 (m, 1H); 2.66 (s, 3H); 2.53 – 2.60 (m, 1H); 2.31 – 2.33 (m, 1H); 2.11 – 2.19 (m, 2H); 1.33 – 1.70 (m, 12H); 1.22 (s, br, 1H); 1.05 – 1.08 (m, 2H); 1.02 (s, 9H); 0.98 (s, 9H).

EXAMPLE 17C

Synthesis of Compound 7003:



17C1 17C2 17C3

Compound **17C1** (Compound 1027, Table 1; 35 mg, 0.045 mmol), N,N-dimethylsulfamide **17C2** (22.3 mg, 0.180 mmol) DIPEA (39.3 µl, 0.225 mmol) and DMAP (22 mg, 0.180 mmol) were dissolved in DMF (2.5 mL) and to the mixture was added DBU (28.5 µl, 0.203 mmol). The reaction mixture was stirred for 5 min, then HATU (18.8 mg, 0.05 mmol) was added. Stirring was continued for 12h and the

residue was filtered through Millex filter and purified by Prep HPLC (Combiscreen ODS-AQ, 20 x 50mm). The pure fractions were pooled together and lyophilized to afford 14 mg (yield, 35%) of compound 17C3 (Compound 7003, Table 7) as a yellow solid.

^{1}HNMR (400MHz, DMSO-d_6): δ 10.23 (s, 1H), 8.74 (s, 1H), 8.07 (d, J=8Hz, 1H), 7.59 (s, 1H), 7.45-7.30 (m, 1H), 7.27 (d, J=8Hz, 1H), 5.53-5.49 (m, 2H), 5.20 (d, J= 17Hz, 1H), 5.10 (d, J=12Hz, 1H), 4.70 (bs, 1H), 4.50-4.30 (m, 3H), 4.15-4.05 (m, 2H), 3.97 (s, 3H), 2.76 (s, 6H), 2.55 (s,3H), 2.38-2.32 (m,1H), 2.23-2.08 (m, 2H), 1.97-1.81 (m, 1H), 1.75-1.45 (m,4H), 1.32-1.14 (m,9H), 1.04-0.86 (m, 11H).

EIMS: (M+H) = 885.4, (M-H) = 883.4

EXAMPLE 18

NS3-NS4A protease assay

The enzymatic assay used to evaluate the present compound is described in WO 00/09543 and WO 00/59929.

EXAMPLE 19

Cell Based HCV RNA Replication Assay

Cell Culture

Huh7 cells that stably maintain a subgenomic HCV replicon were established as previously described (Lohman et al., 1999. Science 285: 110-113) and designated as the S22.3 cell-line. S22.3 cells are maintained in Dulbecco's Modified Earle Medium (DMEM) supplemented with 10% FBS and 1 mg/mL neomycin (Standard Medium). During the assay, DMEM medium supplemented with 10% FBS, containing 0.5% DMSO and lacking neomycin was used (Assay Medium). 16 hours prior to compound addition, S22.3 cells are trypsinized and diluted to 50 000 cells/mL in Standard Medium. 200 µL (10 000 cells) are distributed into each well of a 96-well plate. The plate was then incubated at 37°C with 5% CO_2 until the next day.

Reagents and Materials:

Product	Company	Catalog #	Storage
DMEM	Wisent Inc.	10013CV	4°C
DMSO	Sigma	D-2650	R.T.

Dulbecco's PBS	Gibco-BRL	14190-136	R.T.
Fetal Bovine Serum	Bio-Whittaker	14-901F	-20°C/4°C
Neomycin (G418)	Gibco-BRL	10131-027	-20°C/4°C
Trypsin-EDTA	Gibco-BRL	25300-054	-20°C/4°C
96-well plates	Costar	3997	R.T.
PVDF 0.22 µm Filter Unit	Millipore	SLGV025LS	R.T.
Deep-Well Titer Plate Polypropylene	Beckman	267007	R.T.

Preparation of Test Compound

10 µL of test compound (in 100% DMSO) was added to 2 mL of Assay Medium for a final DMSO concentration of 0.5% and the solution was sonicated for 15 min and filtered through a 0.22 µM Millipore Filter Unit. 900 µL was transferred into row A of a Polypropylene Deep-Well Titer Plate. Rows B to H contain 400 µL aliquots of Assay Medium (containing 0.5% DMSO), and are used to prepare serial dilutions (1/2) by transferring 400 µL from row to row (no compound was included in row H).

Application of test compound to cells

Cell culture medium was aspirated from the 96-well plate containing the S22.3 cells. 175 µL of assay medium with the appropriate dilution of test compound was transferred from each well of the compound plate to the corresponding well of the cell culture plate (row H was used as the "No inhibition control"). The cell culture plate was incubated at 37°C with 5% CO_2 for 72 h.

Extraction of Total Cellular RNA

Following the 72 h incubation period, the total cellular RNA was extracted from the S22.3 cells of the 96-well plate using the RNeasy 96 kit (Qiagen®, RNeasy Handbook. 1999.). Briefly, assay medium was completely removed from cells and 100 µL of RLT buffer (Qiagen®) containing 143 mM β-mercaptoethanol was added to each well of the 96-well cell-culture plate. The microplate was gently shaken for 20 sec. 100 µL of 70% ethanol was then added to each microplate well, and mixed by pipetting. The lysate was removed and applied to the wells of a RNeasy 96 (Qiagen®) plate that was placed on top of a Qiagen® Square-Well Block. The RNeasy 96 plate was sealed with tape and the Square-Well Block with the RNeasy

96 plate was loaded into the holder and placed in a rotor bucket of a 4K15C centrifuge. The sample was centrifuged at 6000 rpm (~5600 x g) for 4 min at room temperature. The tape was removed from the plate and 0.8 mL of Buffer RW1 (Qiagen® RNeasy 96 kit) was added to each well of the RNeasy 96 plate. The RNeasy 96 plate was sealed with a new piece of tape and centrifuged at 6000 rpm for 4 min at room temperature. The RNeasy 96 plate was placed on top of another clean Square-Well Block, the tape removed and 0.8 mL of Buffer RPE (Qiagen® RNeasy 96 kit) was added to each well of the RNeasy 96 plate. The RNeasy 96 plate was sealed with a new piece of tape and centrifuged at 6000 rpm for 4 min at room temperature. The tape was removed and another 0.8 mL of Buffer RPE (Qiagen® RNeasy 96 kit) was added to each well of the RNeasy 96 plate. The RNeasy 96 plate was sealed with a new piece of tape and centrifuged at 6000 rpm for 10 min at room temperature. Tape was removed, the RNeasy 96 plate was placed on top of a rack containing 1.2-mL collection microtubes. The RNA was eluted by adding 50 µL of RNase-free water to each well, sealing plate with a new piece of tape and incubated for 1 min at room temperature. The plate was then centrifuged at 6000 rpm for 4 min at room temperature. The elution step was repeated with a second volume of 50 µL RNase-free water. The microtubes with total cellular RNA are stored at –70°.

Quantification of Total Cellular RNA

RNA was quantified on the STORM® system (Molecular Dynamics®) using the RiboGreen® RNA Quantification Kit (Molecular Probes®). Briefly, the RiboGreen reagent was diluted 200-fold in TE (10 mM Tris-HCl pH =7.5, 1 mM EDTA). Generally, 50 µL of reagent was diluted in 10 mL TE. A Standard Curve of ribosomal RNA was diluted in TE to 2 µg/mL and pre-determined amounts (100, 50, 40, 20, 10, 5, 2 and 0 µL) of the ribosomal RNA solution are then transferred in a new 96-well plate (COSTAR # 3997) and the volume was completed to 100 µL with TE. Generally, column 1 of the 96-well plate was used for the standard curve and the other wells are used for the RNA samples to be quantified. 10 µL of each RNA sample that was to be quantified, was transferred to the corresponding well of the 96-well plate and 90 µL of TE was added. One volume (100 µL) of diluted RiboGreen reagent was added to each well of the 96-well plate and incubated for 2 to 5 minutes at room temperature, protected from light (a 10 µL RNA sample in a

200 µL final volume generates a 20X dilution). The fluorescence intensity of each well was measured on the STORM® system (Molecular Dynamics®). A standard curve was created on the basis of the known quantities of the ribosomal RNA and the resulting fluorescent intensities. The RNA concentration in the experimental samples was determined from the standard curve and corrected for the 20X dilution.

Reagents and Materials:

Product	Company	Catalog #	Storage
DEPC	Sigma	D5758	4°C
EDTA	Sigma	E5134	R.T.
Trizma-Base	Sigma	T8524	R.T.
Trizma-HCl	Sigma	T7149	R.T.
Collection Tube Strips	Qiagen	19582	R.T.
Ribogreen RNA Quantitation Kit	Molecular Probe	R11490	-20°C
Rneasy 96 Kit	Qiagen	74183	R.T.
Square-Well Blocks	Qiagen	19573	R.T.

Real-Time R.T.-PCR

The Real-Time R.T.-PCR was performed on the ABI Prism 7700 Sequence Detection System using the TaqMan EZ R.T.-PCR Kit from (Perkin-Elmer Applied Biosystems®). R.T.-PCR was optimized for the quantification of the 5' IRES of HCV RNA by using the Taqman technology (Roche Molecular Diagnostics Systems) similar to the technique previously described (Martell et al., 1999. J. Clin. Microbiol. 37: 327-332). The system exploits the 5'-3' nucleolytic activity of AmpliTaq DNA polymerase. Briefly, the method utilizes a dual-labeled fluorogenic hybridization probe (PUTR Probe) that specifically anneals to the template between the PCR primers (primers 8125 and 7028). The 5' end of the probe contains a fluorescent reporter (6-carboxyfluorescein [FAM]) and the 3' end contains a fluorescent quencher (6-carboxytetramethylrhodamine [TAMRA]). The FAM reporter's emission spectrum was suppressed by the quencher on the intact hybridization probe. Nuclease degradation of the hybridization probe releases the reporter, resulting in an increase in fluorescence emission. The ABI Prism 7700 sequence detector measures the increase in fluorescence emission continuously during the PCR amplification such that the amplified product was directly proportion to the signal.

The amplification plot was analysed early in the reaction at a point that represents the logarithmic phase of product accumulation. A point representing a defined detection threshold of the increase in the fluorescent signal associated with the exponential growth of the PCR product for the sequence detector was defined as the cycle threshold (C_T). C_T values are inversely proportional to the quantity of input HCV RNA; such that under identical PCR conditions, the larger the starting concentration of HCV RNA, the lower the C_T. A standard curve was created automatically by the ABI Prism 7700 detection system by plotting the C_T against each standard dilution of known HCV RNA concentration.

Reference samples for the standard curve are included on each R.T.-PCR plate. HCV Replicon RNA was synthesized (by T7 transcription) *in vitro*, purified and quantified by OD_{260}. Considering that 1 µg of this RNA = 2.15 X 10^{11} RNA copies, dilutions are made in order to have 10^8, 10^7, 10^6, 10^5, 10^4, 10^3 or 10^2 genomic RNA copies / 5 µL. Total cellular Huh-7 RNA was also incorporated with each dilution (50 ng / 5 µL). 5 µL of each reference standard (HCV Replicon + Huh-7 RNA) was combined with 45 µL of Reagent Mix, and used in the Real-Time R.T.-PCR reaction.

The Real-Time R.T.-PCR reaction was set-up for the experimental samples that were purified on RNeasy 96 –well plates by combining 5 µL of each total cellular RNA sample with 45 µL of Reagent Mix.

Reagents and Materials:

Product	COMPANY	Catalog #	Storage
TaqMan EZ R.T.-PCR Kit	PE Applied Biosystems	N808-0236	-20°C
MicroAmp Optical Caps	PE Applied Biosystems	N801-0935	R.T.
MicroAmp Optical 96-Well Reaction Plate	PE Applied Biosystems	N801-0560	R.T.

Reagent Mix preparation:

Component	Volume for one sample (µL)	Volume for One Plate (µL) (91 samples + Dead Volume)	Final conc.
Rnase-free water	16.5	1617	

5X TaqMan EZ buffer	10	980	1X
$Mn(OAc)_2$ (25 mM)	6	588	3 mM
dATP (10 mM)	1.5	147	300 µM
dCTP (10 mM)	1.5	147	300 µM
dGTP (10 mM)	1.5	147	300 µM
dUTP (20 mM)	1.5	147	600 µM
Forward Primer (10 µM)	1	98	200 nM
Reverse Primer (10 µM)	1	98	200 nM
PUTR probe (5 µM)	2	196	200 nM
rTth DNA polymerase (2.5 U/µL)	2	196	0.1 U/µL
AmpErase UNG (1U/µL)	0.5	49	0.01 U/µL
Total Volume	45	4410	

Forward Primer Sequence (SEQ ID. 1): 5' - ACG CAG AAA GCG TCT AGC CAT GGC GTT AGT - 3'

Reverse Primer Sequence (SEQ ID NO. 2): 5' - TCC CGG GGC ACT CGC AAG CAC CCT ATC AGG - 3'

Note: Those primers amplify a region of 256-nt present within the 5' untranslated region of HCV.

PUTR Probe Sequence (SEQ ID NO. 3): 6FAM - TGG TCT GCG GAA CCG GTG AGT ACA CC - TAMRA

No Template Controls (NTC): On each plate, 4 wells are used as "NTC". For these controls, 5 µL of water are added to the well in place of RNA.

Thermal Cycling Conditions:

50°C 2 min
60°C 30 min
95°C 5 min

95°C 15 sec
60°C 1 min } for 2 cycles

90°C 15 sec
60°C 1 min } for 40 cycles

Following the termination of the R.T.-PCR reaction the data analysis requires setting of threshold fluorescence signal for the PCR plate and a standard curve was constructed by plotting the C_T value versus RNA copy number used in each reference reaction. The C_T values obtained for the assay samples are used to interpolate an RNA copy number based on the standard curve.
Finally, the RNA copy number was normalized (based on the RiboGreen RNA quantification of the total RNA extracted from the cell culture well) and expressed as genome equivalents / µg of total RNA [g.e./µg].

The RNA copy number [g.e./µg] from each well of the cell culture plate was a measure of the amount of replicating HCV RNA in the presence of various concentrations of inhibitor. The % Inhibition was calculated with the following equation:

100 - [(g.e./µg inh)/(g.e./µg ctl)x 100].

A non-linear curve fit with the Hill model was applied to the inhibition-concentration data, and the 50% effective concentration (EC_{50}) was calculated by the use of SAS software (Statistical Software System; SAS Institute, Inc. Cary, N.C.).

When the compounds of this invention are evaluated in the preceding enzymatic and cell based assays, the compounds are found to be highly active.

EXAMPLE 20

Specificity assays

The specificity assays used to evaluate the selectivity of this compound are described in WO 00/09543.
When the compounds were evaluated in the specificity assays, the compounds of

formula 1 were found to be selective in that they do not show significant inhibition (no measurable activity at concentrations up to 30 μM) in the Human Leukocyte Elastase and Cathepsin B assays.

EXAMPLE 21

Pharmacokinetic properties

The present invention comprises compounds that show pharmacokinetic properties such as detectable plasma levels in the rat at 1 hour and 2 h after an oral dose of 5 mg/kg.

More explicitly, the following assay, an *in vivo* oral absorption screen, is used to determine plasma levels of test compounds in a rat after oral administration:

Materials and Methods:

1. **Method used to pool compounds ("cassette selection"):**

The selection of compounds to be pooled into a "cassette" was based on their structural similarity and physicochemical properties. A solid phase extraction method applicable to all the selected compounds was established. Based on the initial testing where each compound was spiked into rat plasma and run through HPLC or HPLC/MS at a concentration of 0.5 μM, the retention time, ionic mass, and the possible separation among compounds by HPLC and/or HPLC/MS were used as basis for pooling 3-4 compounds into one "cassette".

2. **Oral vehicle and compound preparation:**

Each "cassette" contains 3-4 compounds at 5 or 4 mg/kg for each compound. The cassettes were prepared as an oral suspension in 0.5% aqueous methylcellulose and 0.3% of polyoxyethylene (20) sorbitan monooleate (Tween-80). The dosing volume was 10 mL/kg via oral gavage.

3. **Dosing and plasma sampling:**

Male Sprague Dawley rats were fasted overnight in individual cages, with access to aqueous 10% dextrose. Two rats were dosed with each "cassette". Plasma samples (~1 mL) were collected at 1 and 2 h post-dosing from the 2 rats and pooled for extraction and analysis.

4. Compound extraction and analysis:

From each cassette, plasma samples at 1 and 2 h, blank plasma, blank plasma spiked with all the compounds at 0.5 µM of each, are extracted by the solid phase extraction method. Samples were analyzed by HPLC and HPLC/MS for comparison purpose. Plasma concentrations are estimated based on the single concentration of 0.5 µM standard.

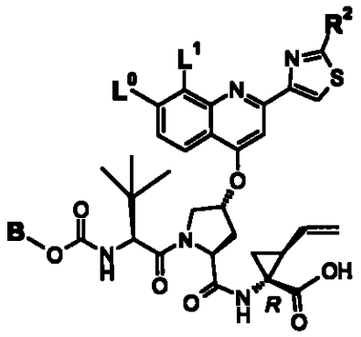
Results

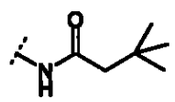
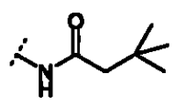
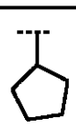
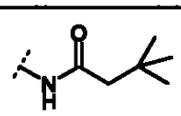
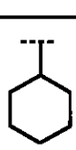
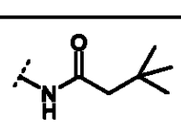
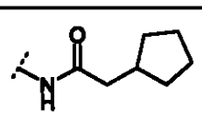
When assayed in the preceding screen, some compounds of this invention are found in the plasma at the 1 hour and 2 hour intervals following oral administration, with blood plasma levels up to 1.5 µM.

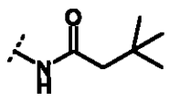
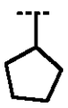
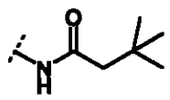
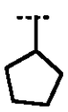
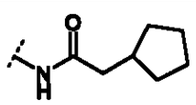
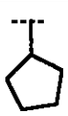
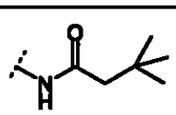
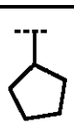
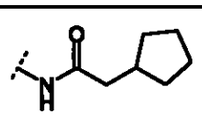
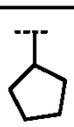
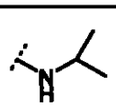
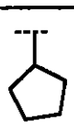
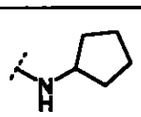
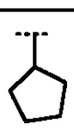
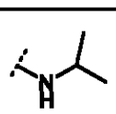
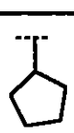
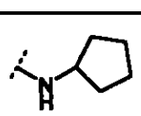
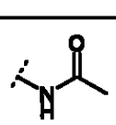
TABLES OF COMPOUNDS

In the following examples of compounds according to this invention are listed in the Tables 1 to 7, wherein Me defines methyl, Et defines ethyl and tBu defines *tert*-butyl. Compounds according to this invention usually show IC_{50} values lower than about 200 nM and EC_{50} values lower than about 300 nM.

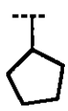
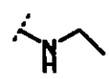
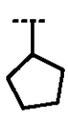
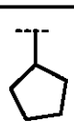
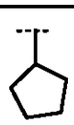
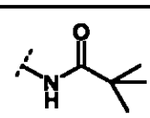
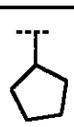
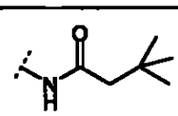
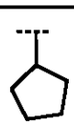
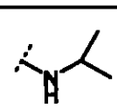
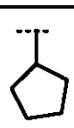
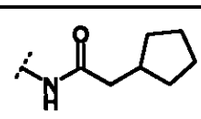
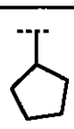
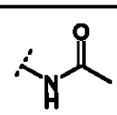
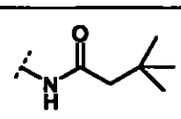
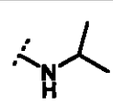
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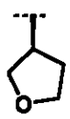
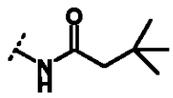
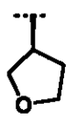
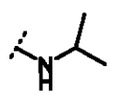
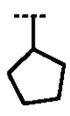
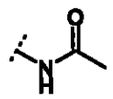
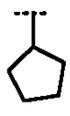
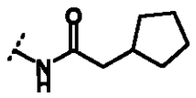
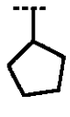
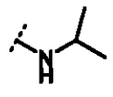
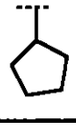
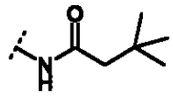
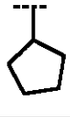
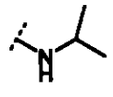
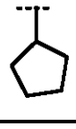
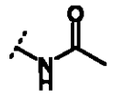
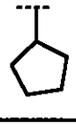
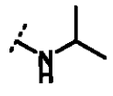
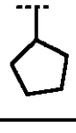
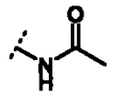


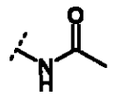
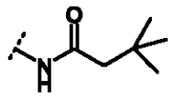
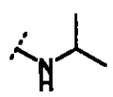
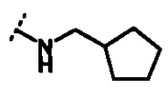
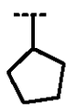
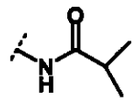
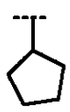
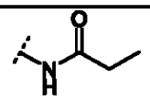
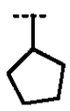
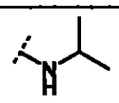
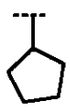
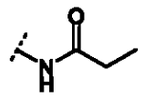
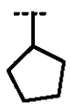
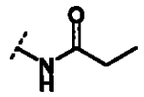
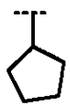
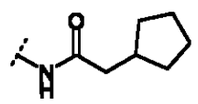
Cpd.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1001		MeO-	MeO-		837.3
1002		MeO-	MeO-		835.3
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1004		MeO-	MeO-		863.4
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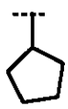
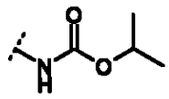
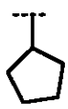
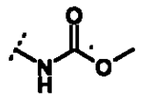
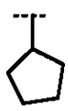
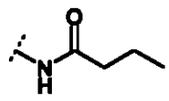
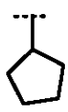
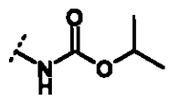
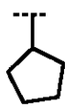
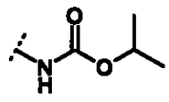
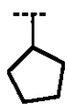
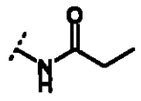
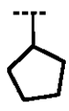
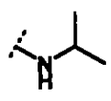
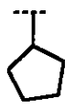
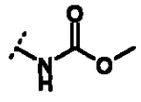
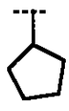
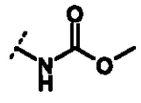
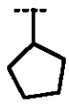
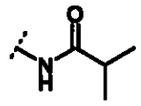
Cpd.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1006		MeO-	Me-		819.5
1007		MeO-	Me-		833.5
1008		MeO-	Me-		845.5
1009		Me_2N-	Me-		846.5
1010		Me_2N-	Me-		858.5
1011		Me_2N-	Me-		790.5
1012		Me_2N-	Me-		816.5
1013		MeO-	Me-		777.5
1014		MeO-	Me-		803.5
1015		MeO-	Me-		777.5

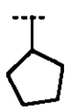
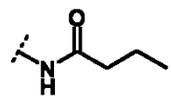
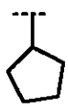
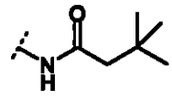
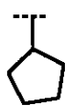
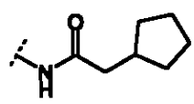
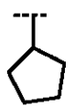
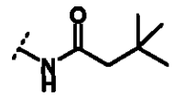
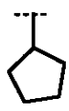
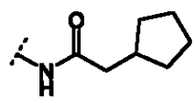
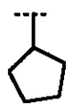
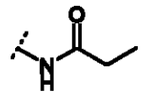
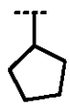
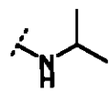
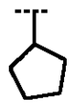
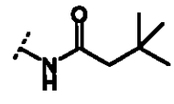
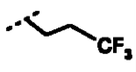
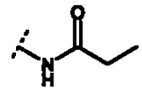
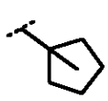
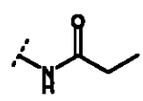
148

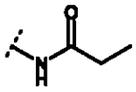
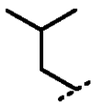
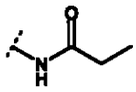
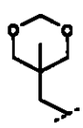
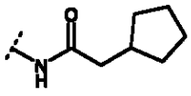
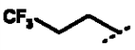
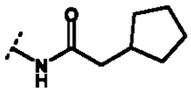
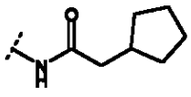
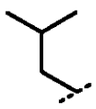
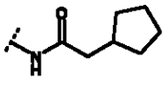
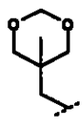
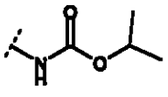
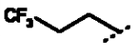
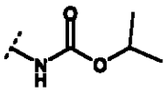
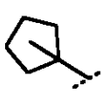
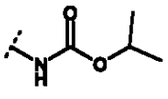
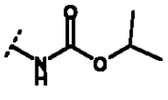
Cpd.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1016		MeO-	Me-		763.5
1017		MeO-	Me-		749.5
1018		MeO-	Me-		735.4
1019		MeO-	Me-		819.4
1020		MeO-	Et-		847.5
1021		MeO-	Et-		791.4
1022		MeO-	Et-		859.5
1023		MeO-	Et-		791.4
1024		MeO-	Me-		811.4
1025		MeO-	Me-		755.5

Cpd.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1026		MeO-	Me-		835.4
1027		MeO-	Me-		779.3
1028		MeO-	Br-		841.3 843.2
1029		MeO-	Br-		911.3 909.3
1030		MeO-	Br-		841.3 843.3
1031		MeO-	Br-		897.3 899.3
1032		tBuO-	Me-		819.4
1033		tBuO-	Me-		819.4
1034		HO-	Me-		763.4
1035		HO-	Me-		763.3

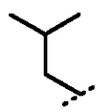
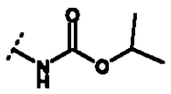
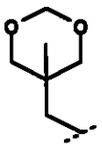
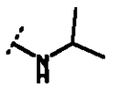
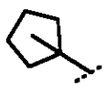
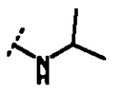
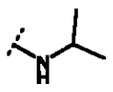
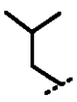
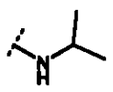
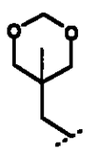
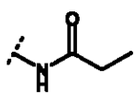
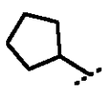
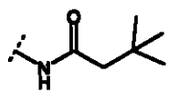
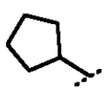
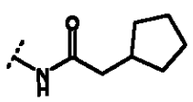
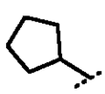
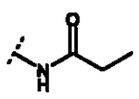
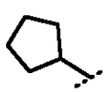
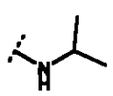
Cpd.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1036		MeO-	Me-		791.4
1037		MeO-	Me-		847.5
1038		MeO-	Me-		791.5
1039		MeO-	Me-		859.5
1040		MeO-	Me-		805.4
1041		MeO-	Me-		791.4
1042		MeO-	Cl		797.4 799.3
1043		MeO-	Br		855.2 857.2
1044		MeO-	Cl		811.3 813.3
1045		MeO-	Cl		865.4 867.4

Cpd.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1046		MeO-	Me-		821.4
1047		MeO-	Me-		793.4
1048		MeO-	Cl		825.3 827.3
1049		MeO-	Br		885.3 887.3
1050		MeO-	Cl		841.3 843.3
1051		MeO-	F		795.3
1052		MeO-	F		781.3
1053		MeO-	Cl		813.2 815.2
1054		MeO-	Br		857.2 859.2
1055		MeO-	Br		869 871.1

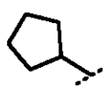
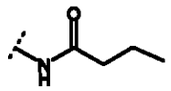
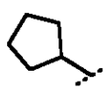
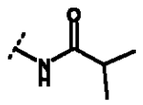
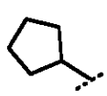
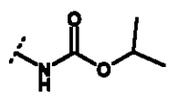
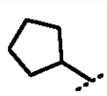
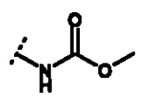
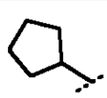
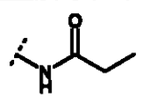
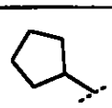
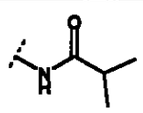
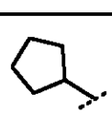
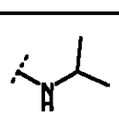
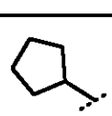
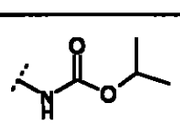
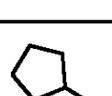
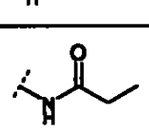
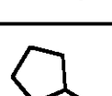
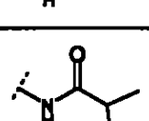
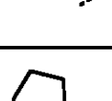
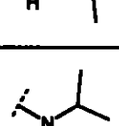
Cpd.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1056		MeO-	Br		869 871.1
1057		HO	Me		819.2
1058		HO	Me		831.2
1059		H	Br		867 869
1060		H	Br		879 881
1061		H	Br		825 827
1062		H	Br		811 813
1063		F	Me		821.3
1064		MeO-	Br		883.2 885.2
1065		MeO-	Br		869.3 871.3

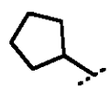
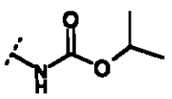
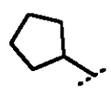
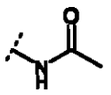
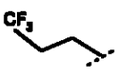
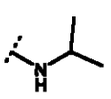
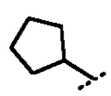
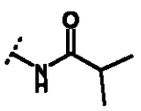
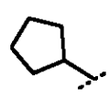
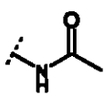
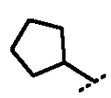
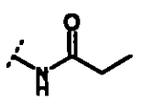
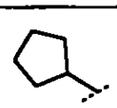
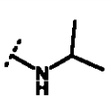
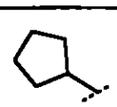
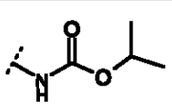
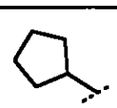
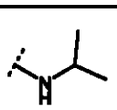
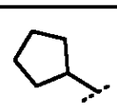
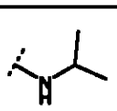
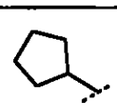
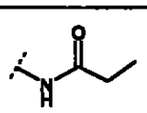
Cpd.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1066		MeO-	Br		815.2 817.2
1067		MeO-	Br		843.3 845.3
1068		MeO-	Br		955.3 957.3
1069		MeO-	Br		937.3 939.3
1070		MeO-	Br		869.3 871.3
1071		MeO-	Br		897.3 899.3
1072		MeO-	Br		931.3 933.3
1073		MeO-	Br		913.2 915.2
1074		MeO-	Br		899.3 901.3
1075		MeO-	Br		845.2 847.2

154

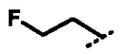
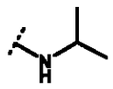
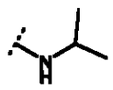
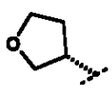
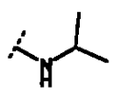
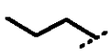
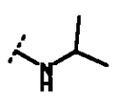
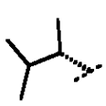
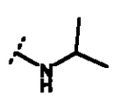
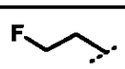
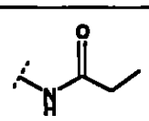
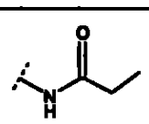
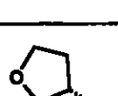
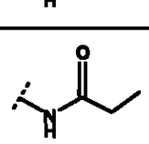
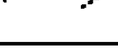
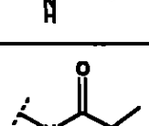
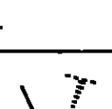
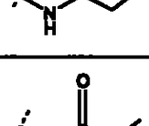
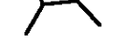
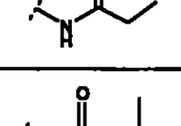
Cpd.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
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1077		MeO-	Br		887.2 889.2
1078		MeO-	Br		855.2 857.2
1079		MeO-	Br		801.2 803.2
1080		MeO	Br		829.2 831.2
1081		MeO	Br		901.3 903.3
1082		H	Cl		823.3 825.3
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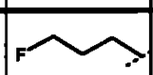
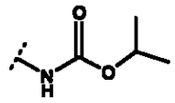
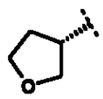
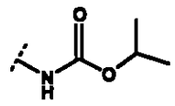
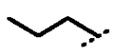
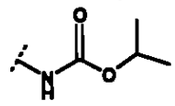
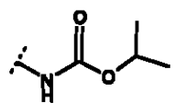
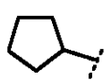
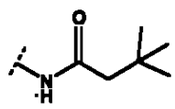
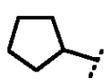
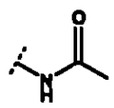
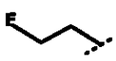
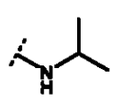
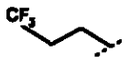
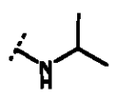
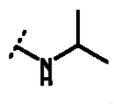
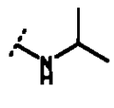
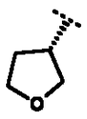
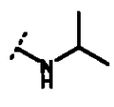
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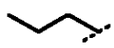
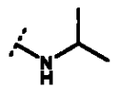
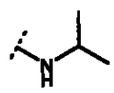
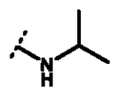
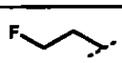
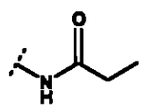
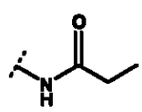
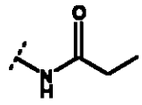
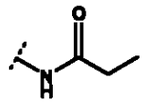
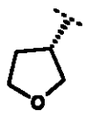
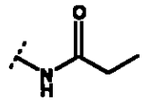
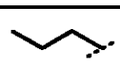
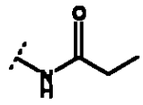
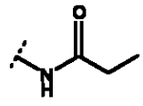
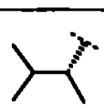
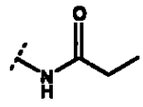
Cpd.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1086		H	Cl		795.2 797.2
1087		H	Cl		795.2 797.2
1088		H	Cl		811.2 813.2
1089		H	Cl		783.2
1090		EtO-	Br		869.2 871.2
1091		EtO-	Br		883.2 885.2
1092		EtO-	Br		855.2 857.2
1093		EtO-	Br		899.2 901.2
1094		PrO-	Br		883.2 885.2
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1096		PrO-	Br		869.2 871.2

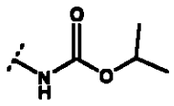
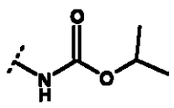
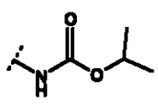
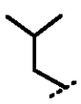
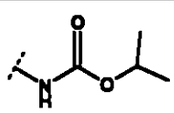
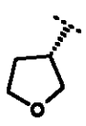
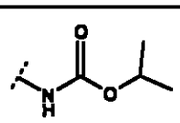
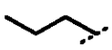
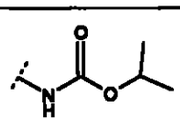
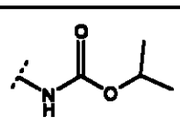
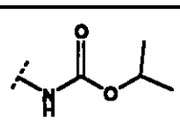
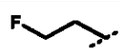
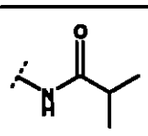
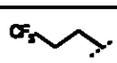
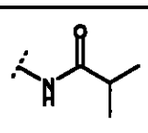
Cpd.	B	L^6	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1097		PrO-	Br		913.2 915.2
1098		H	Br		811 813
1099		MeO-	Br		869.2 871.1
1100		MeO-	Cl		825.2 827.2
1101		EtO-	Me		791.2
1102		EtO-	Me		805.2
1103		EtO-	Me		791.2
1104		EtO-	Me		835.3
1105		MeO-	CN		786.2
1106		Br	MeO-		841.2 843.2
1107		MeO-	CN		800.2

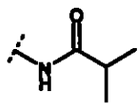
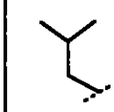
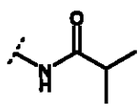
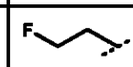
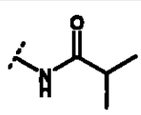
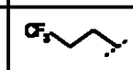
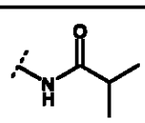
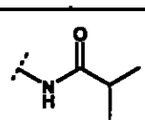
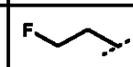
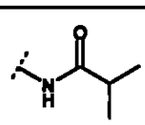
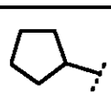
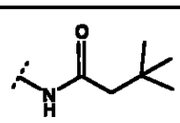
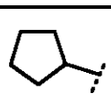
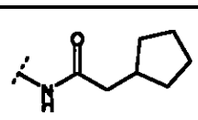
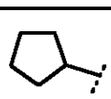
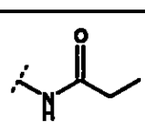
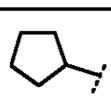
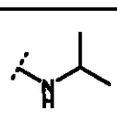
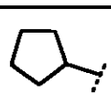
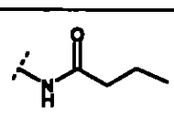
157

Cpd.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1108		MeO-	Br		819.1 821.1
1109		MeO	Br		833.1 835.2
1110		MeO-	Br		843.2 845.2
1111		MeO-	Br		815.2 817.2
1112		MeO-	Br		843.2 845.2
1113		MeO-	Br		833.1 835.1
1114		MeO	Br		847.2 849.2
1115		MeO-	Br		857.2 859.2
1116		MeO	Br		829.2 831.2
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1118		MeO	Br		863.2 865.2

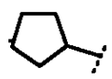
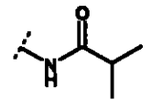
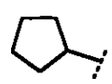
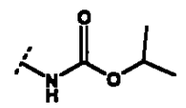
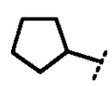
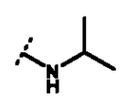
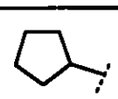
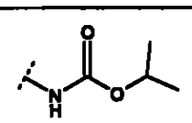
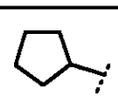
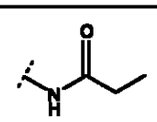
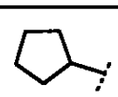
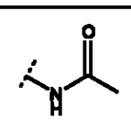
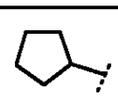
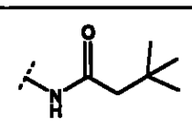
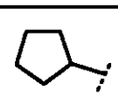
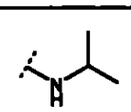
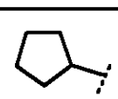
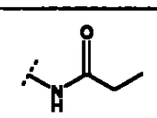
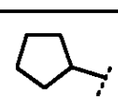
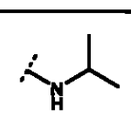
Cpd.	B	L^6	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1119		MeO	Br		877.2 879.2
1120		MeO	Br		887.2 889.2
1121		MeO	Br		859.2 861.2
1122		MeO	Br		887.2 889.2
1123		MeO	CN		842.2
1124		MeO	CN		786.2
1125		MeO-	Cl		775.4 777.3
1126		MeO-	Cl		825.4 827.4
1127		MeO	Cl		757.4 759.4
1128		MeO	Cl		785.4 787.4
1129		MeO	Cl		799.3 801.3

Cpd.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1130		MeO	Cl		771.3 773.3
1131		MeO	Cl		789.3 791.3
1132		MeO	Cl		799.5 801.4
1133		MeO	Cl		789.4 791.4
1134		MeO	Cl		839.4 841.4
1135		MeO	Cl		771.4 773.4
1136		MeO	Cl		799.4 801.4
1137		MeO	Cl		813.3 815.3
1138		MeO	Cl		785.3 787.3
1139		MeO	Cl		803.3 805.3
1140		MeO	Cl		813.5 815.4

Cpd.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1141		MeO	Cl		819.4 821.4
1142		MeO	Cl		869.4 871.4
1143		MeO	Cl		801.4 803.4
1144		MeO	Cl		829.5 831.5
1145		MeO	Cl		843.4 845.3
1146		MeO	Cl		815.3 817.3
1147		MeO	Cl		833.3 835.3
1148		MeO	Cl		843.5 845.5
1149		MeO	Cl		803.2 805.2
1150		MeO	Cl		853.2 855.2

Cpd.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1151		MeO	Cl		785.2
1152		MeO	Cl		813.3
1153		MeO	Cl		817.2
1154		MeO	Br		897.3 899.2
1155		MeO	Br		829.2 831.2
1156		MeO	Br		847.3 849.2
1157		H	-SMe		835.4
1158		H	-SMe		847.4
1159		H	-SMe		79.3.
1160		H	-SMe		779.3
1161		H	-SMe		807.3

147
162

Cpd.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1162		H	-SMe		807.3
1163		H	-SMe		823.3
1164		H	$-CF_3$		801.4
1165		H	$-CF_3$		845.4
1166		H	$-CF_3$		815.4
1167		Cl	Cl		801.3 803.3 805.3
1168		Cl	Cl		857.2
1169		Cl	Cl		801.3
1170		Cl	Cl		815.3 817.3 819.3
1171		H	$-SO_2Me$		811.3

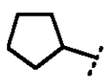
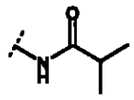
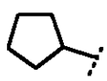
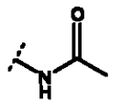
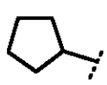
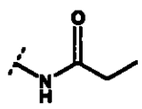
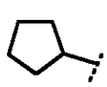
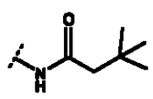
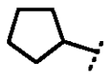
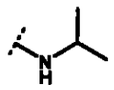
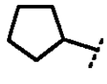
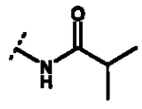
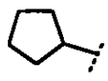
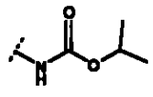
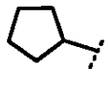
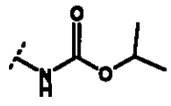
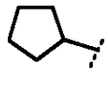
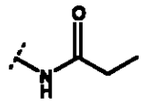
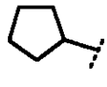
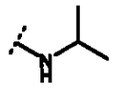
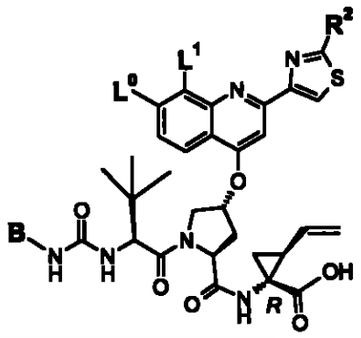
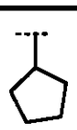
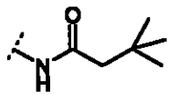
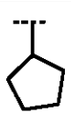
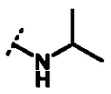
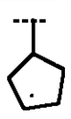
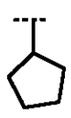
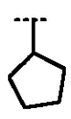
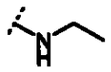
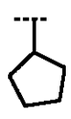
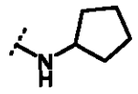
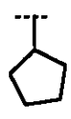
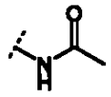
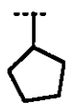
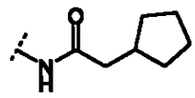
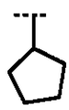
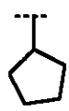
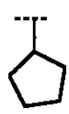
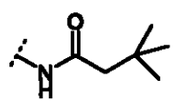
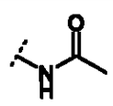
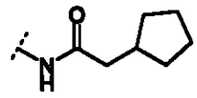
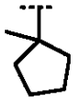
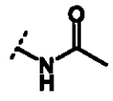
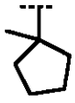
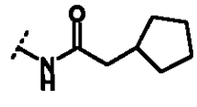
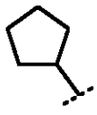
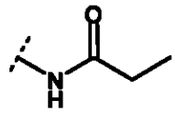
Cpd.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1172		H	$-SO_2Me$		839.3
1173		H	Me-		747.3
1174		H	Me-		761.4
1175		H	Me-		803.4
1176		H	Me-		747.4
1177		H	Me-		775.4
1178		H	Me-		791.4
1179		H	$-SO_2Me$		855.3
1180		H	$-SO_2Me$		825.2
1181		H	-OMe		763.4

TABLE 2



Cpd. #	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
2001		MeO-	Me-		832.6
2002		MeO-	Me-		776.5
2003		MeO-	Me-		734.4
2004		MeO-	Me-		748.5
2005		MeO-	Me-		762.5
2006		MeO-	Me-		802.5
2007		MeO-	Me-		776.4

163
165

Cpd. #	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
2008		MeO-	Me-		844.5
2009		MeO-	Me-		733.4
2010		MeO-	Me-		747.4
2011		MeO-	Me-		761.4
2012		MeO-	Me-		846.5
2013		MeO-	Me-		764.4
2014		MeO-	Me-		832.5
2015		MeO-	Me-		790.4
2016		MeO-	Me-		858.5
2017		MeO-	Br-		854.3 856.3

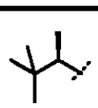
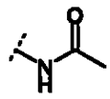
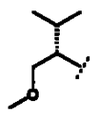
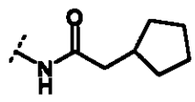
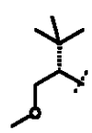
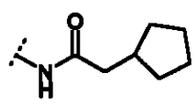
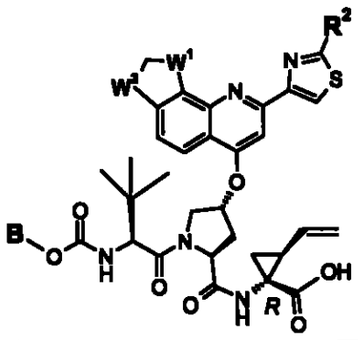
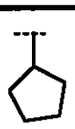
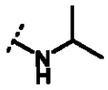
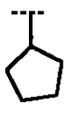
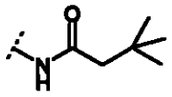
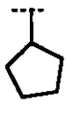
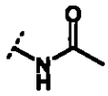
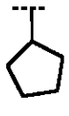
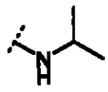
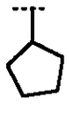
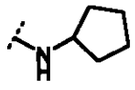
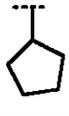
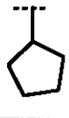
Cpd. #	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
2018		MeO-	Me-		792.4
2019		MeO-	Me		876.5
2020		MeO-	Me		890.5

TABLE 3



Cpd. #	B	W^1	W^2	R^2	m/z $(M+H)^+$ $(MH+2)^+$
3001		-O-	-O-		777.6
3002		-O-	-O-		833.6
3003		$-CH_2-$	-O-		775.4
3004		$-CH_2-$	-O-		775.4
3005		$-CH_2-$	-O-		801.4
3006		$-CH_2-$	-O-		747.3
3007		$-CH_2-$	-O-		733.3

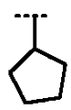
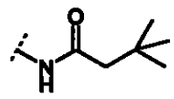
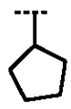
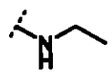
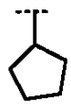
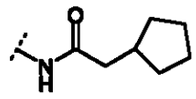
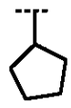
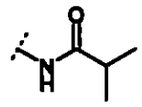
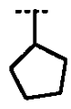
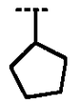
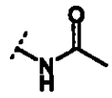
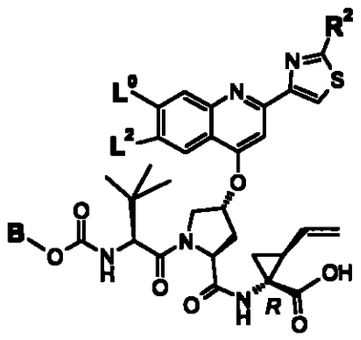
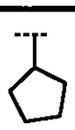
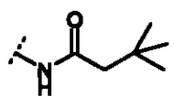
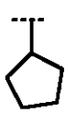
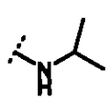
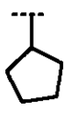
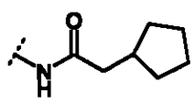
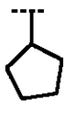
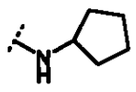
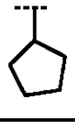
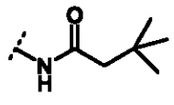
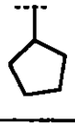
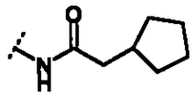
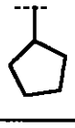
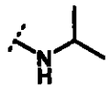
Cpd. #	B	W^1	W^2	R^2	m/z $(M+H)^+$ $(MH+2)^+$
3008		$-CH_2-$	-O-		831.5
3009		$-CH_2-$	-O-		761.5
3010		$-CH_2-$	-O-		843.3
3011		$-CH_2-$	$-CH_2-$		801.5
3012		$-CH_2-$	$-CH_2-$		745.4
3013		$-CH_2-$	$-CH_2-$		773.4

TABLE 4



Cpd. #	B	L^1	L^2	R^2	m/z $(M+H)^+$ $(MH+2)^+$
4001		MeO-	Me-		833.5
4002		MeO-	Me-		777.5
4003		MeO-	Me-		845.5
4004		MeO-	Me-		803.5
4005		Me_2N-	Me-		846.5
4006		Me_2N-	Me-		858.5
4007		Me_2N-	Me-		790.5

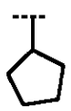
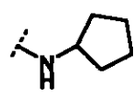
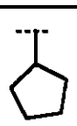
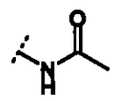
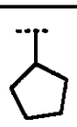
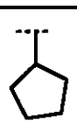
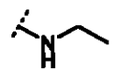
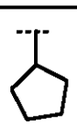
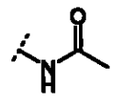
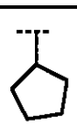
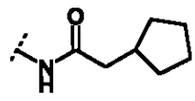
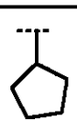
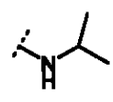
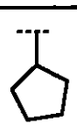
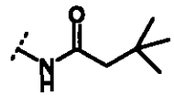
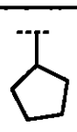
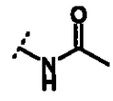
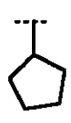
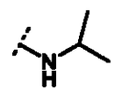
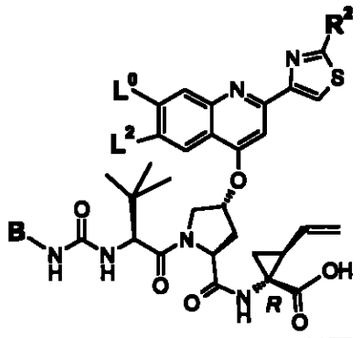
Cpd. #	B	L^0	L^2	R^2	m/z $(M+H)^+$ $(MH+2)^+$
4008		Me_2N-	Me-		816.5
4009		MeO-	Me-		777.4
4010		MeO-	Me-		749.4
4011		MeO-	Me-		763.4
4012		MeO-	MeO-		793.3
4013		MeO-	MeO-		861.4
4014		MeO-	MeO-		793.4
4015		MeO-	MeO-		849.4
4016		Me-	MeO-		777.4
4017		Me-	MeO-		777.5

TABLE 5



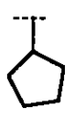
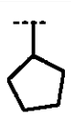
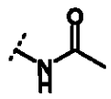
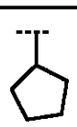
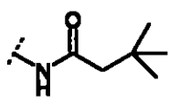
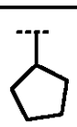
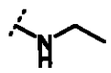
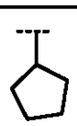
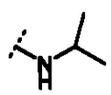
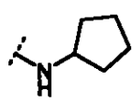
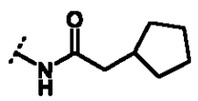
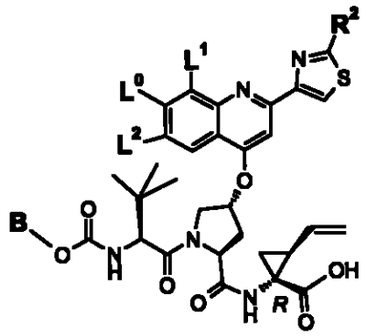
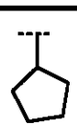
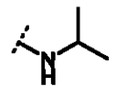
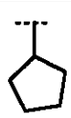
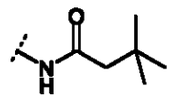
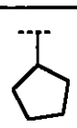
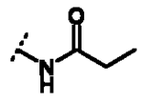
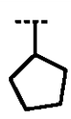
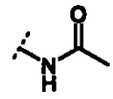
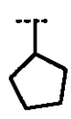
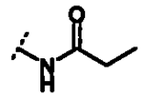
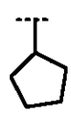
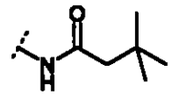
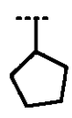
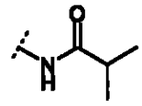
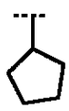
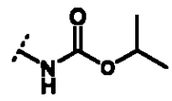
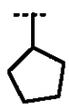
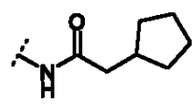
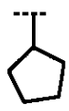
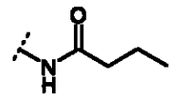
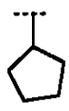
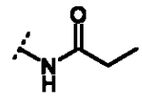
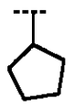
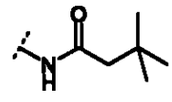
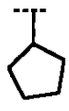
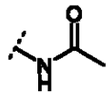
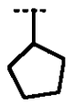
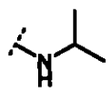
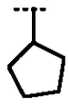
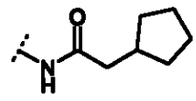
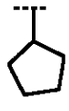
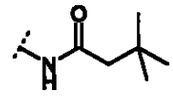
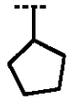
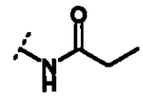
Cpd. #	B	L^0	L^2	R^2	m/z $(M+H)^+$ $(MH+2)^+$
5001		MeO-	Me-		748.4
5002		MeO-	Me-		776
5003		MeO-	Me-		832.5
5004		MeO-	Me-		762
5005		MeO-	Me-		776.5
5006		MeO-	Me-		802.5
5007		MeO-	Me-		844.5

TABLE 6



Cpd. #	B	L^2	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
6001		MeO-	H	Me		777.3
6002		MeO-	H	Me		833.4
6003		MeO-	H	Me		791.3
6004		MeO-	H	Me		777.2
6005		Me	H	Br		839.2 841.2
6006		Me	H	Br		881.2 883.2
6007		Me	H	Br		853.2 855.2

Cpd. #	B	L^2	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
6008		Me	H	Br		869.2 871.2
6009		Me	H	Br		893.2 895.2
6010		Me	H	Br		853.2 855.2
6011		Me	H	Me		775.3
6012		Me	H	Me		817.3
6013		Me	H	Me		761.3
6014		Me	H	Me		761.4
6015		Me	MeO-	Me		859.5
6016		Me	MeO-	Me		847.5
6017		Br	H	Br		905.2

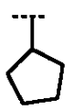
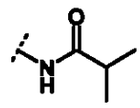
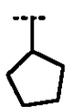
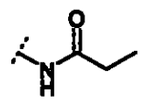
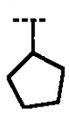
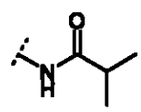
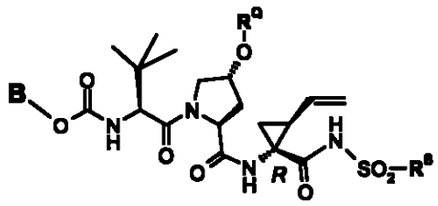
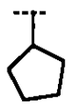
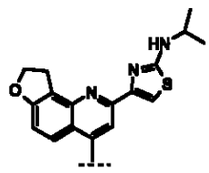
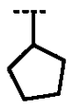
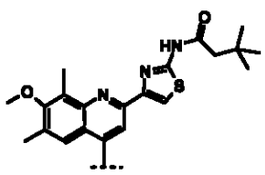
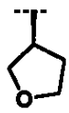
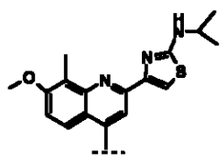
Cpd. #	B	L^2	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
6018		Br	H	Br		919.2
6019		Br	H	Cl		861.2
6020		Br	H	Cl		875.2

TABLE 7

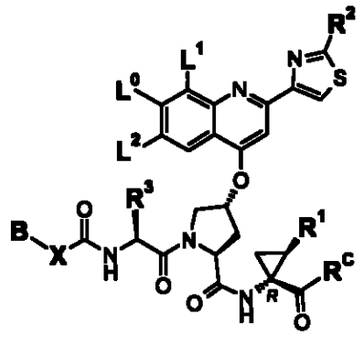


Cpd. #	B	R^Q	R^S	m/z $(M+H)^+$ $(MH+2)^+$
7001				878.8
7002				950.4
7003				885.4

CLAIMS

What is claimed is:

1. A racemate, diastereoisomer, or optical isomer of a compound of formula (I):



I

wherein

B is (C_{1-10})alkyl, (C_{3-7})cycloalkyl, or (C_{1-4})alkyl-(C_{3-7})cycloalkyl,

a) wherein said alkyl, cycloalkyl, and alkyl-cycloalkyl may be mono-, di- or tri-substituted with (C_{1-3})alkyl; and

b) wherein said alkyl, cycloalkyl, and alkyl-cycloalkyl may be mono- or di-substituted with substituents selected from hydroxy and O-(C_{1-4})alkyl; and

c) wherein each of said alkyl groups may be mono-, di- or tri-substituted with halogen; and

d) wherein each of said cycloalkyl groups being 4-, 5-, 6- or 7-membered having optionally one (for the 4-, 5, 6, or 7-membered) or two (for the 5-, 6- or 7-membered) $-CH_2$-groups not directly linked to each other replaced by -O- such that the O-atom is linked to the group X via at least two C-atoms;

X is O or NH;

R^3 is (C_{2-8})alkyl, (C_{3-7})cycloalkyl or (C_{1-3})alkyl-(C_{3-7})cycloalkyl, wherein said alkyl, cycloalkyl, and alkyl-cycloalkyl groups may be mono-, di- or tri-substituted with (C_{1-4})alkyl;

L^0 is H, halogen, (C_{1-4})alkyl, –OH, –O-(C_{1-4})alkyl, $-NH_2$, –NH(C_{1-4})alkyl or -N$((C_{1-4})$alkyl$)_2$;

L^1, L^2 are each independently halogen, cyano, (C_{1-4})alkyl, -O-(C_{1-4})alkyl, -S-(C_{1-4})alkyl, -SO-(C_{1-4})alkyl, or $–SO_2$-(C_{1-4})alkyl, wherein each of said alkyl groups is optionally substituted with from one to three halogen atoms; and either L^1 or L^2 (but not both at the same time) may also be H; or

L^0 and L^1 or

L^0 and L^2 may be covalently bonded to form, together with the two C-atoms to which they are linked, a 5- or 6-membered carbocyclic ring wherein one or two $-CH_2$-groups not being directly linked to each other may be replaced each independently by -O- or NR^a wherein R^a is H or (C_{1-4})alkyl, and wherein said carbo- or heterocyclic ring is optionally mono- or di-substituted with (C_{1-4})alkyl;

R^2 is R^{20}, $-NR^{22}COR^{20}$, $-NR^{22}COOR^{20}$ $-NR^{22}R^{21}$ or $-NR^{22}CONR^{21}R^{23}$, wherein R^{20} is selected from (C_{1-8})alkyl, (C_{3-7})cycloalkyl and (C_{1-4})alkyl-(C_{3-7})cycloalkyl, wherein said cycloalkyl and alkyl-cycloalkyl may be mono-, di- or tri-substituted with (C_{1-3})alkyl;

R^{21} is H or R^{20} as defined above,

R^{22} and R^{23} are independently selected from H and methyl,

R^1 is ethyl or vinyl;

R^C is hydroxy or $NHSO_2R^6$ wherein R^6 is (C_{1-8})alkyl, (C_{3-7})cycloalkyl, (C_{1-8})alkyl-(C_{3-7})cycloalkyl, phenyl, naphthyl, pyridinyl, (C_{1-4})alkyl-phenyl, (C_{1-4})alkyl-naphthyl or (C_{1-4})alkyl-pyridinyl; each of which optionally being mono-, di- or tri-substituted with substituents selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-8})alkyl, $-CO-NH_2$, $-CO-NH(C_{1-4})$alkyl, $-CO-N((C_{1-4})alkyl)_2$, $-NH_2$, $-NH(C_{1-4})$alkyl and $-N((C_{1-4})alkyl)_2$, wherein (C_{1-4})alkyl and O-(C_{1-8})alkyl are optionally substituted with one to three halogen atoms; and each of which optionally being monosubstituted with nitro;

or R^6 is $-N(R^{N2})R^{N1})$, wherein R^{N1} and R^{N2} are independently selected from H, (C_{1-8})alkyl, (C_{3-7})cycloalkyl, (C_{1-8})alkyl-(C_{3-7})cycloalkyl, aryl and (C_{1-8})alkyl-aryl; wherein said (C_{1-8})alkyl, (C_{3-7})cycloalkyl, (C_{1-8})alkyl-(C_{3-7})cycloalkyl, aryl and (C_{1-8})alkyl-aryl are optionally substituted with one or more substituents independently selected from halogen, (C_{1-8})alkyl, hydroxy, cyano, O-(C_{1-8})alkyl, $-NH_2$, $-NH(C_{1-4})$alkyl, $-N((C_{1-4})alkyl)_2$, $-CO-NH_2$, $-CO-NH(C_{1-4})$alkyl, $-CO-N((C_{1-4})alkyl)_2$, $-COOH$, and $-COO(C_{1-8})$alkyl; or

R^{N2} and R^{N1} are linked, together with the nitrogen to which they are bonded, to form a 3- to 7-membered monocyclic saturated or unsaturated heterocycle or a 9- or 10-membered bicyclic saturated or unsaturated heterocycle, each of which optionally containing from one to three further heteroatoms independently selected from N, S and O, and each of which being optionally

substituted with one or more substituents independently selected from halogen, (C_{1-8})alkyl, hydroxy, cyano, O-(C_{1-8})alkyl, $-NH_2$, -NH(C_{1-4})alkyl, -N$((C_{1-4})alkyl)_2$, $-CO-NH_2$, -CO-NH(C_{1-4})alkyl, -CO-N$((C_{1-4})alkyl)_2$, –COOH, and –COO(C_{1-8})alkyl;

or a pharmaceutically acceptable salt or ester thereof.

2. The compound according to claim 1 wherein

B is (C_{1-10})alkyl, (C_{3-7})cycloalkyl, or (C_{1-4})alkyl-(C_{3-7})cycloalkyl,

a) wherein said cycloalkyl, and alkyl-cycloalkyl may be mono-, di- or tri-substituted with (C_{1-3})alkyl; and

b) wherein said alkyl, cycloalkyl, and alkyl-cycloalkyl may be mono- or di-substituted with substituents selected from hydroxy and O-(C_{1-4})alkyl; and

c) wherein all said alkyl-groups may be mono-, di- or tri-substituted with halogen; and

d) wherein all said cycloalkyl-groups being 4-, 5-, 6- or 7-membered having optionally one (for the 4-, 5, 6, or 7-membered) or two (for the 5-, 6- or 7-membered) $-CH_2$-groups not directly linked to each other replaced by -O- such that the O-atom is linked to the group **X** via at least two C-atoms;

X is O or NH;

R^3 is (C_{2-8})alkyl, (C_{3-7})cycloalkyl or (C_{1-3})alkyl-(C_{3-7})cycloalkyl, wherein said cycloalkyl groups may be mono-, di- or tri-substituted with (C_{1-4})alkyl;

L^0 is H, –OH, –O-(C_{1-4})alkyl, $-NH_2$, –NH(C_{1-4})alkyl or –N$((C_{1-4})alkyl)_2$;

L^1, L^2 are each independently halogen, (C_{1-4})alkyl, -O-(C_{1-4})alkyl or -S-(C_{1-4})alkyl (in any oxidized state such as SO or SO_2); and either L^1 or L^2 (but not both at the same time) may also be H; or

L^0 and L^1 or

L^0 and L^2 may be covalently bonded to form, together with the two C-atoms to which they are linked, a 5- or 6-membered carbocyclic ring wherein one or two $-CH_2$-groups not being directly linked to each other may be replaced each independently by -O- or NR^a wherein R^a is H or (C_{1-4})alkyl, and wherein said carbo- or heterocyclic ring is optionally

178

mono- or di-substituted with (C_{1-4})alkyl;

R^2 is R^{20}, $-NR^{22}COR^{20}$, $-NR^{22}COOR^{20}$ $-NR^{22}R^{21}$ and $-NR^{22}CONR^{21}R^{23}$, wherein

R^{20} is selected from (C_{1-8})alkyl, (C_{3-7})cycloalkyl and (C_{1-4})alkyl-(C_{3-7})cycloalkyl, wherein said cycloalkyl and alkyl-cycloalkyl may be mono-, di- or tri-substituted with (C_{1-3})alkyl;

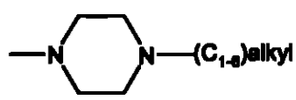
R^{21} is H or has one of the meanings of R^{20} as defined above,

R^{22} and R^{23} are independently selected from H and methyl,

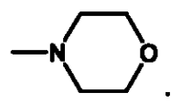
R^1 is ethyl or vinyl;

R^C is hydroxy or $NHSO_2R^S$ wherein R^S is (C_{1-8})alkyl, (C_{3-7})cycloalkyl, (C_{1-8})alkyl-(C_{3-7})cycloalkyl, phenyl, naphthyl, pyridinyl, (C_{1-4})alkyl-phenyl, (C_{1-4})alkyl-naphthyl or (C_{1-4})alkyl-pyridinyl; all of which optionally being mono-, di- or tri-substituted with substituents selected from halogen, hydroxy, cyano, (C_{1-4})alkyl, O-(C_{1-8})alkyl, $-CO-NH_2$, $-CO-NH(C_{1-4})$alkyl, $-CO-N((C_{1-4})alkyl)_2$, $-NH_2$, $-NH(C_{1-4})$alkyl and $-N((C_{1-4})alkyl)_2$; and all of which optionally being monosubstituted with nitro;

or R^S can be further selected from: $-NH(C_{1-8})$alkyl, $N((C_{1-8})alkyl)_2$, -Het,



or



;

or a pharmaceutically acceptable salt or ester thereof.

3. The compound according to one or more of the preceding claims wherein B is selected from (C_{2-8})alkyl, (C_{3-7})cycloalkyl and (C_{1-3})alkyl-(C_{3-7})cycloalkyl,

a) wherein said alkyl, cycloalkyl, and alkyl-cycloalkyl may be mono-, di- or tri-substituted with (C_{1-3})alkyl; and

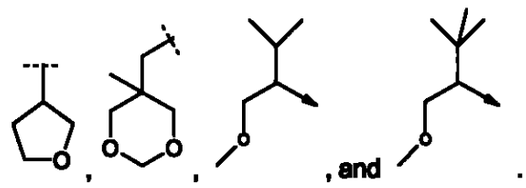
b) wherein said alkyl, cycloalkyl, and alkyl-cycloalkyl may be mono- or di-substituted with substituents selected from hydroxy and O-(C_{1-4})alkyl; and

c) wherein each of said alkyl groups may be mono-, di- or tri-substituted with fluorine or mono-substituted with chlorine or bromine; and

d) wherein in each of said cycloalkyl groups being 5-, 6- or 7-membered, one or two $-CH_2$-groups not being directly linked to each other may be replaced by -O- such that the O-atom is linked to the group X via at least

two C-atoms.

4. The compound according to claim 3 wherein B is selected from ethyl, n-propyl, *tert*-butyl, 2-methylpropyl, 1,2-dimethylpropyl, 1,2,2-trimethylpropyl, 2-fluoroethyl, 3-fluoropropyl, 3,3,3-trifluoropropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclopentyl and 1-methylcyclohexyl, and a group selected from:



, and .

5. The compound according to claim 4 wherein B is selected from ethyl, *n*-propyl, *tert*-butyl, cyclopentyl, 1-methylcyclopentyl, 2-fluoroethyl or 3-fluoropropyl.

6. The compound according to one or more of the preceding claims wherein X is O.

7. The compound according to one or more of the preceding claims wherein X is NH.

8. The compound according to one or more of the preceding claims wherein R^3 is (C_{2-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-3})alkyl-(C_{3-7})cycloalkyl, each of which being optionally substituted with 1 to 3 substituents selected from (C_{1-4})alkyl.

9. The compound according to claim 8 wherein R^3 is selected from 1,1-dimethylethyl, cyclopentyl, cyclohexyl and 1-methylcyclohexyl.

10. The compound according to one or more of the preceding claims wherein L^9 is selected from H, halogen, CH_3, -OH, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-OCH(CH_3)_2$, $-NHCH_3$, $-NHC_2H_5$, $-NHC_3H_7$, $-NHCH(CH_3)_2$, $-N(CH_3)_2$, $-N(CH_3)C_2H_5$, $-N(CH_3)C_3H_7$ and $-N(CH_3)CH(CH_3)_2$.

11. The compound according to claim 10 wherein L^0 is selected from H, -OH, -OCH_3, halogen and -$N(CH_3)_2$.

12. The compound according to claim 11 wherein L^0 is selected from H, -OH or -OCH_3.

13. The compound according to one or more of the preceding claims wherein L^1 and L^2 are each independently selected from: halogen, -CH_3, -C_2H_5, -OCH_3, -OC_2H_5, -OC_3H_7, -$OCH(CH_3)_2$, CF_3, -SMe, -SOMe, and SO_2Me whereby either L^1 or L^2 may be H.

14. The compound according to claim 13 wherein either one of L^1 and L^2 is -CH_3, -F, -Cl, -Br, -OMe, -SMe, or -SO_2Me and the other of L^1 and L^2 is H.

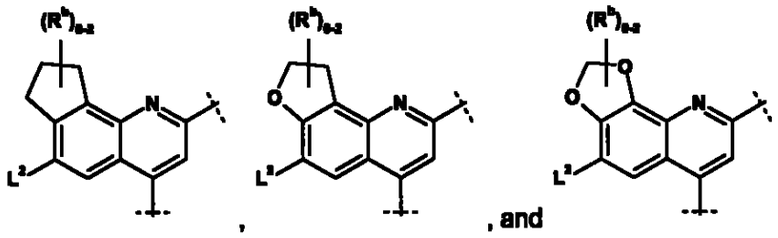
15. The compound according to claim 14 wherein L^1 is CH_3, -F, -Cl, -Br, -OMe, -SMe, or -SO_2Me and L^2 is H.

16. The compound according to one or more of the preceding claims wherein L^0 is selected from H, -OH and -OCH_3; and either one of L^1 and L^2 is CH_3, -F, -Cl, -Br, -OMe, -SMe, or -SO_2Me and the other of L^1 and L^2 is H.

17. The compound according to claim 16 wherein L^0 is selected from H, -OH and -OCH_3; L^1 is CH_3, -F, -Cl, -Br, -OMe, -SMe, or -SO_2Me and L^2 is H.

18. The compound according to claim 17 wherein L^0 is selected from H and -OCH_3; L^1 is CH_3, -Cl or -Br and L^2 is H.

19. The compound according to one or more of the preceding claims wherein L^0 and L^1 are covalently bonded to form, together with the quinoline residue to which they are linked, a ring system which is selected from:



, and

wherein each R^b is independently (C_{1-4})alkyl and L^2 is defined as in claim 1.

20. The compound according to claim 19 wherein L^2 is H or methyl.

21. The compound according to one or more of the preceding claims wherein R^2 is R^{20}, -NHCOR^{20}, -NHCOOR^{20}, -NHR^{21} or –NHCONR^{21}R^{23}, wherein
R^{20} is selected from (C_{1-8})alkyl, (C_{3-7})cycloalkyl, and (C_{1-3})alkyl-(C_{3-7})cycloalkyl, wherein each of said cycloalkyl and alkyl-cycloalkyl groups may be mono-, di- or tri-substituted with (C_{1-3})alkyl; and
R^{21} is H or R^{20} as defined above; and
R^{23} is H or methyl.

22. The compound according to claim 21 wherein R^2 is -NHCOR^{20}, -NHCOOR^{20}, or -NHR^{21}.

23. The compound according to claim 22 wherein R^{20} and R^{21} are independently selected from: methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, 1-methylpropyl, 2-methylpropyl, *tert*-butyl, 2,2-dimethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1,2,2-trimethylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, each of said cycloalkyl or alkyl-cycloalkyl groups optionally being mono- or di-substituted with methyl or ethyl.

24. The compound according to claim 23 wherein R^{20} and R^{21} are independently selected from methyl, ethyl, *n*-propyl, *i*-propyl, 2,2-dimethylpropyl, cyclopentyl and cyclopentylmethyl.

25. The compound according to one or more of the preceding claims wherein R^1 is vinyl.

26. The compound according to one or more of the preceding claims wherein R^C is hydroxy, $NHSO_2$-methyl, $NHSO_2$-ethyl, $NHSO_2$-(1-methyl)ethyl, $NHSO_2$-propyl, $NHSO_2$-cyclopropyl, $NHSO_2$-CH_2-cyclopropyl, $NHSO_2$-cyclobutyl, $NHSO_2$-cyclopentyl or $NHSO_2$-phenyl.

27. The compound according to claim 26 wherein R^C is hydroxy.

28. The compound according to claim 26 wherein R^C is $NHSO_2$-cyclopropyl.

29. The compound according to one or more of the preceding claims wherein R^C is $NHSO_2N(R^{N2})R^{N1})$, wherein R^{N1} and R^{N2} are independently selected from H, (C_{1-4})alkyl, (C_{3-7})cycloalkyl, (C_{1-3})alkyl-(C_{3-7})cycloalkyl, phenyl, and (C_{1-3})alkyl-phenyl; wherein said (C_{1-4})alkyl, (C_{3-7})cycloalkyl, (C_{1-3})alkyl-(C_{3-7})cycloalkyl, phenyl and (C_{1-3})alkyl-phenyl are optionally substituted with one, two or three substituents independently selected from halogen, (C_{1-6})alkyl, hydroxy, cyano, O-(C_{1-6})alkyl, $-NH_2$, $-NH(C_{1-4})$alkyl, $-N((C_{1-4})alkyl)_2$, $-CO-NH_2$, $-CO-NH(C_{1-4})$alkyl, $-CO-N((C_{1-4})alkyl)_2$, –COOH, and $–COO(C_{1-6})$alkyl; or
R^{N2} and R^{N1} are linked, together with the nitrogen to which they are bonded, to form a 5 or 6-membered monocyclic heterocycle which may be saturated or unsaturated, optionally containing from one to three further heteroatoms independently selected from N, S and O, and optionally substituted with one, two or three substituents independently selected from halogen, (C_{1-6})alkyl, hydroxy, cyano, O-(C_{1-6})alkyl, $-NH_2$, $-NH(C_{1-4})$alkyl, $-N((C_{1-4})alkyl)_2$, $-CO-NH_2$, $-CO-NH(C_{1-4})$alkyl, $-CO-N((C_{1-4})alkyl)_2$, –COOH, and $–COO(C_{1-6})$alkyl.

30. The compound according to claim 1 wherein

B is (C_{2-6})alkyl, (C_{3-7})cycloalkyl or (C_{1-3})alkyl-(C_{3-7})cycloalkyl,

a) wherein said alkyl, cycloalkyl, and alkyl-cycloalkyl may be mono-, di- or tri-substituted with (C_{1-3})alkyl; and

b) wherein said alkyl, cycloalkyl, and alkyl-cycloalkyl may be mono- or di-substituted with substituents selected from hydroxy and O-(C_{1-4})alkyl; and

c) wherein each of said alkyl groups may be mono-, di- or tri-substituted with fluorine or mono-substituted with chlorine or bromine; and

d) wherein in each of said cycloalkyl groups being 5-, 6- or 7-membered, one or two $-CH_2-$groups not being directly linked to each other may be replaced by -O- such that the O-atom is linked to the group X via at least two C-atoms;

X is O or NH;

R^3 is (C_{2-6})alkyl or (C_{3-7})cycloalkyl, both of which being optionally substituted with 1 to 3 substituents selected from (C_{1-4})alkyl;

L^0 is H, -OH, $-OCH_3$, halogen or $-N(CH_3)_2$;

L^1 and L^2 are each independently selected from: halogen, $-CH_3$, $-C_2H_5$, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-OCH(CH_3)_2$, CF_3, -SMe, -SOMe, and SO_2Me, whereby either L^1 or L^2 may be H;

R^2 is R^{20}, $-NHCOR^{20}$, $-NHCOOR^{20}$, $-NHR^{21}$ and $-NHCONR^{21}R^{22}$, wherein

R^{20} is selected from (C_{1-6})alkyl, (C_{3-7})cycloalkyl, (C_{1-3})alkyl-(C_{3-7})cycloalkyl, wherein said cycloalkyl and alkyl-cycloalkyl may be mono-, di- or tri-substituted with (C_{1-3})alkyl; and

R^{21} is H or R^{20} as defined above; and

R^{22} is H or methyl;

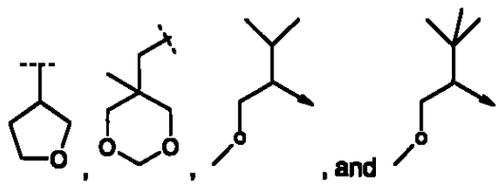
R^1 is ethyl or vinyl; and

R^C is hydroxy, $NHSO_2$-methyl, $NHSO_2$-ethyl, $NHSO_2$-(1-methyl)ethyl, $NHSO_2$-propyl, $NHSO_2$-cyclopropyl, $NHSO_2-CH_2$-cyclopropyl, $NHSO_2$-cyclobutyl, $NHSO_2$-cyclopentyl or $NHSO_2$-phenyl.

31. The compound according to claim 30 wherein

B is selected from: ethyl, n-propyl, *tert*-butyl, 2-methylpropyl, 1,2-

dimethylpropyl, 1,2,2-trimethylpropyl, 2-fluoroethyl, 3-fluoropropyl, 3,3,3-trifluoropropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclopentyl and 1-methylcyclohexyl, and a group selected from:



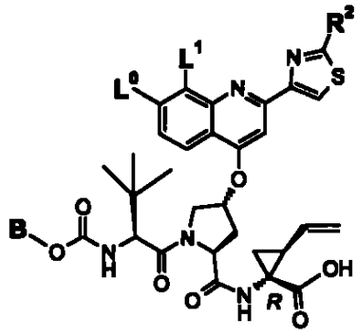
; R^3 is selected from 1,1-dimethylethyl, cyclopentyl, cyclohexyl and 1-methylcyclohexyl; L^0 is H, -OH or-OCH_3; L^1 is CH_3, -F, -Cl, -Br, -OMe, -SMe, or -SO_2Me; L^2 is H;

R^2 is -NHCOR^{20}, -NHCOOR^{20} or -NHR^{21}, wherein R^{20} and R^{21} are independently selected from methyl, ethyl, *n*-propyl, *i*-propyl, 2,2-dimethylpropyl, cyclopentyl and cyclopentylmethyl;

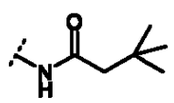
R^1 is vinyl; and R^C is hydroxy or $NHSO_2$-cyclopropyl.

32. The compound according to claim 31 wherein B is selected from ethyl, *n*-propyl, *tert*-butyl, cyclopentyl, 1-methylcyclopentyl, 2-fluoroethyl and 3-fluoropropyl; R^3 is selected from 1,1-dimethylethyl and cyclohexyl; L^0 is H or -OCH_3; L^1 is -CH_3, -Cl, or -Br; L^2 is H; and R^C is hydroxy.

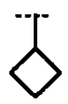
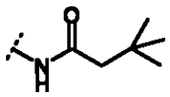
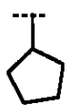
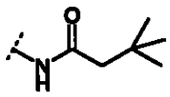
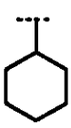
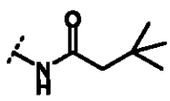
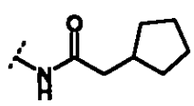
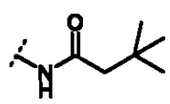
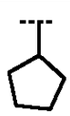
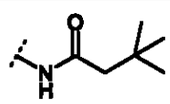
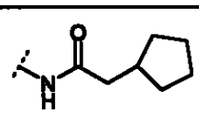
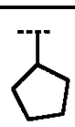
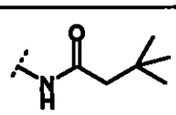
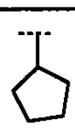
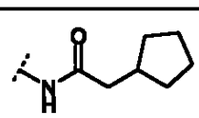
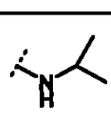
33. The compound according to claim 1 of the formula



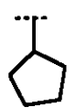
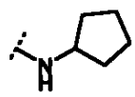
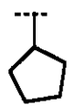
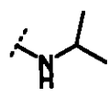
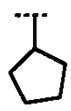
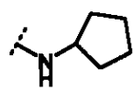
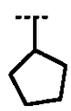
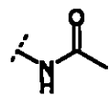
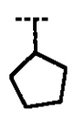
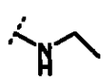
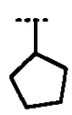
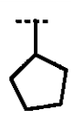
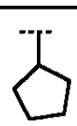
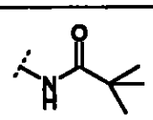
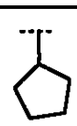
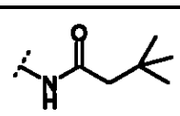
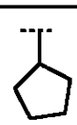
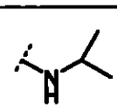
wherein B, L^0, L^1 and R^2 are defined as in the table below

Cpd.	B	L^0	L^1	R^2
1001		MeO-	MeO-	

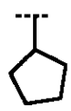
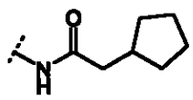
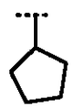
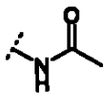
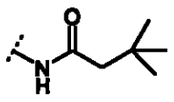
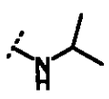
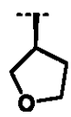
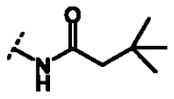
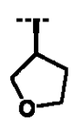
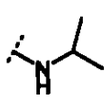
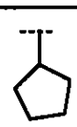
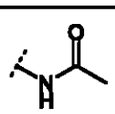
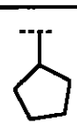
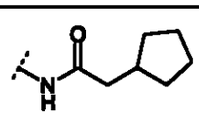
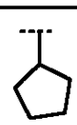
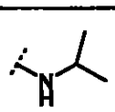
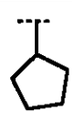
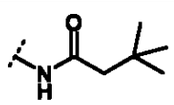
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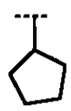
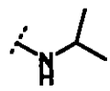
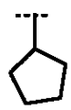
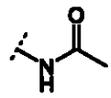
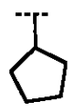
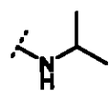
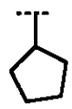
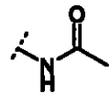
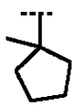
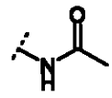
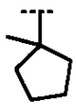
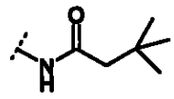
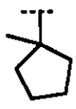
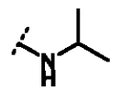
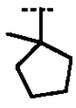
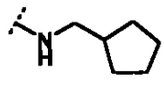
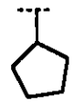
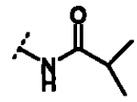
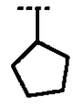
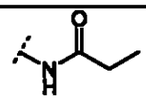
Cpd.	B	L^0	L^1	R^2
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1003		MeO-	MeO-	
1004		MeO-	MeO-	
1005		MeO-	Me-	
1006		MeO-	Me-	
1007		MeO-	Me-	
1008		MeO-	Me-	
1009		Me_2N-	Me-	
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1011		Me_2N-	Me-	

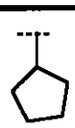
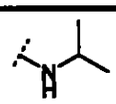
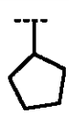
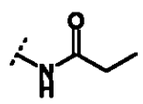
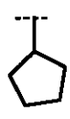
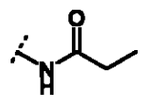
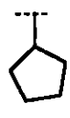
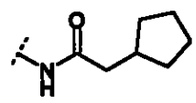
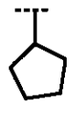
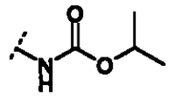
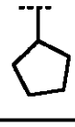
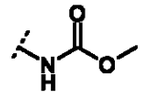
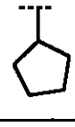
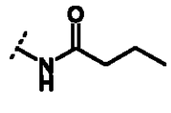
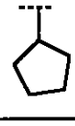
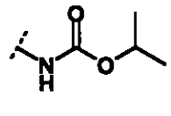
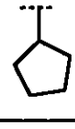
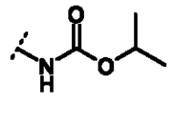
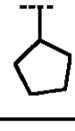
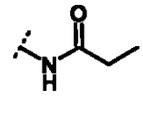
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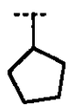
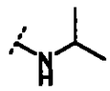
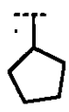
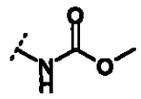
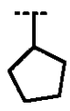
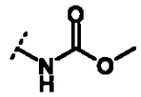
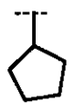
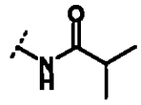
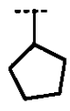
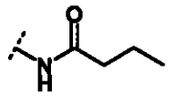
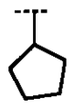
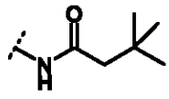
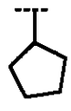
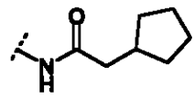
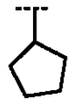
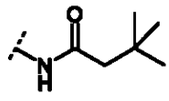
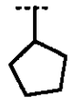
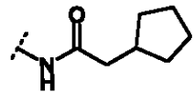
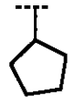
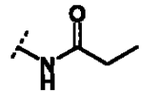
Cpd.	B	L^0	L^1	R^2
1012		Me_2N-	Me-	
1013		MeO-	Me-	
1014		MeO-	Me-	
1015		MeO-	Me-	
1016		MeO-	Me-	
1017		MeO-	Me-	
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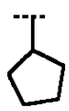
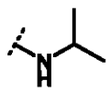
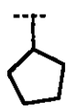
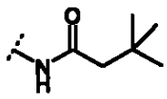
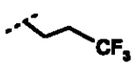
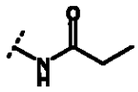
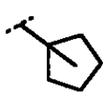
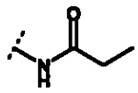
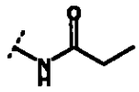
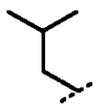
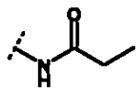
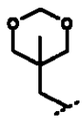
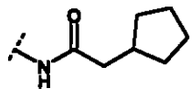
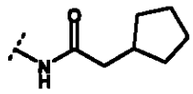
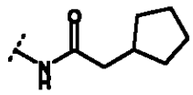
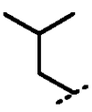
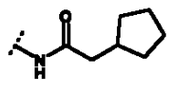
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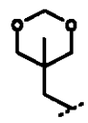
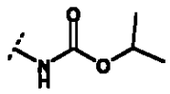
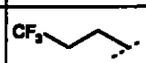
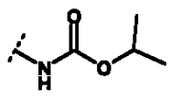
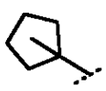
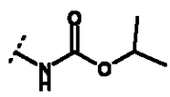
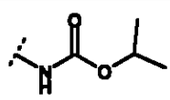
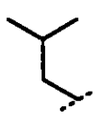
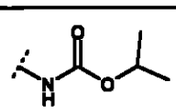
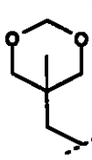
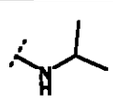
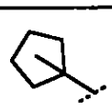
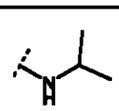
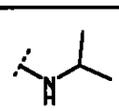
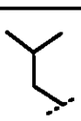
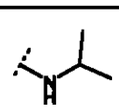
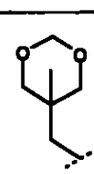
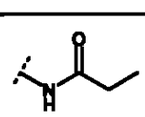
Cpd.	B	L^0	L^1	R^2
1022		MeO-	Et-	
1023		MeO-	Et-	
1024		MeO-	Me-	
1025		MeO-	Me-	
1026		MeO-	Me-	
1027		MeO-	Me-	
1028		MeO-	Br-	
1029		MeO-	Br-	
1030		MeO-	Br-	
1031		MeO-	Br-	

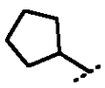
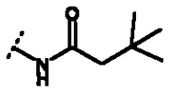
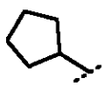
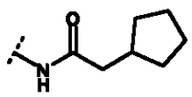
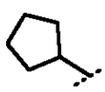
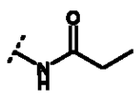
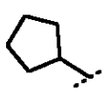
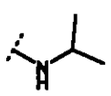
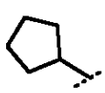
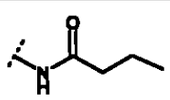
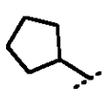
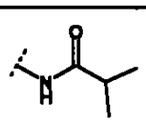
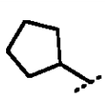
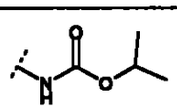
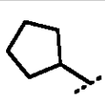
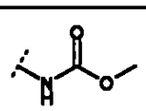
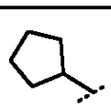
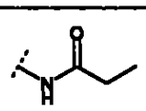
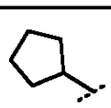
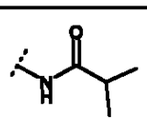
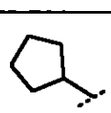
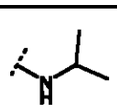
Cpd.	B	L^0	L^1	R^2
1032		tBuO-	Me-	
1033		tBuO-	Me-	
1034		HO-	Me-	
1035		HO-	Me-	
1036		MeO-	Me-	
1037		MeO-	Me-	
1038		MeO-	Me-	
1039		MeO-	Me-	
1040		MeO-	Me-	
1041		MeO-	Me-	

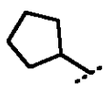
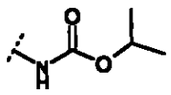
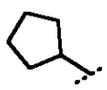
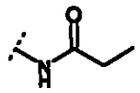
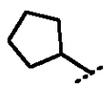
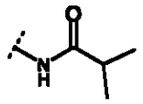
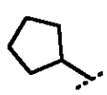
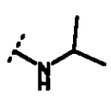
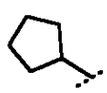
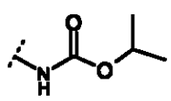
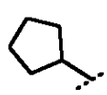
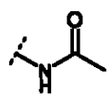
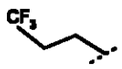
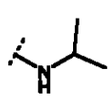
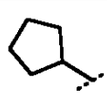
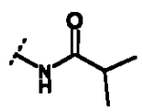
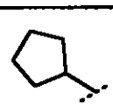
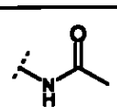
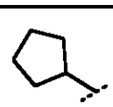
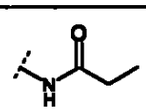
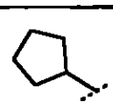
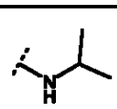
Cpd.	B	L^0	L^1	R^2
1042		MeO-	Cl	
1043		MeO-	Br	
1044		MeO-	Cl	
1045		MeO-	Cl	
1046		MeO-	Me-	
1047		MeO-	Me-	
1048		MeO-	Cl	
1049		MeO-	Br	
1050		MeO-	Cl	
1051		MeO-	F	

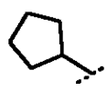
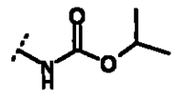
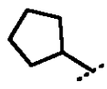
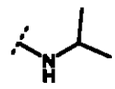
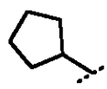
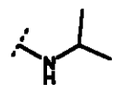
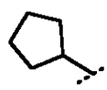
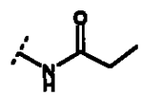
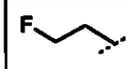
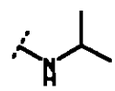
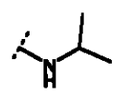
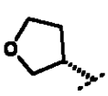
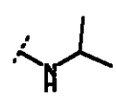
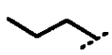
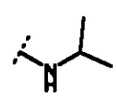
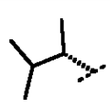
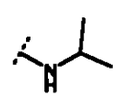
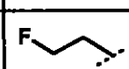
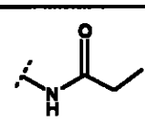
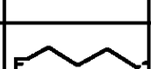
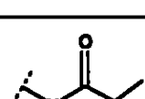
Cpd.	B	L^0	L^1	R^2
1052		MeO-	F	
1053		MeO-	Cl	
1054		MeO-	Br	
1055		MeO-	Br	
1056		MeO-	Br	
1057		HO	Me	
1058		HO	Me	
1059		H	Br	
1060		H	Br	
1061		H	Br	

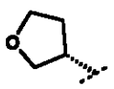
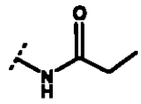
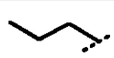
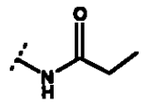
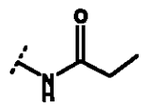
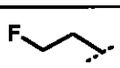
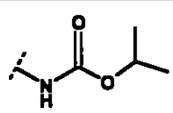
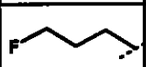
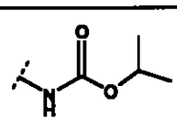
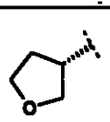
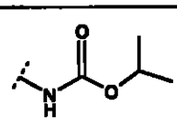
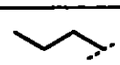
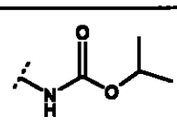
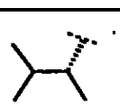
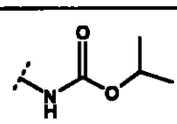
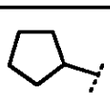
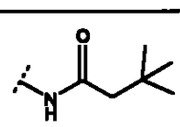
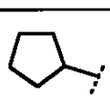
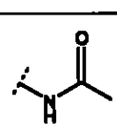
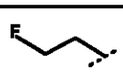
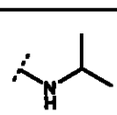
Cpd.	B	L^0	L^1	R^2
1062		H	Br	
1063		F	Me	
1064		MeO-	Br	
1065		MeO-	Br	
1066		MeO-	Br	
1067		MeO-	Br	
1068		MeO-	Br	
1069		MeO-	Br	
1070		MeO-	Br	
1071		MeO-	Br	

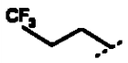
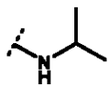
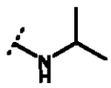
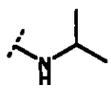
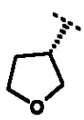
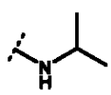
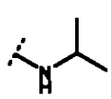
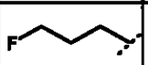
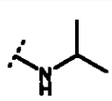
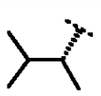
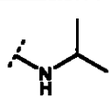
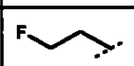
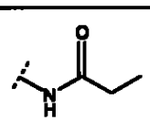
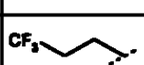
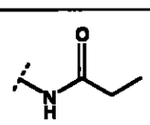
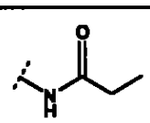
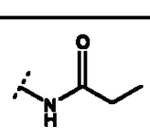
Cpd.	B	L^0	L^1	R^2
1072		MeO-	Br	
1073		MeO-	Br	
1074		MeO-	Br	
1075		MeO-	Br	
1076		MeO-	Br	
1077		MeO-	Br	
1078		MeO-	Br	
1079		MeO-	Br	
1080		MeO	Br	
1081		MeO	Br	

Cpd.	B	L^0	L^1	R^2
1082		H	Cl	
1083		H	Cl	
1084		H	Cl	
1085		H	Cl	
1086		H	Cl	
1087		H	Cl	
1088		H	Cl	
1089		H	Cl	
1090		EtO-	Br	
1091		EtO-	Br	
1092		EtO-	Br	

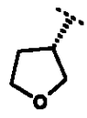
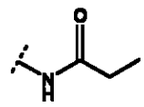
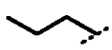
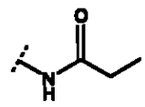
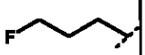
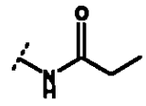
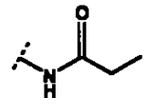
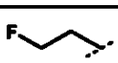
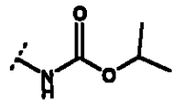
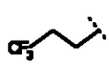
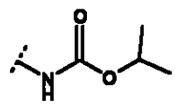
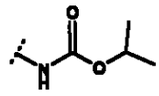
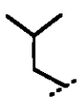
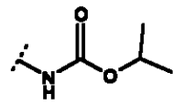
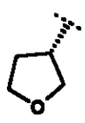
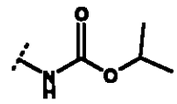
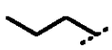
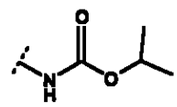
Cpd.	B	L^0	L^1	R^2
1093		EtO-	Br	
1094		PrO-	Br	
1095		PrO-	Br	
1096		PrO-	Br	
1097		PrO-	Br	
1098		H	Br	
1099		MeO-	Br	
1100		MeO-	Cl	
1101		EtO-	Me	
1102		EtO-	Me	
1103		EtO-	Me	

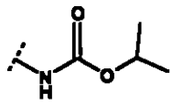
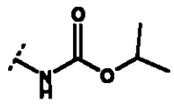
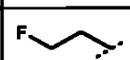
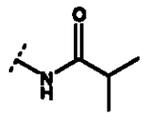
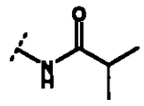
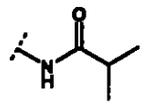
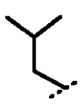
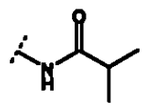
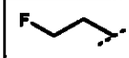
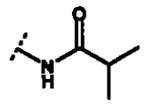
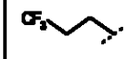
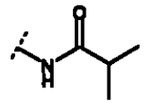
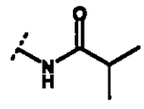
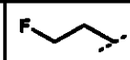
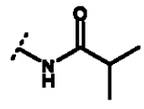
Cpd.	B	L^0	L^1	R^2
1104		EtO-	Me	
1105		MeO-	CN	
1106		Br	MeO-	
1107		MeO-	CN	
1108		MeO-	Br	
1109		MeO	Br	
1110		MeO-	Br	
1111		MeO-	Br	
1112		MeO-	Br	
1113		MeO-	Br	
1114		MeO	Br	

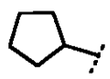
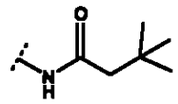
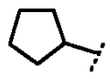
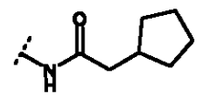
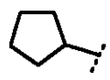
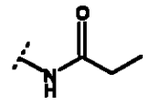
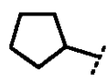
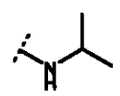
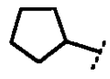
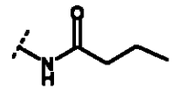
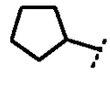
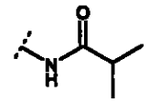
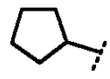
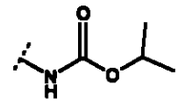
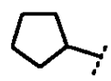
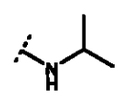
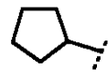
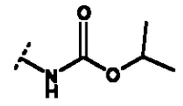
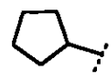
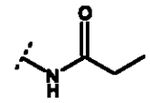
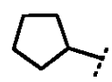
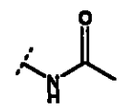
Cpd.	B	L^0	L^1	R^2
1115		MeO-	Br	
1116		MeO	Br	
1117		MeO	Br	
1118		MeO	Br	
1119		MeO	Br	
1120		MeO	Br	
1121		MeO	Br	
1122		MeO	Br	
1123		MeO	CN	
1124		MeO	CN	
1125		MeO-	Cl	

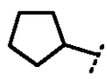
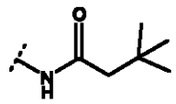
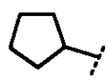
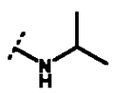
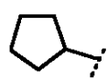
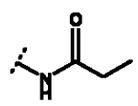
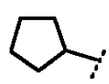
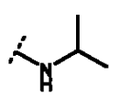
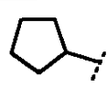
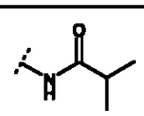
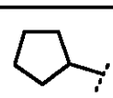
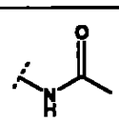
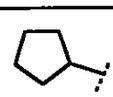
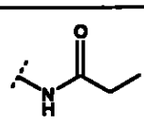
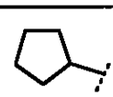
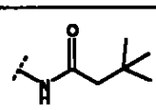
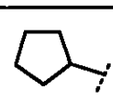
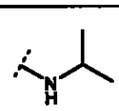
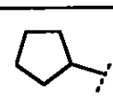
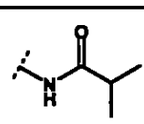
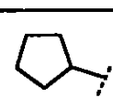
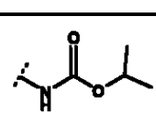
Cpd.	B	L^0	L^1	R^2
1126		MeO-	Cl	
1127		MeO	Cl	
1128		MeO	Cl	
1129		MeO	Cl	
1130		MeO	Cl	
1131		MeO	Cl	
1132		MeO	Cl	
1133		MeO	Cl	
1134		MeO	Cl	
1135		MeO	Cl	
1136		MeO	Cl	

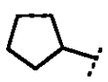
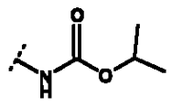
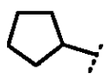
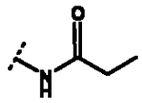
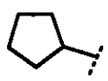
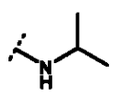
~~195~~
198

Cpd.	B	L^0	L^1	R^2
1137		MeO	Cl	
1138		MeO	Cl	
1139		MeO	Cl	
1140		MeO	Cl	
1141		MeO	Cl	
1142		MeO	Cl	
1143		MeO	Cl	
1144		MeO	Cl	
1145		MeO	Cl	
1146		MeO	Cl	

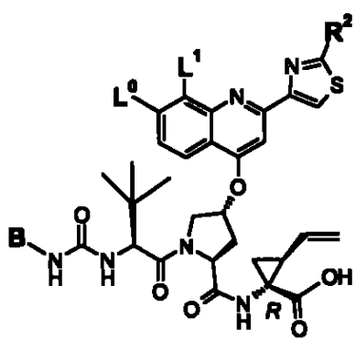
Cpd.	B	L^0	L^1	R^2
1147		MeO	Cl	
1148		MeO	Cl	
1149		MeO	Cl	
1150		MeO	Cl	
1151		MeO	Cl	
1152		MeO	Cl	
1153		MeO	Cl	
1154		MeO	Br	
1155		MeO	Br	
1156		MeO	Br	

Cpd.	B	L^0	L^1	R^2
1157		H	-SMe	
1158		H	-SMe	
1159		H	-SMe	
1160		H	-SMe	
1161		H	-SMe	
1162		H	-SMe	
1163		H	-SMe	
1164		H	$-CF_3$	
1165		H	$-CF_3$	
1166		H	$-CF_3$	
1167		Cl	Cl	

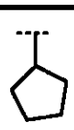
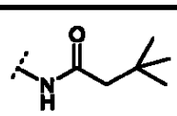
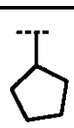
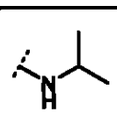
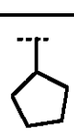
Cpd.	B	L^0	L^1	R^2
1168		Cl	Cl	
1169		Cl	Cl	
1170		Cl	Cl	
1171		H	$-SO_2Me$	
1172		H	$-SO_2Me$	
1173		H	Me-	
1174		H	Me-	
1175		H	Me-	
1176		H	Me-	
1177		H	Me-	
1178		H	Me-	

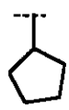
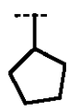
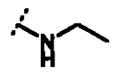
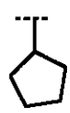
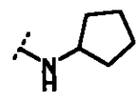
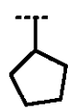
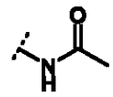
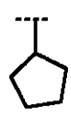
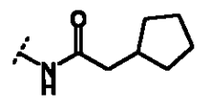
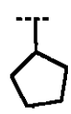
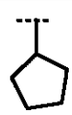
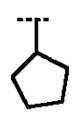
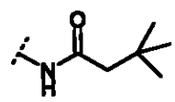
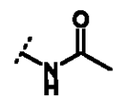
Cpd.	B	L^0	L^1	R^2
1179		H	$-SO_2Me$	
1180		H	$-SO_2Me$	
1181		H	-OMe	

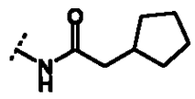
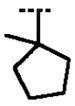
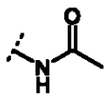
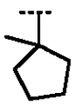
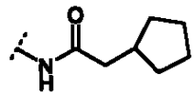
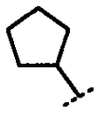
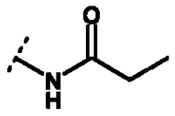
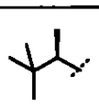
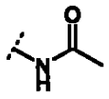
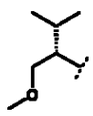
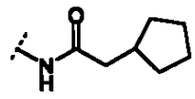
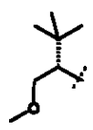
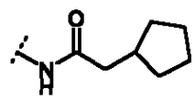
34. The compound according to claim 1 of the formula



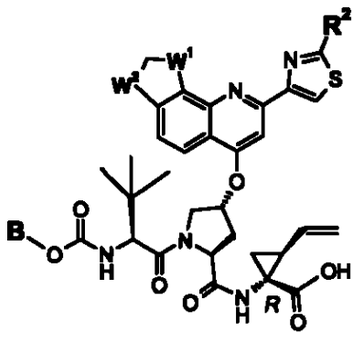
wherein B, L^0, L^1 and R^2 are defined as in the table below

Cpd. #	B	L^0	L^1	R^2
2001		MeO-	Me-	
2002		MeO-	Me-	
2003		MeO-	Me-	

Cpd. #	B	L^0	L^1	R^2
2004		MeO-	Me-	
2005		MeO-	Me-	
2006		MeO-	Me-	
2007		MeO-	Me-	
2008		MeO-	Me-	
2009		MeO-	Me-	
2010		MeO-	Me-	
2011		MeO-	Me-	
2012		MeO-	Me-	
2013		MeO-	Me-	

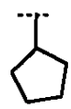
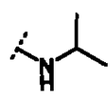
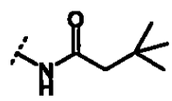
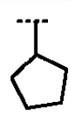
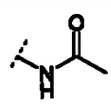
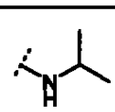
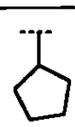
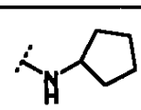
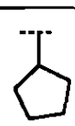
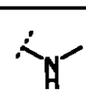
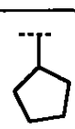
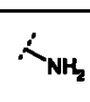
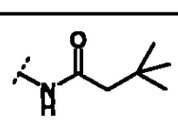
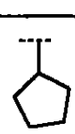
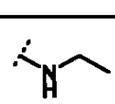
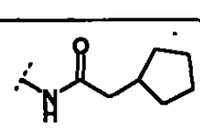
Cpd. #	B	L^6	L^1	R^2
2014		MeO-	Me-	
2015		MeO-	Me-	
2016		MeO-	Me-	
2017		MeO-	Br-	
2018		MeO-	Me-	
2019		MeO-	Me	
2020		MeO-	Me	

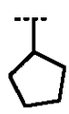
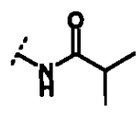
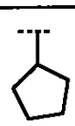
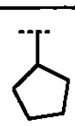
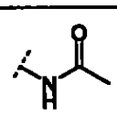
35. The compound according to claim 1 of the formula



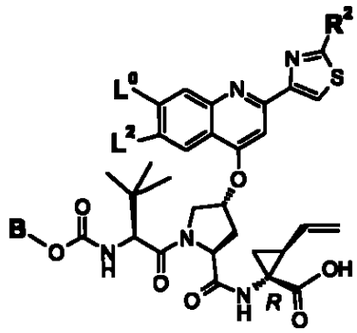
202
205

wherein B, W^1, W^2 and R^2 are defined as in the table below

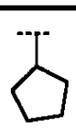
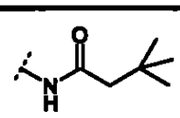
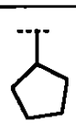
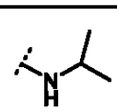
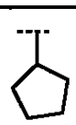
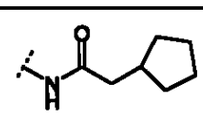
Cpd. #	B	W^1	W^2	R^2
3001		-O-	-O-	
3002		-O-	-O-	
3003		$-CH_2-$	-O-	
3004		$-CH_2-$	-O-	
3005		$-CH_2-$	-O-	
3006		$-CH_2-$	-O-	
3007		$-CH_2-$	-O-	
3008		$-CH_2-$	-O-	
3009		$-CH_2-$	-O-	
3010		$-CH_2-$	-O-	

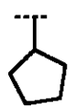
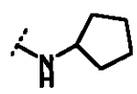
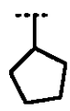
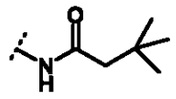
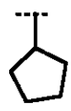
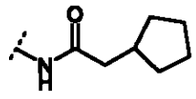
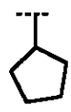
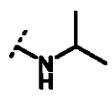
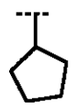
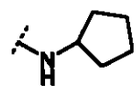
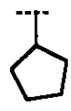
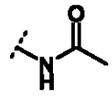
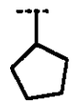
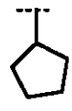
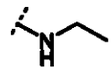
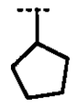
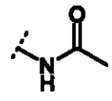
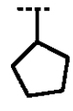
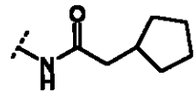
Cpd. #	B	W^1	W^2	R^2
3011		$-CH_2-$	$-CH_2-$	
3012		$-CH_2-$	$-CH_2-$	
3013		$-CH_2-$	$-CH_2-$	

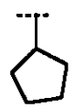
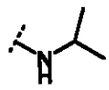
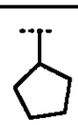
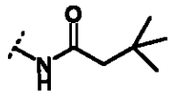
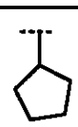
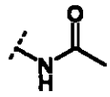
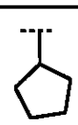
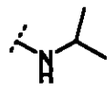
36. The compound according to claim 1 of the formula



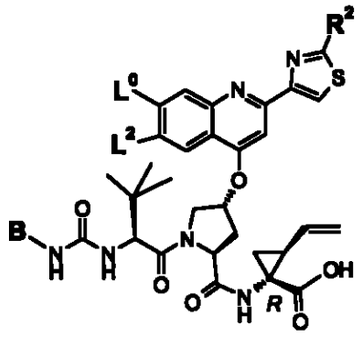
wherein B, L^0, L^2 and R^2 are defined as in the table below

Cpd. #	B	L^0	L^2	R^2
4001		MeO-	Me-	
4002		MeO-	Me-	
4003		MeO-	Me-	

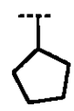
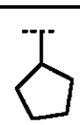
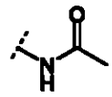
Cpd. #	B	L^1	L^2	R^2
4004		MeO-	Me-	
4005		Me_2N-	Me-	
4006		Me_2N-	Me-	
4007		Me_2N-	Me-	
4008		Me_2N-	Me-	
4009		MeO-	Me-	
4010		MeO-	Me-	
4011		MeO-	Me-	
4012		MeO-	MeO-	
4013		MeO-	MeO-	

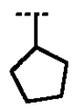
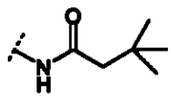
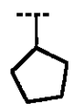
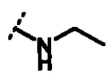
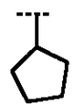
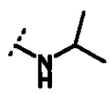
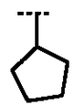
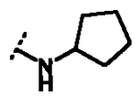
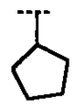
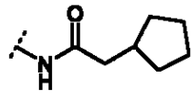
Cpd. #	B	L^0	L^2	R^2
4014		MeO-	MeO-	
4015		MeO-	MeO-	
4016		Me-	MeO-	
4017		Me-	MeO-	

37. The compound according to claim 1 of the formula

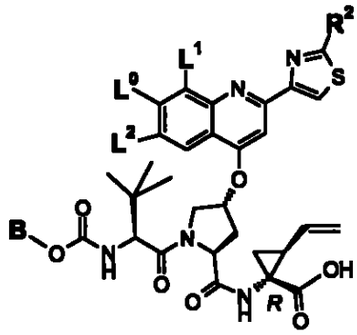


wherein B, L^0, L^2 and R^2 are defined as in the table below

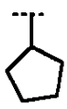
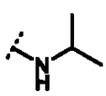
Cpd. #	B	L^0	L^2	R^2
5001		MeO-	Me-	
5002		MeO-	Me-	

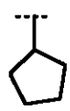
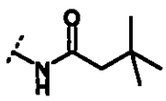
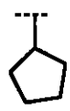
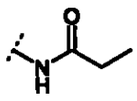
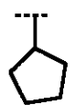
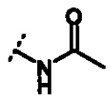
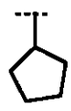
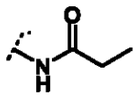
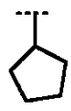
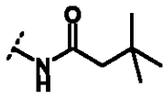
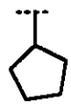
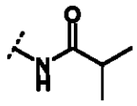
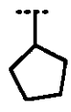
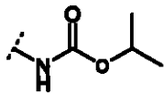
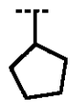
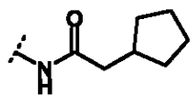
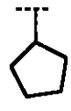
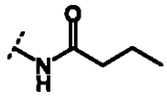
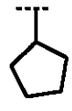
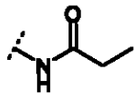
Cpd. #	B	L^0	L^2	R^2
5003		MeO-	Me-	
5004		MeO-	Me-	
5005		MeO-	Me-	
5006		MeO-	Me-	
5007		MeO-	Me-	

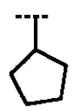
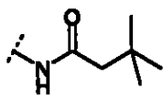
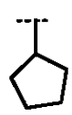
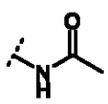
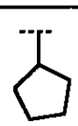
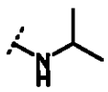
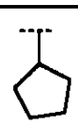
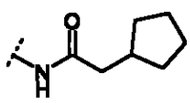
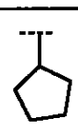
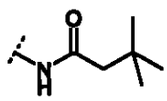
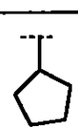
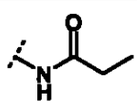
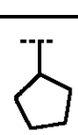
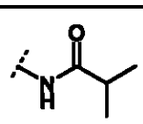
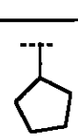
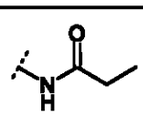
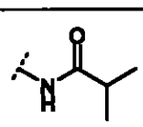
38. The compound according to claim 1 of the formula



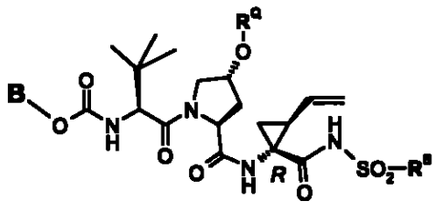
wherein B, L^0, L^1, L^2 and R^2 are defined as in the table below

Cpd. #	B	L^2	L^0	L^1	R^2
6001		MeO-	H	Me	

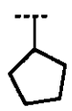
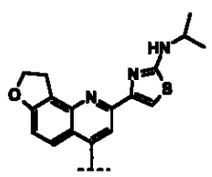
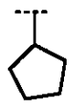
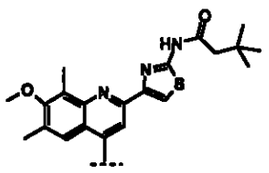
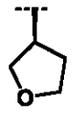
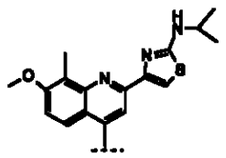
Cpd. #	B	L^3	L^0	L^1	R^2
6002		MeO-	H	Me	
6003		MeO-	H	Me	
6004		MeO-	H	Me	
6005		Me	H	Br	
6006		Me	H	Br	
6007		Me	H	Br	
6008		Me	H	Br	
6009		Me	H	Br	
6010		Me	H	Br	
6011		Me	H	Me	

Cpd. #	B	L^2	L^9	L^1	R^2
6012		Me	H	Me	
6013		Me	H	Me	
6014		Me	H	Me	
6015		Me	MeO-	Me	
6016		Me	MeO-	Me	
6017		Br	H	Br	
6018		Br	H	Br	
6019		Br	H	Cl	
6020		Br	H	Cl	

39. The compound according to claim 1 of the formula



wherein B, R^Q and R^S are defined as in the table below

Cpd. #	B	R^Q	R^S
7001			
7002			
7003			

40. A pharmaceutical composition comprising an anti-hepatitis C virally effective amount of a compound of formula I according to one or more of claims 1 to 39 or a pharmaceutically acceptable salt or ester thereof, in admixture with a pharmaceutically acceptable carrier medium or auxiliary agent.

41. The pharmaceutical composition according to claim 40 further comprising a therapeutically effective amount of at least one other antiviral agent.

42. The pharmaceutical composition according to claim 41, wherein said antiviral agent is ribavirin.

43. The pharmaceutical composition according to claim 41, wherein said antiviral agent is selected from another anti-HCV agent, HIV inhibitor, HAV inhibitor and HBV inhibitor.

44. The pharmaceutical composition according to claim 43, wherein said other anti-HCV agent is selected from immunomodulatory agents, other inhibitors of HCV NS3 protease, inhibitors of HCV polymerase and inhibitors of another target in the HCV life cycle.

45. The pharmaceutical composition according to claim 44, wherein said immunomodulatory agent is selected from α-interferon and pegylated α-interferon.

46. The pharmaceutical composition according to claim 44, wherein said inhibitor of another target in the HCV life cycle is selected from inhibitors of: helicase, NS2/3 protease and internal ribosome entry site (IRES).

47. A method for the treatment or prevention of a hepatitis C viral infection in a mammal by administering to the mammal an anti-hepatitis C virally effective amount of a compound of formula I according to one or more of claims 1 to 39, or a pharmaceutically acceptable salt or ester thereof.

48. A method for the treatment or prevention of a hepatitis C viral infection in a mammal by administering thereto an anti-hepatitis C virally effective amount of a compound of formula I according to one or more of claims 1 to 39, or a pharmaceutically acceptable salt or ester thereof in combination with at least one other antiviral agent.

49. The method according to claim 48, wherein said antiviral agent is ribavirin.

50. The method according to claim 48, wherein said other antiviral agent is

selected from another anti-HCV agent, HIV inhibitor, HAV inhibitor and HBV inhibitor.

51. The method according to claim 50, wherein said other anti-HCV agent is selected from immunomodulatory agents, other inhibitors of HCV NS3 protease, inhibitors of HCV polymerase and inhibitors of another target in the HCV life cycle.

52. The method according to claim 51, wherein said immunomodulatory agent is selected from α-interferon and pegylated α-interferon.

53. The method according to claim 51, wherein said inhibitor of another target in the HCV life cycle is selected from inhibitors of: helicase, NS2/3 protease and internal ribosome entry site (IRES).

54. Use of a compound of formula I, including a pharmaceutically acceptable salt or ester thereof, according to one or more of claims 1 to 39 for the manufacture of a medicament for the treatment or prevention of hepatitis C viral infection in a mammal.

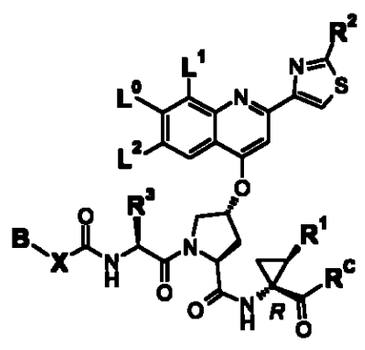
55. A method of inhibiting the replication of hepatitis C virus by exposing the virus to a hepatitis C viral NS3 protease inhibiting amount of the compound of formula (I) according to one or more of claims 1 to 39, or a pharmaceutically acceptable salt or ester thereof.

56. An article of manufacture comprising packaging material contained within which is a composition effective to treat an HCV infection or to inhibit the NS3 protease of HCV and the packaging material comprises a label which indicates that the composition can be used to treat infection by the hepatitis C virus, and wherein said composition comprises a compound of formula (I) according to one or more of claims 1 to 39 or a pharmaceutically acceptable salt or ester thereof.

212
275

ABSTRACT

Compounds of formula (I):



(I)

wherein B, X, R^3, L^0, L^1, L^2, R^2, R^1 and R^C are defined herein. The compounds are useful as inhibitors of HCV NS3 protease for the treatment of hepatitis C viral infection.

SEQUENCE LISTING

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<140> 60/472709
<141> 2003-05-21

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COMPUESTOS INHIBIDORES DE LA HEPATITIS C

CAMPO DE LA INVENCIÓN

La presente invención se refiere a compuestos, a procesos para su síntesis, a composiciones y métodos para el tratamiento de la infección por el virus de la hepatitis C (VHC). En particular, la presente invención provee nuevos análogos de péptidos, composiciones farmacéuticas que contienen tales análogos y métodos para utilizar estos análogos en el tratamiento de la infección por el VHC.

ANTECEDENTES DE LA INVENCIÓN

El virus de la hepatitis C (VHC) es el principal agente etiológico de la post-transfusión, de hepatitis que no es A ni B adquirido por la comunidad en el mundo. Se estima que más de 200 millones de personas en el mundo se encuentran infectadas por el virus. Un alto porcentaje de portadores se infectan de manera crónica y muchos progresan a la enfermedad hepática crónica, denominada hepatitis C crónica. A su vez, este grupo se encuentra en alto riesgo de enfermedad hepática grave, tal como cirrosis hepática, carcinoma hepatocelular y enfermedad hepática terminal que produce la muerte.

El mecanismo mediante el cual el VHC establece una persistencia viral y produce un alto grado de enfermedad hepática crónica aún no se dilucidó completamente. No se sabe cómo el VHC interactúa y evade el sistema inmune del huésped. Además, los roles de las respuestas inmunes celulares y humorales en protección contra la infección y enfermedad del VHC aún se deben determinar. Se reportaron inmunoglobulinas para la profilaxis de hepatitis viral asociada con la transfusión, sin embargo el Centro de Control de Enfermedades no recomienda actualmente el tratamiento de inmunoglobulina con este fin. La falta de una respuesta inmune protectora efectiva dificulta el desarrollo de una vacuna o de medidas adecuadas de profilaxis posteriores a la exposición, por lo tanto, a corto plazo, se tienen firmes esperanzas en las intervenciones antivirales.

Se llevaron a cabo varios estudios clínicos con el fin de identificar agentes farmacéuticos capaces de tratar efectivamente la infección del VHC en pacientes que padecen hepatitis C crónica. Estos estudios involucraron el uso del interferón alfa, solo y en combinación con otros agentes antivirales. Tales estudios mostraron que una cantidad significativa de participantes no responde a estas terapias, y de aquellos que responden favorablemente, se descubrió que una gran cantidad sufría una recidiva después de terminar el tratamiento.

Hasta hace poco el interferón (IFN) fue la única terapia disponible de beneficio probado aprobado en las prácticas clínicas para pacientes que padecen hepatitis C

crónica. Sin embargo, el grado de respuesta prolongada es bajo, y el tratamiento de interferón también induce efectos secundarios graves (es decir, retinopatía, tiroiditis, pancreatitis aguda, depresión) que disminuyen la calidad de vida de los pacientes tratados. Recientemente, el interferón en combinación con ribavirin se aprobó para pacientes que no respondieron al IFN solo. No obstante, los efectos secundarios producidos por el IFN no se alivian con esta terapia de combinación. Las formas pegiladas de interferones tales como PEG-Intron® y Pegasys® se pueden referir en apariencia parcialmente a estos efectos secundarios perjudiciales pero los fármacos antivirales aún persisten como la opción para el tratamiento oral del VHC.

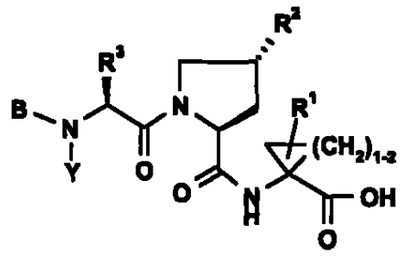
Por lo tanto, existe la necesidad de desarrollar agentes antivirales efectivos para el tratamiento de la infección del VHC que superen las limitaciones de las teraplas farmacéuticas existentes.

El VCH es un virus de ARN de hebra positiva envuelta en la familia Flaviviridae. El genoma de ARN del VHC de hebra simple es de aproximadamente 9500 nucleótidos en extensión y posee un marco de lectura abierto simple (ORF) que codifica una poliproteína grande simple de alrededor de 3000 aminoácidos. En células infectadas, esta poliproteína se escinde en múltiples lugares mediante proteasas celulares y virales para producir las proteínas estructurales y no estructurales (NS). En el caso del VHC, la generación de proteínas no estructurales maduras (NS2, NS3, NS4A, NS4B, NS5A y NS5B) se lleva a cabo mediante dos proteasas virales. La primera, según se caracterizó escasamente, se escinde en la unión NS2-NS3 (en la presente en lo sucesivo denominada proteasa NS2/3); la segunda es una serino proteasa incluida en la región de terminal N de NS3 (proteasa NS3) y todas las escisiones posteriores corriente abajo de NS3, ambas en *cis*, en el lugar de escisión NS3-NS4A, y en *trans*, para los lugares de NS4A-NS4B, NS4B-NS5A, NS5A-NS5B restantes. La proteína NS4A parece desempeñar múltiples funciones, actuando como co-factor para la proteasa NS3 y posiblemente asistiendo en la localización en membrana de NS3 y de otros componentes de replicasa virales. La formación compleja de la proteasa de NS3 con NS4A parece necesaria para los eventos de procesamiento, mejorando la eficiencia proteolítica en todos los sitios. La proteína NS3 también muestra actividades de nucleosida trifosfatasa y ARN helicasa. NS5B es una ARN polimerasa dependiente del ARN que está involucrada en la replicación del VHC.

Una estrategia general para el desarrollo de agentes antivirales es inactivar las enzimas viralmente codificadas que son esenciales para la replicación del virus.

Más recientemente, se descubrió que la proteasa NS3 posee potencialmente un impacto adicional bloqueando la actividad antiviral celular mediada por IFN en la célula infectada (Foy *et al.*, *Science*, 17 April 2003). Esto da crédito a una hipótesis de que la proteasa NS3/NS4A puede representar un blanco terapéutico doble, cuya inhibición puede bloquear la replicación viral y restaurar la respuesta del interferón de las células infectadas por el VHC.

En WO 00/09543, los compuestos de fórmula



en la cual un significado preferido de R^2 es un residuo de quinolinilo no sustituido o mono- o disustituido según se definió en la misma, se describen como inhibidores de proteasa NS3 viral de la hepatitis C, una enzima esencial para la replicación del virus de la hepatitis C.

La presente invención provee compuestos tripeptídicos que poseen potencia mejorada contra la proteasa NS3 del VHC. Además, se proporcionan compuestos sumamente activos en cultivo celular.

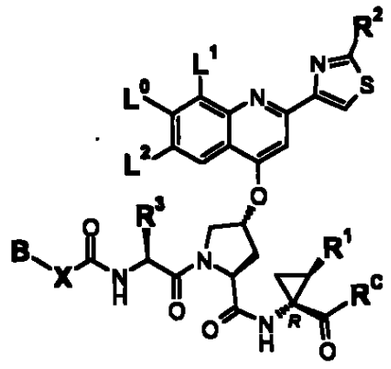
Una ventaja de un aspecto de la presente invención reside en que los compuestos de acuerdo con la presente invención inhiben específicamente la proteasa NS3 y no muestran actividad inhibidora significativa contra otras serina proteasas humanas tales como la leucocito elastasa humana (HLE), o cisteína proteasas tales como la catepsina B humana hepática (Cat B).

En comparación con los compuestos según revelados en WO 00/09543, los compuestos provistos en la presente invención muestran ventajas inesperadas. En general, estos muestran una o más de las siguientes ventajas:

- Valores inferiores de IC_{50} en un ensayo de proteasa de NS3-NS4A;
- Valores inferiores de EC_{50} en un ensayo de replicación de ARN del VHC basado en células;
- Mejor solubilidad; y/o
- Niveles plasmáticos superiores cuando se administran por vía oral en rata.

SÍNTESIS DE LA INVENCIÓN

En el alcance de la invención se incluye un racemato, diasteroisómero o isómero óptico de un compuesto de fórmula (I):



I

en la cual

B es alquilo (C_{1-10}), cicloalquilo (C_{3-7}), o alquil (C_{1-4})-cicloalquilo (C_{3-7}),

a) donde dicho alquilo, cicloalquilo y alquil-cicloalquilo pueden estar mono-, di- o tri-sustituidos con alquilo (C_{1-3}); y

b) donde dicho alquilo, cicloalquilo y alquil-cicloalquilo pueden estar mono- o disustituidos con sustituyentes seleccionados de hidroxi y O-alquilo -(C_{1-4}); y

c) donde cada uno de dichos grupos alquilo puede estar mono-, di- o tri-sustituido con halógeno; y

d) donde cada uno de dichos grupos cicloalquilo es de 4, 5, 6 o 7 miembros que poseen opcionalmente uno (para los de 4, 5, 6, o 7 miembros) o dos (para el de 5, 6 o 7 miembros) grupos $-CH_2-$ no se encuentran unidos entre sí directamente se reemplazan con -O- de manera que el átomo de O se una al grupo X mediante al menos dos átomos de C;

X es O o NH;

R^3 es alquilo (C_{2-6}), cicloalquilo (C_{3-7}) o alquil (C_{1-3})-cicloalquilo (C_{3-7}), donde cada uno de dichos grupos alquilo, cicloalquilo y alquil-cicloalquilo puede estar mono-, di- o tri-sustituido con alquilo (C_{1-4});

L^0 es H, halógeno, alquilo (C_{1-4}), –OH, –O-alquilo (C_{1-4}), $-NH_2$, –NHalquilo (C_{1-4}) o -N(alquil (C_{1-4}))$_2$;

L^1, L^2 son cada uno independientemente halógeno, ciano, alquilo (C_{1-4}), -O-alquilo (C_{1-4}), -S-alquilo (C_{1-4}), -SO-alquilo (C_{1-4}), o $-SO_2$-alquilo (C_{1-4}), donde cada uno de dichos grupos alquilo está sustituido opcionalmente con uno a tres átomos de halógeno; y cualquiera de L^1 o L^2 (pero no los dos al mismo tiempo) también puede ser H; o

L^0 y L^1 o

L^0 y L^2 pueden estar unidos covalentemente para formar, junto con los dos átomos de C a los cuales están unidos, un anillo carbocíclico de 5 o 6 miembros donde uno o dos grupos $-CH_2-$ que no se encuentran vinculados directamente entre sí se pueden reemplazar cada uno directamente con -O- o NR^a, donde R^a es H o alquilo (C_{1-4}) y donde cada anillo carbocíclico o heterocíclico está monosustituido o polisustituido opcionalmente con alquilo (C_{1-4});

R^2 es R^{20}, $-NR^{22}COR^{20}$, $-NR^{22}COOR^{20}$ $-NR^{22}R^{21}$ y $-NR^{22}CONR^{21}R^{23}$, donde

R^{20} se selecciona de alquilo (C_{1-6}), cicloalquilo (C_{3-7}) y alquil (C_{1-4})-cicloalquilo (C_{3-7}), donde dicho cicloalquilo y alquil-cicloalquilo pueden estar mono-, di- o tri-sustituidos con alquilo (C_{1-3});

R^{21} es H o R^{20} según se definió anteriormente,

R^{22} y R^{23} se seleccionan independientemente de H y metilo,

R^1 es etilo o vinilo;

R^C es hidroxi o $NHSO_2R^8$ donde R^8 es alquilo (C_{1-6}), cicloalquilo (C_{3-7}), alquil (C_{1-6})-cicloalquilo (C_{3-7}), fenilo, naftilo, piridinilo, alquil (C_{1-4})-fenilo, alquil (C_{1-4})-naftilo o alquil (C_{1-4})-piridinilo; estando cada uno de los cuales mono-, di- o tri-sustituido opcionalmente con sustituyentes seleccionados de halógeno, hidroxi, ciano, alquilo (C_{1-4}), O-alquilo (C_{1-6}), $-CO-NH_2$, -CO-NHalquilo (C_{1-4}), -CO-N(alquil (C_{1-4}))$_2$, $-NH_2$, -NHalquilo (C_{1-4}) y -N(alquil (C_{1-4}))$_2$, donde alquilo (C_{1-4}) y O-alquilo (C_{1-6}) están sustituidos opcionalmente con uno a tres átomos de halógeno; y estando cada uno de los mismos monosustituido opcionalmente con nitro;

o R^8 es $-N(R^{N2})R^{N1})$, donde R^{N1} y R^{N2} se seleccionan independientemente de H, alquilo (C_{1-6}), cicloalquilo (C_{3-7}), alquil (C_{1-6})-cicloalquilo (C_{3-7}), arilo y alquil (C_{1-6})-arilo; donde dicho alquilo (C_{1-6}), cicloalquilo (C_{3-7}), alquil (C_{1-6})-cicloalquilo (C_{3-7}), arilo y alquil (C_{1-6})-arilo están sustituidos opcionalmente con uno o más sustituyentes seleccionados independientemente de halógeno, alquilo (C_{1-6}), hidroxi, ciano, O-alquilo (C_{1-6}), $-NH_2$, -NHalquilo (C_{1-4}), -N(alquil (C_{1-4}))$_2$, $-CO-NH_2$, -CO-NHalquilo (C_{1-4}), -CO-N(alquil (C_{1-4}))$_2$, -COOH y –COO-alquilo (C_{1-6}); o

R^{N2} y R^{N1} se unen, junto con el nitrógeno al cual están unidos, para formar un heterociclo monocíclico saturado o no saturado de 3 a 7 miembros o un heterociclo bicíclico saturado o no saturado de 9 o 10 miembros, cada uno de los cuales conteniendo opcionalmente de uno a tres heteroátomos adicionales seleccionados independientemente de N, S y O y estando cada uno de los cuales sustituido opcionalmente con uno o más sustituyentes seleccionados independientemente de halógeno, alquilo (C_{1-6}), hidroxi, ciano, O-alquilo (C_{1-6}), $-NH_2$, -NHalquilo (C_{1-4}), -N(alquil

$(C_{1-4}))_2$, -CO-NH_2, -CO-NHalquilo (C_{1-4}), -CO-N(alquil (C_{1-4}))$_2$, –COOH y –COO-alquilo (C_{1-6});

o una sal o éster aceptable para uso farmacéutico del mismo.

En el alcance de la presente invención se incluye una composición farmacéutica que comprende una cantidad efectiva anti-hepatitis C para combatir virus de un compuesto de fórmula I, o una sal o éster aceptable para uso farmacéutico del mismo, en mezcla con al menos un medio vehículo o agente auxiliar aceptable para uso farmacéutico.

De acuerdo con un aspecto adicional de la presente invención, la composición farmacéutica de acuerdo con la presente invención comprende adicionalmente una cantidad terapéuticamente efectiva de al menos un agente antiviral.

Otro aspecto importante de la presente invención incluye un método para tratar o prevenir una infección por el virus de la hepatitis C en un mamífero en un mamífero administrando al mamífero una cantidad anti-hepatitis C efectiva para combatir virus de un compuesto de fórmula I, una sal o éster aceptable para uso farmacéutico del mismo, o una composición según se describió anteriormente, solos o en combinación con al menos un agente antiviral, administrados juntos o por separado.

También se encuentran dentro del alcance de la presente invención el uso de un compuesto de fórmula I, o una sal o éster aceptable para uso farmacéutico del mismo, según se describe en la presente, para la fabricación de un medicamento para el tratamiento o prevención de la infección por el virus de la hepatitis C en un mamífero.

DESCRIPCIÓN DETALLADA DE LAS REALIZACIONES PREFERIDAS

Definiciones

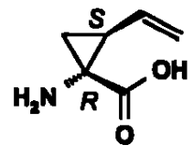
Según se emplea en la presente, las siguientes definiciones se aplican salvo que se indique lo contrario:

Con referencia a las instancias donde *(R)* o *(S)* se emplea para designar la configuración absoluta de un sustituyente o centro asimétrico de un compuesto de fórmula I, la designación se realiza en el contexto del compuesto completo y no en el contexto del sustituyente o centro asimétrico solo.

La designación "P1, P2 y P3" según se emplea en la presente se refiere a la posición de los residuos de aminoácidos comenzando desde el extremo C-terminal de los análogos peptídicos y extendiéndose hacia el extremo N-terminal (es decir, P1 se refiere a la posición 1 desde el extremo C-terminal, P2: segunda posición desde el extremo C-terminal, etc.) (ver Berger A. & Schechter I., Transactions of the Royal Society London series B257, 249-264 (1970)).

223

Según se emplea en la presente, el término "(1*R*, 2*S*)-vinil-ACCA" se refiere a un compuesto de fórmula:



a saber, ácido (*1R, 2S*) 1-amino-2-etenilciclopropancarboxílico.

El término "alquilo (C1-n)" según se emplea en la presente, ya sea solo o en combinación con otro sustituyente, significa sustituyentes alquilo de cadena acíclica, recta o ramificada que contienen de 1 a n átomos de carbono. "Alquilo (C_{1-6})" incluye, pero sin limitación, metilo, etilo, n-propilo, n-butilo, 1-metiletilo (i-propilo), 1-metilpropilo, 2-metilpropilo, 1,1-dimetiletilo (*ter*-butilo), pentilo y hexilo. Las abreviaturas Me y Pr denotan un grupo metilo y n-propilo, respectivamente.

El término "cicloalquilo (C_{3-7})" según se emplea en la presente, ya sea solo o en combinación con otro sustituyente, significa un sustituyente cicloalquilo que contiene de 3 a 7 átomos de carbono e incluye, pero sin limitación, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo.

El término "alquil (C1-n)-cicloalquilo (C_{3-7})" según se emplea en la presente significa un radical alquileno que contiene 1 a n átomos de carbono al cual se encuentra unido directamente un radical cicloalquilo que contiene de 3 a 7 átomos de carbono; e incluye, pero sin limitación, ciclopropilmetilo, ciclobutilmetilo, ciclopentilmetilo, 1-ciclopentiletilo, 2-ciclopentiletilo, ciclohexilmetilo, 1-ciclohexiletilo, 2-ciclohexiletilo y cicloheptilpropilo.

El término arilo o "arilo C_6 o C_{10}" según se emplea en la presente de manera intercambiable, ya sea solo o en combinación con otro radical, significa ya sea un grupo aromático monocíclico que contiene 6 átomos de carbono o un grupo aromático bicíclico que contiene 10 átomos de carbono. Arilo incluye, pero sin limitación, fenilo, 1-naftilo o 2-naftilo.

Según se emplea en la presente, el término "alquil (C1-n)-arilo" significa un radical alquilo que contiene de 1 a n átomos de carbono al cual se encuentra unido un arilo. Ejemplos de alquil (C_{1-3})-arilo incluyen, pero sin limitaciónn, bencil (fenilmetilo), 1-feniletilo, 2-feniletilo y fenilpropilo.

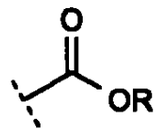
El término "O-alquilo (C_{1-n})" o "alcoxi (C_{1-n})" según se emplea en la presente, ya sea solo o en combinación con otro radical, significa el radical -O-alquilo (C1-n) donde alquilo es según se definió anteriormente que contiene de 1 a n átomos de carbono e

224

incluye metoxi, etoxi, propoxi, 1-metiletoxi, butoxi y 1,1-dimetiletoxi. El último radical se conoce comúnmente como *ter*-butoxi.

El término "halo" o "halógeno" según se emplea en la presente significa un sustituyente halógeno seleccionado de fluoro, cloro, bromo o yodo.

El término "éster aceptable para uso farmacéutico" según se emplea en la presente, ya sea solo o en combinación con otro sustituyente, significa ésteres del compuesto de fórmula I en el cual cualquiera de las funciones del carboxilo de la molécula, pero preferentemente el extremo carboxi, se reemplaza por una función alcoxicarbonilo:



en la cual el resto R del éster se selecciona de alquilo (incluyendo, pero sin limitación, metilo, etilo, *n*-propilo, t-butilo, *n*-butilo); alcoxialquilo (incluyendo, pero sin limitarse a metoximetilo); alcoxiacilo (incluyendo, pero sin limitarse a acetoximetilo); alquil-arilo (incluyendo, pero sin limitación a bencilo); ariloxialquilo (incluyendo, pero sin limitación a fenoximetilo); arilo (incluyendo, pero sin limitación a fenilo), sustituido opcionalmente con halógeno, alquilo (C_{1-4}) o alcoxi (C_{1-4}). Otros ésteres pro-fármacos adecuados se puede encontrar en Design of prodrugs, Bundgaard, H. Ed. Elsevier (1985). Tales ésteres aceptables para uso farmacéutico se hidrolizan comúnmente *in vivo* cuando se inyectan en un mamífero y se transforman en la forma ácida del compuesto de fórmula I. Con respecto a los ésteres descriptos anteriormente, salvo que se especifique lo contrario, cualquier resto alquilo presente contiene ventajosamente 1 a 16 átomos de carbono, en especial 1 a 6 átomos de carbono. Cualquier resto arilo presente en tales ésteres comprende de manera ventajosa un grupo fenilo. En especial, los ésteres pueden ser un éster alquilo C_{1-16}, un éster bencilo no sustituido o un bencil éster sustituido con al menos un halógeno, alquilo C_{1-6}, alcoxi C_{1-6}, nitro o trifluorometilo.

El término "sal aceptable para uso farmacéutico" significa una sal de un compuesto de fórmula (I) que es, en el alcance del criterio médico acertado, adecuado para emplear en contacto con los tejidos de seres humanos y animales inferiores sin toxicidad, irritación, respuesta alérgica indebidas y similares, conmensuradas con una relación razonable riesgo/beneficio, en general soluble o dispersable en agua o aceite y efectivos para el fin que se pretende.

222
225

El término incluye sales ácidos de adición aceptables para uso farmacéutico y sales base de adición aceptables para uso farmacéutico. Se pueden encontrar listados de sales adecuadas en, por ej., S.M. Birge et al., J. Pharm. Sci., 1977, 66, pp. 1-19.

El término "sal de adición con ácido aceptable para uso farmacéutico" significa aquellas sales que retiene la efectividad biológica y las propiedades de las bases libres y que no son indeseables ni biológicamente ni de otra manera, formadas con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido sulfámico, ácido nítrico, ácido fosfórico y similares y ácidos orgánicos tales como ácido acético, ácido trifluoroacético, ácido adípico, ácido ascórbico, ácido aspártico, ácido bencensulfónico, ácido benzoico, ácido butírico, ácido alcanfórico, ácido alcanforsulfónico, ácido cinámico, ácido cítrico, ácido diglucónico, ácido etansulfónico, ácido glutámico, ácido glicólico, ácido glicerofosfórico, ácido hemisulfónico, ácido hexanoico, ácido fórmico, ácido fumárico, ácido 2-hidroxietansulfónico (ácido isetiónico), ácido láctico, ácido hidroximaleico, ácido málico, ácido malónico, ácido mandélico, ácido mesitilensulfónico, ácido metansulfónico, ácido naftalensulfónico, ácido nicotínico, ácido 2-naftalensulfónico, ácido oxálico, ácido pamoico, ácido pectínico, ácido fenilacético, ácido 3-fenilpropiónico, ácido piválico, ácido propiónico, ácido pirúvico, ácido salicílico, ácido esteárico, ácido succínico, ácido sulfanílico, ácido tartárico, ácido p-toluensulfónico, ácido undecanoico y similares.

El término "sal de adición con base aceptable para uso farmacéutico" significa aquellas sales que retienen la efectividad biológica y las propiedades los de ácidos libres y que no son indeseables biológicamente o de otra manera, formadas con bases orgánicas tales como amoníaco o hidróxido, carbonato o bicarbonato de amonio o un catión metálico tal como sodio, potasio, litio, calcio, magnesio, hierro, cinc, cobre, manganeso, aluminio y similares. Se prefieren, en especial, sales de amonio, potasio, sodio, calcio y magnesio. Las sales que derivan de bases no tóxicas orgánicas aceptables para uso farmacéutico incluyen sales de aminas primarias, secundarias y terciarias, compuestos cuaternarios de amina, aminas sustituidas incluyendo aminas sustituidas de origen natural, aminas cíclicas y resinas de básicas de intercambio iónico, tal como metilamina, dimetilamina, trimetilamina, etilamina, dietilamina, trietilamina, isopropilamina, tripropilamina, tributilamina, etanolamina, dietanolamina, 2-dimetilaminoetanol, 2-dietilaminoetanol, diciclohexilamina, lisina, arginina, histidina, cafeína, hidrabamina, colina, betaína, etilendiamina, glucosamina, metilglucamina, teobromina, purinas, piperazina, piperidina, N-etilpiperidina, compuestos de tetrametilamonio, compuestos de tetraetilamonio, piridina, N,N-dimetilanilina, N-

metilpiperidina, N-metilmorfolino, diciclohexilamina, dibencilamina, N,N-dibencilfentilamina, 1-efenamina, N,N'-dibenciletilendiamina, resinas de poliamina y similares. Las bases no tóxicas orgánicas que se prefieren especialmente son isopropilamina, dietilamina, etanolamina, trimetilamina, diciclohexilamina, colina y cafeína.

El término "mamífero" según se emplea en la presente significa que comprende seres humanos, al igual que mamíferos no humanos, que son susceptibles a la infección por el virus de la hepatitis C incluyendo animales domésticos, tales como vacas, cerdos, caballos, perros y gatos y animales no domésticos.

El término "agente antiviral" según se emplea en la presente significa un agente (compuesto o biológico) que es efectivo para inhibir la formación y/o replicación de un virus en un mamífero. Este incluye agentes que interfieren con cualquiera de mecanismos huésped o virales necesarios para la formación y/o replicación de un virus en un mamífero. Tales agentes se pueden seleccionar de: otro agente anti-VHC, un inhibidor del VIH, un inhibidor del VHA y un inhibidor del VHB. Los agentes antivirales incluyen, por ejemplo, ribavirin, amantadina, VX-497 (merimepodib, Vertex Pharmaceuticals), VX-498 (Vertex Pharmaceuticals), Levovirin, Viramidina, Ceplene (maxamina), XTL-001 y XTL-002 (XTl Biopharmaceuticals).

El término "otro agente anti-VHC" según se emplea en la presente significa aquellos agentes que son efectivos para disminuir o prevenir el progreso de los síntomas de enfermedad relacionados con la hepatitis C. Tales agentes se pueden seleccionar de: agentes inmunomoduladores, inhibidores de la proteasa NS3 del VHC, inhibidores de polimerasa del VHC o inhibidores de otro objetivo en el ciclo de vida del VHC.

El término "agente inmunomodulador" según se emplea en la presente significa aquellos agentes (compuestos o biológicos) que son efectivos para mejorar o potenciar la respuesta del sistema inmune en un mamífero. Los agentes inmunomoduladores incluyen, por ejemplo, interferones clase I (tales como interferones α, β, δ ,ω y τ, interferones consensuales y asialo-interferones), interferones de clase II (tales como γ-nterferones) y formas pegiladas de los mismos.

El término "inhibidor de proteasa NS3 del VHC" según se emplea en la presente significa un agente (compuesto o biológico) que es efectivo para inhibir la función de la proteasa de NS3 del VHC en un mamífero. Los inhibidores de la proteasa NS3 del VHC incluyen, por ejemplo, aquellos compuestos descriptos en WO 99/07733, WO 99/07734, WO 00/09558, WO 00/09543, WO 00/59929, WO 03/064416, WO 03/064455, WO 03/064456, WO 02/060926, WO 03/053349, WO 03/099316 o WO 03/099274 y el candidato Vertex del pre-desarrollo identificado como VX-950.

227

El término "inhibidor de la polimerasa del VHC" según se emplea en la presente significa un agente (compuesto o biológico) que es efectivo para inhibir la función de una polimerasa del VHC en un mamífero. Este incluye, por ejemplo, inhibidores de la polimerasa NSB5 del VHC N. Los inhibidores de la polimerasa del VHC incluyen no-nucleósidos, por ejemplo aquellos compuestos descriptos en:

- Solicitud Estadounidense No. 60/441.674 presentada el 22 de enero de 2003, que se incorpora en su totalidad a la presente a modo de referencia (Boehringer Ingelheim),
- Solicitud Estadounidense No. 60/441.871 presentada el 22 de enero de 2003, que se incorpora en su totalidad a la presente a modo de referencia (Boehringer Ingelheim), WO 04/005286 (Gilead), WO 04/002977 (Pharmacia), WO 04/002944 (Pharmacia), WO 04/002940 (Pharmacia), WO 03/101993 (Neogenesis), WO 03/099824 (Wyeth), WO 03/099275 (Wyeth), WO 03/099801 (GSK)), WO 03/097646 (GSK), WO 03/095441 (Pfizer), WO 03/090674 (Viropharma), WO 03/084953 (B&C Biopharm), WO 03/082265 (Fujisawa), WO 03/082848 (Pfizer), WO 03/062211 (Merck), WO 03/059356 (GSK), EP 1321463 (Shire), WO 03/040112 (Rigel), WO 03/037893 (GSK), WO 03/037894 (GSK), WO 03/037262 (GSK), WO 03/037895 (GSK), WO 03/026587 (BMS), WO 03/002518 (Dong Wha), WO 03/000254 (Japan Tobacco), WO 02/100846 A1 (Shire), WO 02/100851 A2 (Shire), WO 02/098424 A1 (GSK), WO 02/079187 (Dong Wha), WO 03/02/20497 (Shionogi), WO 02/06246 (Merck), WO 01/47883 (Japan Tobacco), WO 01/85172 A1 (GSK), WO 01/85720 (GSK), WO 01/77091 (Tularik), WO 00/18231 (Viropharma), WO 00/13708 (Viropharma), WO 01/10573 (Viropharma) WO 00/06529 (Merck), EP 1 256 628 A2 (Agouron), WO 02/04425 (Boehringer Ingelheim) WO 03/007945 (Boehringer Ingelheim), WO 03/010140 (Boehringer Ingelheim) y WO 03/010141 (Boehringer Ingelheim). Además, otros inhibidores de la polimerasa del VHC también incluyen análogos nucleosidos, por ejemplo, aquellos compuestos descriptos en: WO 04/007512 (Merck/Isis), WO 04/003000 (Idenix), WO 04/002999 (Idenix), WO 04/0002422 (Idenix), WO 04/003138 (Merck), WO 03/105770 (Merck), WO 03/105770 (Merck), WO 03/093290 (Genelabs), WO 03/087298 (Biocryst), WO 03/062256 (Ribapharm), WO 03/062255 (Ribapharm), WO 03/061385 (Ribapharm), WO 03/026675 (Idenix), WO 03/026589 (Idenix), WO 03/020222 (Merck), WO 03/000713 (Glaxo), WO 02/100415 (Hoffmann-La Roche), WO 02/1094289 (Hoffmann-La Roche), WO 02/051425 (Mitsubishi), WO 02/18404 (Hoffmann-La Roche), WO 02/069903 (Biocryst Pharmaceuticals Inc.), WO 02/057287 (Merck/Isis), WO 02/057425 (Merck/Isis), WO 01/90121 (Idenix), WO 01/60315 (Shire) y WO 01/32153 (Shire). Ejemplos específicos de

227
228

inhibidores de una polimerasa del VHC, incluyen JTK-002, JTK-003 y JTK-109 (Japan Tobacco).

El término "inhibidor de otro blanco en el ciclo de vida del VHC" según se emplea en la presente significa un agente (compuesto o biológico) que es efectivo para inhibir la formación y/o replicación del VHC en un mamífero que no sea inhibiendo la función de la Proteasa NS3 del VHC. Este incluye agentes que interfieren con mecanismos del huésped o virales del VHC necesarios para la formación y/o replicación del VHC en un mamífero. Inhibidores de otro objetivo en el ciclo de vida del VHC incluyen, por ejemplo, agentes que inhiben un blanco seleccionado de helicasa, proteasa NS2/3 y sitio de entrada del ribosoma interno (IRES). Ejemplos específicos de inhibidores de otro objetivo en el ciclo de vida del VHC incluyen ISIS-14803 (ISIS Pharmaceuticals).

El término "inhibidor del VIH" según se emplea en la presente significa un agente (compuesto o biológico) que es efectivo para inhibir la formación y/o replicación del VIH en un mamífero. Esto incluye agentes que interfieren con mecanismos del huésped o virales necesario para la formación y/o replicación del VIH en un mamífero. Los inhibidores del VIH incluyen, por ejemplo, inhibidores nucleosidos, inhibidores no nucleosidos, inhibidores de proteasa, inhibidores de fusión e inhibidores de integrasa.

El término "inhibidor del VHA" según se emplea en la presente significa un agente (compuesto o biológico) que es efectivo para inhibir la formación y/o replicación del VHA en un mamífero. Esto incluye agentes que interfieren con mecanismos huésped o virales necesarios para la formación y/o replicación de VHA en un mamífero. Los inhibidores del VHA incluyen vacunas de Hepatitis A, por ejemplo, Havrix® (GlaxoSmithKline), VAQTA® (Merck) y Avaxim® (Aventis Pasteur).

El término "inhibidor del VHB" según se emplea en la presente significa un agente (compuesto o biológico) que es efectivo para inhibir la formación y/o replicación de VHB en un mamífero. Esto incluye agentes que interfieren con mecanismos del huésped o virales necesarios para la formación y/o replicación de VHB en un mamífero. Los inhibidores del VHB incluyen, por ejemplo, agentes que inhiben polimerasa del ADN viral del VHB o vacunas del VHB. Ejemplos específicos de inhibidores del VHB incluyen Lamivudine (Epivir-VHB®), Adefovir Dipivoxil, Entecavir, FTC (Coviracil®), DAPD (DXG), L-FMAU (Clevudine®), AM365 (Amrad), Ldt (Telbivudine), monoval-LdC (Valtorcitabine), ACH-126,443 (L-Fd4C) (Achillion), MCC478 (Eli Lilly), Racivir (RCV), Fluoro-l y nucleosidos D, Robustaflavone, ICN 2001-3 (ICN), Bam 205 (Novelos), XTL-001 (XTL), Imino-azúcares (Nonyl-DNJ) (Synergy), HepBzyme; y productos inmunomoduladores tales como: interferón alfa 2b, HE2000 (Hollis-Eden), Theradigm (Epimmune), EHT899

(Enzo Biochem), Thymosin alfa-1 (Zadaxin®), vacuna de ADN del VHB (PowderJect), vacuna del ADN del VHB (Jefferon Center), antígeno del VHB (OraGen), BayHep B® (Bayer), Nabi-HB® (Nabi) y Anti-hepatitis B (Cangene); y productos de la vacuna del VHB tales como los siguientes: Engerix B, Recombivax HB, GenHevac B, Hepacare, Bio-Hep B, TwinRix, Comvax, Hexavac.

El término "interferón de clase I" según se emplea en la presente significa un interferón seleccionado del grupo de interferones que se unen al receptor de tipo I. Este incluye los interferones de clase I que son de origen natural o sintético. Ejemplos de interferones de clase I incluyen interferones α, β, δ, ω e interferones τ, interferones consensuales, asialo-interferones y formas pegiladas de los mismos.

El término "interferón de clase II" según se emplea en la presente significa un interferón seleccionado de un grupo de interferones seleccionado de un grupo de interferones que se unen al todos al receptor de tipo II. Ejemplos de interferones de clase II incluyen γ-interferones.

Ejemplos específicos preferidos de algunos de estos agentes se enumeran a continuación:

- Agentes antivirales: ribavirin o amantadina;
- Agentes inmunomoduladores: interferones de clase I, interferones de clase II o formas pegiladas de los mismos;
- Inhibidores de polimerasa del VHC: análogos nucleosídicos o no nucleosídicos;
- inhibidor de otro blanco en el ciclo de vida del VHC que inhibe un objetivo seleccionado de: helicasa NS3, proteasa NS2/3 o sitio interno de entrada del ribosoma (IRES);
- Inhibidores del VIH: inhibidores nucleosídicos, inhibidores no nucleosídicos, inhibidores de proteasa, inhibidores de fusión o inhibidores de integrasa; o
- inhibidores del VHB: agentes que inhiben la ADN polimerasa viral o es una vacuna del VHB.

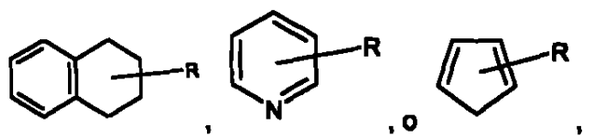
Según se expuso anteriormente, se contempla la terapia de combinación en la cual un compuesto de fórmula (I), o una sal aceptable para uso farmacéutico del mismo, se co-administra con al menos un agente adicional seleccionado de: un agente antiviral, un agente inmunoregulador, otro inhibidor de proteasa NS3 del VHC, un inhibidor de la polimerasa del VHC, un inhibidor de otro blanco en el ciclo de vida del VHC, un inhibidor del VIH, un inhibidor del VHA y un inhibidor del VHB. Ejemplos de tales agentes se proporcionan en la sección anterior de Definiciones. Estos agentes adicionales pueden

estar combinados con los compuestos de la presente invención para crear una forma de dosificación farmacéutica única. De manera alternativa, estos agentes adicionales se pueden administrar por separado al paciente como parte de una forma de dosificación múltiple, por ejemplo, usando un kit. Tales agentes adicionales se pueden administrar al paciente antes de, o de manera concurrente con, o a continuación de la administración de un compuesto de fórmula (I), o una sal aceptable para uso farmacéutico del mismo.

Según se emplea en la presente, el término "tratamiento" significa la administración de un compuesto o composición de acuerdo con la presente invención para aliviar o eliminar síntomas de la enfermedad de la hepatitis C y/o para reducir la carga viral en un paciente.

Según se emplea en la presente, el término "prevención" significa la administración de un compuesto o composición de acuerdo con la presente invención posterior a la exposición del individuo al virus pero antes de la aparición de los síntomas de la enfermedad y/o antes de la detección del virus en sangre, para prevenir la aparición de los síntomas de la enfermedad.

Según se emplea en la presente, la designación mediante la cual un enlace a un sustituyente R se dibuja como surgiendo del centro de un anillo, tal como, por ejemplo,



significa que el sustituyente R se puede encontrar unido a cualquier posición libre en el anillo que de otra manera se podría encontrar sustituida con un átomo de hidrógeno, salvo que se especifique lo contrario.

El siguiente símbolo - - - o → se emplea de manera indistinta en sub-fórmulas para indicar el enlace que se conecta al resto de la molécula, según se definió.

Realizaciones preferidas

En las siguientes realizaciones preferidas, se describen en detalle grupos y sustituyentes de los compuestos de acuerdo con la presente invención.

B se selecciona preferentemente de alquilo (C_{2-6}), cicloalquilo (C_{3-7}) y alquil (C_{1-3})-cicloalquilo (C_{3-7}),

a) donde dicho alquilo, cicloalquilo y alquil-cicloalquilo pueden ser mono-, di- o tri-sustituidos con alquilo (C_{1-3}); y

b) donde dicho alquilo, cicloalquilo y alquil-cicloalquilo pueden estar mono- o disustituidos con sustituyentes seleccionados de hidroxi y O-alquilo (C_{1-4}); y

228
231

c) donde cada uno de dichos grupos alquilo puede estar mono-, di- o tri-sustituido con flúor o mono-sustituido con cloro o bromo; y

d) donde en cada uno de dichos grupos cicloalquilo que son de 5, 6 o 7 miembros, uno o dos grupos $-CH_2-$ que no se encuentran unidos directamente entre sí se pueden reemplazar por -O- de manera que el átomo de O se encuentra unido al grupo **X** mediante al menos dos átomos de C.

Más preferentemente, **B** se selecciona de etilo, n-propilo, i-propilo, n-butilo, 1-metilpropilo, 2-metilpropilo, *ter*-butilo, ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo,

a) donde cada uno de dicho grupos está sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de metilo y etilo;

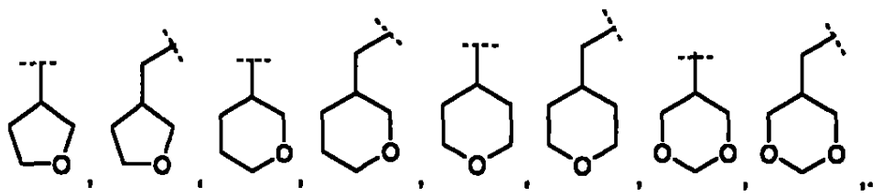
b) donde cada uno de dicho grupos se encuentra mono-sustituido o disustituido opcionalmente por sustituyentes seleccionados de hidroxi, metoxi y etoxi; y

c) donde cada uno de dichos grupos alquilo puede estar mono-, di- o tri-sustituido con flúor o mono-sustituido con cloro o bromo; y

d) donde en cada uno de dichos grupos cicloalquilo que son de 5, 6 o 7 miembros, uno o dos grupos $-CH_2-$ que no se encuentran unidos directamente entre sí se pueden reemplazar por -O- de manera que el átomo de O se encuentra unido al grupo **X** mediante al menos dos átomos de C.

B se selecciona aún más preferentemente de etilo, 1-metiletilo, 1,1-dimetiletilo, propilo, 1-metilpropilo, 2-metilpropilo, 1,1-dimetilpropilo, 1,2-dimetilpropilo, 2,2-dimetilpropilo, 1,1,2-trimetilpropilo, 1,2,2-trimetilpropilo, 1-etilpropilo, 1-etil-2-metilpropilo, 1-(1-metiletil)-2-metilpropilo, 1-etil-2,2-dimetilpropilo, butilo, 1-metilbutilo, 2-metilbutilo, 3-metilbutilo, 1,2-dimetilbutilo, 1,1-dimetilbutilo, 1,3-dimetilbutilo, 2,2-dimetilbutilo, 2,3-dimetilbutilo, 3,3-dimetilbutilo, 1,2,2-trimetilbutilo, 1,2,3-trimetilbutilo, 2,2,3-trimetilbutilo, 2,3,3-trimetilbutilo y 2,2,3-trimetilbutilo, mediante los cuales estos grupos alquilo se pueden sustituir con cloro o bromo, o con 1, 2 o 3 sustituyentes de flúor. Ejemplos de los grupos fluorados preferidos incluyen grupos alquilo, pero sin limitación, 2-fluoroetilo, 3-fluoropropilo y 3,3,3-trifluoropropilo.

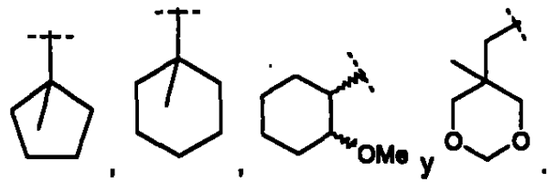
Además, aún más preferentemente, **B** es ciclopropilo, ciclobutilo, ciclopentilo, o ciclohexilo o se selecciona de las siguientes fórmulas, donde uno o dos grupos CH_2 de un grupo cicloalquilo se reemplazan por oxígeno:



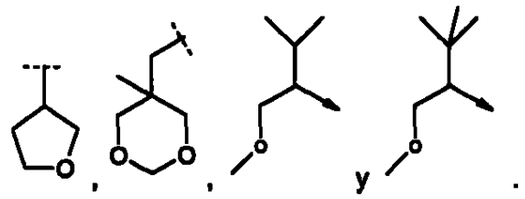
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A partir de la lista anterior, grupos cicloalquilo y alquil-cicloalquilo que comprenden opcionalmente 1 o 2 átomos de O están sustituidos opcionalmente con 1, 2 o 3 grupos metilo. Se prefieren en especial aquellos grupos cicloalquilo que opcionalmente comprenden 1 o 2 átomos de O, donde el átomo de C-α se sustituye con metilo.

Ejemplos adicionales de grupos cíclicos sustituidos preferidos son



De mayor preferencia, **B** se selecciona de etilo, n-propilo, *ter*-butilo, 2-metilpropilo, 1,2-dimetilpropilo, 1,2,2-trimetilpropilo, 2-fluoroetilo, 3-fluoropropilo, 3,3,3-trifluoropropilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, 1-metilciclopentilo y 1-metilciclohexilo y un grupo seleccionado de:



Aún de mayor preferencia, **B** se selecciona de etilo, *n*-propilo, *ter*-butilo, ciclopentilo, 1-metilciclopentilo, 2-fluoroetilo o 3-fluoropropilo.

De acuerdo con una realización de la presente invención **X** es O.

De acuerdo con otra realización de la presente invención **X** es NH.

R^3 es preferentemente alquilo (C_{2-6}), cicloalquilo (C_{3-7}) o alquil (C_{1-3})-cicloalquilo (C_{3-7}), estando cada uno de los cuales sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo (C_{1-4}).

R^3 se selecciona con mayor preferencia de etilo, propilo, butilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclopropilmetilo, ciclobutilmetilo, ciclopentilmetilo, o ciclohexilmetilo, estando cada uno de los cuales sustituido opcionalmente con 1 o 2 sustituyentes seleccionados de metilo, etilo y propilo.

Aún más preferentemente R^3 se selecciona de 1-metiletilo, 1,1-dimetiletilo, 1-metilpropilo, 2-metilpropilo, 1,1-dimetilpropilo, 1,2-dimetilpropilo, 2,2-dimetilpropilo, ciclopentilo, ciclohexilo, 1-metilciclopentilo, 1-metilciclohexilo, ciclopentilmetilo, ciclohexilmetilo, (1-metilciclopentil)metilo y (1-metilciclohexil)metilo.

R^3 se selecciona de mayor preferencia de 1,1-dimetiletilo, ciclopentilo, ciclohexilo y 1-metilciclohexilo.

230
233

Aún más, R^3 se selecciona de mayor preferencia de 1,1-dimetiletilo y ciclohexilo.

L^0 se selecciona preferentemente de H, halógeno, CH_3, -OH, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-OCH(CH_3)_2$, $-NHCH_3$, $-NHC_2H_5$, $-NHC_3H_7$, $-NHCH(CH_3)_2$, $-N(CH_3)_2$, $-N(CH_3)C_2H_5$, $-N(CH_3)C_3H_7$ y $-N(CH_3)CH(CH_3)_2$.

De mayor preferencia, L^0 se selecciona de H, -OH, $-OCH_3$, halógeno y $-N(CH_3)_2$.

Aún de mayor preferencia, L^0 es H, -OH or-OCH_3.

Aún más, de mayor preferencia, L^0 es H o $-OCH_3$.

L^1 y L^2 preferentemente se seleccionan cada uno independientemente de: halógeno, $-CH_3$, $-C_2H_5$, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-OCH(CH_3)_2$, CF_3, -SMe, -SOMe y SO_2Me, por lo cual cualquiera de L^1 o L^2 pueden ser H.

Más preferentemente cualquiera de L^1 y L^2 es $-CH_3$, -F, -Cl, -Br, -OMe, -SMe, o $-SO_2Me$ y el otro de L^1 y L^2 es H.

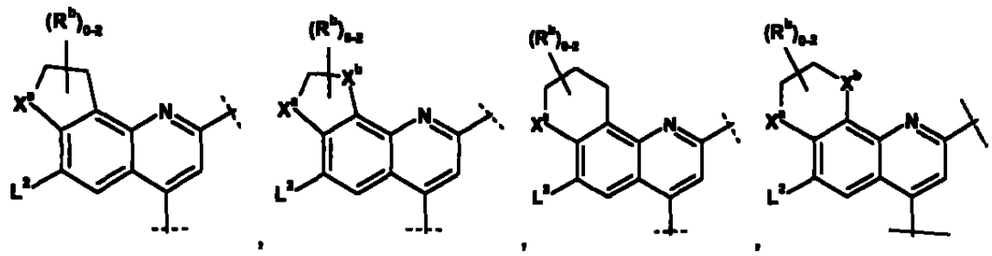
De mayor preferencia, L^1 es CH_3, -F, -Cl, -Br, -OMe, -SMe, o $-SO_2Me$ y L^2 es H.

Por consiguiente, preferentemente L^0 se selecciona de: H, -OH y $-OCH_3$; y cualquiera de L^1 y L^2 es CH_3, -F, -Cl, -Br, -OMe, -SMe, o $-SO_2Me$ y el otro de L^1 y L^2 es H.

Más preferentemente L^0 se selecciona de H, -OH y $-OCH_3$; L^1 es $-CH_3$, -F, -Cl, -Br, -OMe, -SMe, o $-SO_2Me$; y L^2 es H.

De mayor preferencia, L^0 es H o $-OCH_3$; L^1 es $-CH_3$, Cl o Br; y L^2 es H.

En el caso que L^0 y L^1 se unen covalentemente para formar, junto con el residuo de quinolina al cual se encuentran unidos, un sistema anular, este sistema de anillos preferentemente se selecciona de:



en el cual

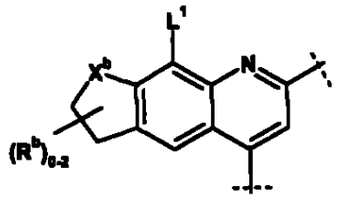
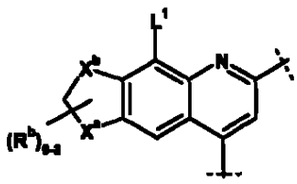
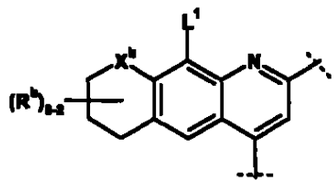
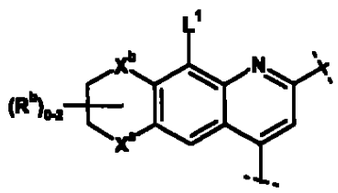
X^a, X^b se seleccionan independientemente de CH_2, O y NR^a; de mayor preferencia O;

R^a es cada uno de manera independiente H o alquilo (C_{1-4});

R^b es cada uno de manera independiente alquilo (C_{1-4});

L^2 es según se definió; preferentemente H o metilo, en especial H.

En el caso que L^0 y L^2 se unan covalentemente para formar, junto con el residuo de quinolina al cual se encuentran unidos, un sistema anular, este sistema anular se selecciona preferentemente de:




y


donde

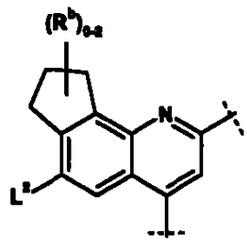
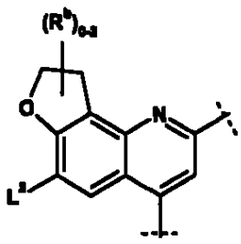
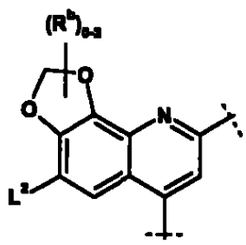
X^a, X^b se seleccionan independientemente de CH_2, O y NR^a; de mayor preferencia O;

R^a es cada uno de manera independiente H o alquilo (C_{1-4});

R^b es cada uno de manera independiente alquilo (C_{1-4});

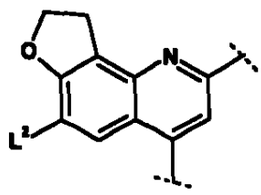
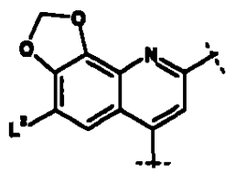
L^1 es según se definió; preferentemente H o metilo, en especial H.

Más preferentemente, L^0 y L^1 se unen covalentemente para formar, junto con el residuo de quinolina al cual se encuentran unidos, un sistema anular que se selecciona de:



y


donde cada R^b es independientemente alquilo (C_{1-4}) y L^2 es según se definió; preferentemente H o metilo, en especial H.

De mayor preferencia, L^0 y L^1 se encuentran unidos covalentemente para formar, junto con el residuo de quinolina al cual se están unidos, un sistema anular seleccionado de


y


donde L^2 es H o $-CH_3$, preferentemente H.

R^2 es preferentemente R^{20}, $-NHCOR^{20}$, $-NHCOOR^{20}$, $-NHR^{21}$ y $-NHCONR^{21}R^{23}$, donde

R^{20} se selecciona de alquilo (C_{1-6}), cicloalquilo (C_{3-7}), alquil (C_{1-3})-cicloalquilo (C_{3-7}), donde dichos cicloalquilo y alquil-cicloalquilo pueden estar mono-, di- o tri-sustituidos con alquilo (C_{1-3}); y

R^{21} es H o R^{20} según se definió anteriormente; y

R^{23} es H o metilo; de mayor preferencia, H.

Más preferentemente, R^2 es R^{20}, $NHCOR^{20}$, $-NHCOOR^{20}$, $-NHR^{21}$ – y $-NHCONR^{21}R^{23}$, donde

R^{20} se selecciona de metilo, etilo, *n*-propilo, *i*-propilo, *n*-butilo, 1-metilpropilo, 2-metilpropilo, *ter*-butilo, 2,2-dimetilpropilo, 1,1-dimetilpropilo, 1,2-dimetilpropilo, 1,2,2-trimetilpropilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclopropil-metilo, ciclobutilmetilo, ciclopentilmetilo y ciclohexilmetilo, estando cada uno de dichos grupos cicloalquilo y alquil-cicloalquilo sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de metilo y etilo, en particular metilo; y

R^{21} es H o R^{20} según se definió anteriormente; y

R^{23} es H o metilo; de mayor preferencia, H.

Preferentemente, R^2 se selecciona de:

a) amino, *N*-metilamino, *N*-etilamino, *N*-propilamino, *N*-(1-metiletil)amino, *N*-(1,1-dimetiletil)amino, *N*-(2-metilpropil)amino, *N*-(1-metilpropil)amino, *N*-(2,2-dimetilpropil)amino, *N*-(1,2-dimetilpropil)amino, *N*-(1,1-dimetilpropil)amino, *N*-ciclopropilamino, *N*-ciclobutilamino, *N*-ciclopentilamino, *N*-ciclohexilamino, *N*-(ciclopropilmetil)amino, *N*-(ciclobutilmetil)amino, *N*-(ciclopentilmetil)amino y *N*-(ciclohexilmetil)amino;

b) metilcarbonilamino, etilcarbonilamino, 1-metiletilcarbonilamino, propilcarbonilamino, 2-metilpropilcarbonilamino, 1-metilpropilcarbonilamino, 2,2-dimetilpropilcarbonilamino, 1,2-dimetilpropilcarbonilamino, 1,1-dimetilpropilcarbonilamino, ciclopropilcarbonilamino, ciclobutylcarbonilamino, ciclopentilcarbonilamino,

ciclohexilcarbonilamino, ciclopropilmetilcarbonilamino, ciclobutilmetilcarbonilamino, ciclopentilmetilcarbonilamino, ciclohexilmetilcarbonilamino; y

c) metoxicarbonilamino, etoxicarbonilamino, 1-metiletoxicarbonilamino, propoxicarbonilamino, *ter*-butoxicarbonilamino, ciclopropiloxicarbonilamino, ciclobutiloxicarbonilamino, ciclopentiloxicarbonilamino, ciclohexiloxicarbonilamino, ciclopropilmetoxicarbonilamino, ciclobutilmetoxicarbonilamino, ciclopentilmetoxi-carbonilamino, ciclohexilmetoxicarbonilamino;

donde todos los grupos cicloalquilo o alquil-cicloalquilo mencionados pueden estar mono- o disustituidos con metilo.

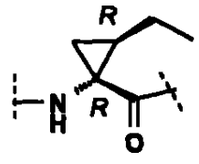
De mayor preferencia, R^2 es -NHCOR^{20}, -NHCOOR^{20}, o -NHR^{21}, donde R^{20} y R^{21} son según se define en la presente.

Preferentemente, R^{20} y R^{21} se seleccionan independientemente de: metilo, etilo, *n*-propilo, *i*-propilo, *n*-butilo, 1-metilpropilo, 2-metilpropilo, *ter*-butilo, 2,2-dimetilpropilo, 1,1-dimetilpropilo, 1,2-dimetilpropilo, 1,2,2-trimetilpropilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclopropilmetilo, ciclobutilmetilo, ciclopentilmetilo, ciclohexilmetilo, estando cada uno de dichos grupos cicloalquilo o alquil-cicloalquilo opcionalmente mono-sustituido o di-sustituido con metilo o etilo.

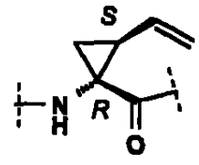
Más preferentemente, R^{20} y R^{21} se seleccionan independientemente de: metilo, etilo, *n*-propilo, *i*-propilo, 2,2-dimetilpropilo, ciclopentyl y ciclopentilmetilo.

En el resto P1, el sustituyente R^1 y el carbonilo adoptan una orientación *syn*.

Por lo tanto, en el caso que R^1 sea etilo, los átomos de carbono asimétricos en el grupo ciclopropilo adoptan una configuración *R,R* de acuerdo con la subfórmula:



Si R^1 es vinilo, los átomos de carbono asimétricos del grupo ciclopropilo adoptan la configuración *R,S* de acuerdo con la subfórmula:



R^1 es preferentemente vinilo.

R^C se selecciona preferentemente de hidroxi o $NHSO_2R^S$, donde R^S es metilo, etilo, *n*-propilo, *i*-propilo, *n*-butilo, 1-metilpropilo, 2-metilpropilo, *ter*-

butilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclopropilmetilo, ciclobutilmetilo, ciclopentilmetilo, ciclohexilmetilo, fenilo, naftilo, piridinilo, fenilmetilo (bencilo), naftilmetilo o piridinilmetilo;

a) estando cada uno de los cuales mono-, di- o tri-sustituido con sustituyentes seleccionados de flúor y metilo; y

b) estando cada uno de los cuales mono- o disustituido con sustituyentes seleccionados de hidroxi, trifluorometilo, metoxi y trifluorometoxi; y

c) estando cada uno de los cuales monosustituido con sustituyentes seleccionados de cloro, bromo, ciano, nitro, -CO-NH_2, -CO-$NHCH_3$, -CO-$N(CH_3)_2$, -NH_2, -$NH(CH_3)$ y -$N(CH_3)_2$.

Preferentemente de manera alternativa, R^C es $NHSO_2R^8$, donde R^8 es -$N(R^{N2})R^{N1}$), donde R^{N1} y R^{N2} se seleccionan independientemente de H, alquilo (C_{1-4}), cicloalquilo (C_{3-7}), alquil (C_{1-3})-cicloalquilo (C_{3-7}), fenilo y alquil (C_{1-3})-fenilo; donde dicho alquilo (C_{1-4}), cicloalquilo (C_{3-7}), alquil (C_{1-3})-cicloalquilo (C_{3-7}), fenilo y alquil (C_{1-3})-fenilo están sustituidos opcionalmente con uno, dos o tres sustituyentes seleccionados de halógeno, alquilo (C_{1-6}), hidroxi, ciano, O-alquilo (C_{1-6}), -NH_2, -NHalquilo (C_{1-4}), -N(alquil (C_{1-4}))$_2$, -CO-NH_2, -CO-NHalquilo (C_{1-4}), -CO-N(alquil (C_{1-4}))$_2$, –COOH y –COO(C_{1-6})alquilo; o

R^{N2} y R^{N1} se unen, junto con el nitrógeno al cual se unen, para formar un heterociclo monocíclico de 5 o 6 miembros que puede ser saturado o no saturado, que contiene opcionalmente de uno a tres heteroátomos adicionales seleccionados independientemente de N, S y O y sustituido opcionalmente con uno, dos o tres sustituyentes seleccionados de halógeno, alquilo (C_{1-6}), hidroxi, ciano, O-alquilo (C_{1-6}), -NH_2, -NHalquilo (C_{1-4}), -N(alquil (C_{1-4}))$_2$, -CO-NH_2, -CO-NHalquilo (C_{1-4}), -CO-N(alquil (C_{1-4}))$_2$, –COOH y –COOalquilo (C_{1-6}).

Preferentemente, el grupo R^C es hidroxi, $NHSO_2$-metilo, $NHSO_2$-etilo, $NHSO_2$-(1-metil)etilo, $NHSO_2$-propilo, $NHSO_2$-ciclopropilo, $NHSO_2$-CH_2-ciclopropilo, $NHSO_2$-ciclobutilo, $NHSO_2$-ciclopentilo, o $NHSO_2$-fenilo.

Más preferentemente, R^C es hidroxi, o $NHSO_2$-ciclopropilo.

De acuerdo con una realización de mayor preferencia, el grupo R^C es hidroxi. De acuerdo con una realización alternativa de mayor preferencia, el grupo R^C es $NHSO_2$-ciclopropilo. De acuerdo con otra realización alternativa de mayor preferencia, el grupo R^C es $NHSO_2N(CH_3)_2$.

También se encuentran en el alcance de la presente invención, compuestos de fórmula (I) en los cuales:

B es alquilo (C_{1-10}), cicloalquilo (C_{3-7}), o alquil (C_{1-4})-cicloalquilo (C_{3-7}),

a) donde dichos cicloalquilo y alquil-cicloalquilo pueden estar mono-, di- o tri-sustituidos con alquilo (C_{1-3}); y

b) donde dichos alquilo, cicloalquilo y alquil-cicloalquilo pueden estar mono- o disustituidos con sustituyentes seleccionados de hidroxi y O-alquilo (C_{1-4}); y

c) donde todos los grupos alquilo mencionados pueden estar mono-, di- o tri-sustituidos con halógeno; y

d) donde todos los grupos cicloalquilo que son de 4, 5, 6 o 7 miembros poseen opcionalmente uno (para los de 4, 5, 6, o 7 miembros) o dos (para los de 5, 6, o 7 miembros) grupos $-CH_2-$ que no están unidos entre sí directamente se reemplazan por -O- de manera que el átomo de O se une al grupo X mediante al menos dos átomos de C;

X es O o NH;

R^3 es alquilo (C_{2-8}), cicloalquilo (C_{3-7}) o alquil (C_{1-3})-cicloalquilo (C_{3-7}), donde dichos grupos cicloalquilo pueden ser mono-, di- o tri-sustituidos con alquilo (C_{1-4});

L^0 es H, –OH, –O-alquilo (C_{1-4}), $-NH_2$, –NHalquilo (C_{1-4}) o $-N(alquil\ (C_{1-4}))_2$;

L^1, L^2 son cada uno independientemente halógeno, alquilo (C_{1-4}), -O-alquilo (C_{1-4}) o -S-alquilo (C_{1-4}) (en cualquier estado de oxidación tal como SO o SO_2); y cualquiera de L^1 o L^2 (pero no los dos al mismo tiempo) también puede ser H; o

L^0 y L^1 o

L^0 y L^2 pueden estar unidos covalentemente para formar, junto con los dos átomos de C a los cuales se encuentran unidos, un anillo carbocíclico de 5 o 6 miembros donde uno o dos grupos $-CH_2-$ que no se encuentran unidos entre sí directamente se pueden reemplazar cada uno independientemente por -O- o NR^8 donde R^8 es H o alquilo (C_{1-4}) y donde dicho anillo carbocíclico o heterocíclico está opcionalmente mono- o disustituido con alquilo (C_{1-4});

R^2 es R^{20}, $-NR^{22}COR^{20}$, $-NR^{22}COOR^{20}$ $-NR^{22}R^{21}$ y $-NR^{22}CONR^{21}R^{23}$, donde

R^{20} se selecciona de alquilo (C_{1-8}), cicloalquilo (C_{3-7}) y alquil (C_{1-4})-cicloalquilo (C_{3-7}), donde dichos cicloalquilo y alquil-cicloalquilo pueden estar mono-, di- o tri-sustituidos con alquilo (C_{1-3});

R^{21} es H o posee uno de los significados de R^{20} según se definió anteriormente,

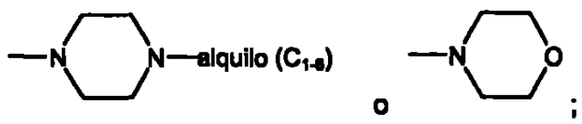
R^{22} y R^{23} se seleccionan independientemente de H y metilo,

R^1 es etilo o vinilo;

R^C es hidroxi o $NHSO_2R^8$ donde R^8 es alquilo (C_{1-6}), cicloalquilo (C_{3-7}), alquil (C_{1-6})-cicloalquilo (C_{3-7}), fenilo, naftilo, piridinilo, alquil (C_{1-4})-fenilo, alquil (C_{1-4})-naftilo o alquil (C_{1-}

$_4$)-piridinilo; estando la totalidad de los mismos mono-, di- o trisustituidos con sustituyentes seleccionados de halógeno, hidroxi, ciano, alquilo (C_{1-4}), O-alquilo (C_{1-6}), -CO-NH_2, -CO-NHalquilo (C_{1-4}), -CO-N(alquil (C_{1-4}))$_2$, -NH_2, -NHalquilo (C_{1-4}) y -N(alquil (C_{1-4}))$_2$; y estando todos los cuales opcionalmente monosustituidos con nitro;

o R^5 se puede seleccionar además de: -NHalquilo (C_{1-6}), N(alquilo (C_{1-6}))$_2$, -Het,



;

o una sal o éster aceptable para uso farmacéutico del mismo.

Preferentemente,

B es alquilo (C_{2-6}), cicloalquilo (C_{3-7}) o alquil (C_{1-3})-cicloalquilo (C_{3-7}),

a) donde dichos alquilo, cicloalquilo y alquil-cicloalquilo pueden estar mono-, di- o tri-sustituidos con alquilo (C_{1-3}); y

b) donde dichos alquilo, cicloalquilo y alquil-cicloalquilo pueden estar mono- o disustituidos con sustituyentes seleccionados de hidroxi y O-alquilo (C_{1-4}); y

c) donde cada uno de dichos grupos alquilo puede estar mono-, di- o tri-sustituido con flúor o mono-sustituido con cloro o bromo; y

d) donde en cada uno de dichos grupos cicloalquilo que son de 5, 6 o 7 miembros, uno o dos grupos -CH_2- que no se encuentran unidos directamente entre sí se pueden reemplazar por -O- de manera que el átomo de O se encuentra unido al grupo X mediante al menos dos átomos de C;

X es O o NH;

R^3 es alquilo (C_{2-6}) o cicloalquilo (C_{3-7}), ambos sustituidos opcionalmente por 1 a 3 sustituyentes seleccionados de alquilo (C_{1-4});

L^0 es H, -OH, -OCH_3, halógeno o -$N(CH_3)_2$;

L^1 y L^2 se seleccionan cada uno independientemente de: halógeno, -CH_3, -C_2H_5, -OCH_3, -OC_2H_5, -OC_3H_7, -$OCH(CH_3)_2$, CF_3, -SMe, -SOMe y SO_2Me, por lo cual cualquiera de L^1 o L^2 puede ser H;

R^2 es R^{20}, -NHCOR^{20}, -NHCOOR^{20}, -NHR^{21} y –NHCONH$R^{21}R^{23}$,

donde

R^{20} se selecciona de alquilo (C_{1-6}), cicloalquilo (C_{3-7}), alquil (C_{1-3})-cicloalquilo (C_{3-7}), donde cada uno de dichos grupos cicloalquilo y alquil-cicloalquilo puede estar mono-, di- o tri-sustituido con alquilo (C_{1-3}); y

R^{21} es H o R^{20} según se definió anteriormente; y

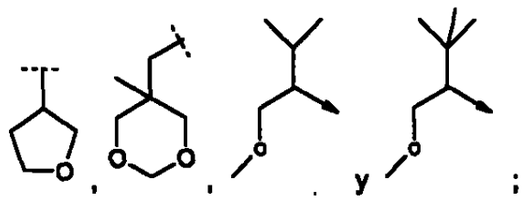
R^{23} es H o metilo;

237
240

R^1 es etilo o vinilo; y

R^C es hidroxi, $NHSO_2$-metilo, $NHSO_2$-etilo, $NHSO_2$-(1-metil)etilo, $NHSO_2$-propilo, $NHSO_2$-ciclopropilo, $NHSO_2$-CH_2-ciclopropilo, $NHSO_2$-ciclobutilo, $NHSO_2$-ciclopentilo o $NHSO_2$-fenilo.

Más preferentemente, B se selecciona de: etilo, n-propilo, *ter*-butilo, 2-metilpropilo, 1,2-dimetilpropilo, 1,2,2-trimetilpropilo, 2-fluoroetilo, 3-fluoropropilo, 3,3,3-trifluoropropilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, 1-metilciclopentilo y 1-metilciclohexilo y un grupo seleccionado de:



R^3 se selecciona de 1,1-dimetiletilo, ciclopentilo, ciclohexilo y 1-metilciclohexilo; L^0 es H, -OH o $-OCH_3$; L^1 es CH_3, -F, -Cl, -Br, -OMe, -SMe, o $-SO_2Me$; L^2 es H;

R^2 es $-NHCOR^{20}$, $-NHCOOR^{20}$ o $-NHR^{21}$, donde R^{20} y R^{21} se seleccionan independientemente de metilo, etilo, *n*-propilo, *i*-propilo, 2,2-dimetilpropilo, ciclopentilo y ciclopentilmetilo;

R^1 es vinilo; y R^C es hidroxi o $NHSO_2$-ciclopropilo.

De mayor preferencia, B se selecciona de etilo, *n*-propilo, *ter*-butilo, ciclopentilo, 1-metilciclopentilo, 2-fluoroetilo y 3-fluoropropilo; R^3 se selecciona de 1,1-dimetiletilo y ciclohexilo; L^0 es H o $-OCH_3$; L^1 es $-CH_3$, -Cl, o -Br; L^2 es H; y R^C es hidroxi.

Cada uno de los compuestos simples enumerados en las siguientes Tablas 1, 2, 3, 4, 5 y 6 es ejemplo de las realizaciones preferidas de acuerdo con la presente invención.

De acuerdo con una realización alternativa, la composición farmacéutica de la presente invención puede comprender adicionalmente al menos otro agente anti-VHC. Ejemplos de agentes anti-VHC incluyen α- (alfa), β- (beta), δ- (delta), γ- (gamma), ω- (omega) o τ- (tau) interferón, α-interferón pegilado, ribavirin y amantadina.

De acuerdo con otra realización alternativa, la composición farmacéutica de la presente invención puede comprender adicionalmente al menos otro inhibidor de proteasa NS3 del VHC.

De acuerdo con otra realización alternativa, la composición farmacéutica de la presente invención puede comprender adicionalmente al menos un inhibidor de polimerasa del VHC.

De acuerdo con aún otra realización alternativa, la composición farmacéutica de la presente invención puede comprender adicionalmente al menos un inhibidor de otros blancos en el ciclo de vida del VHC, incluyendo, pero sin limitación, helicasa, proteasa NS2/3 o sitio interno de entrada del ribosoma (IRES).

La composición farmacéutica de la presente invención se puede administrar por vía oral, parenteral o mediante un reservorio implantado. Se prefiere la administración oral o la administración mediante inyección. La composición farmacéutica de la presente invención puede contener cualquier portador, adyuvante o vehículo no tóxico convencional aceptable para uso farmacéutico. En algunos casos, la formulación del pH se puede regular con ácidos, bases o buffers aceptables para uso farmacéutico para mejorar la estabilidad del compuesto formulado o su forma de administración. El término parenteral según se emplea en la presente, incluye técnicas de inyección o infusión subcutánea, intracutánea, intravenosa, intramuscular, intra-articular, intrasinovial, intraesternal, intratecal e intralesional.

La composición farmacéutica se puede encontrar en forma de una preparación estéril inyectable, por ejemplo, como una suspensión inyectable estéril acuosa u oleaginosa. Esta suspensión se puede formular de acuerdo con técnicas conocidas en el arte empleando agentes de dispersión o humectantes adecuados (tales como, por ejemplo Tween 80) y agentes de suspensión.

La composición farmacéutica de la presente invención se puede administrar oralmente en cualquier forma de dosificación oral aceptable incluyendo, pero sin limitación, cápsulas, comprimidos y suspensiones y soluciones acuosas. En el caso de los comprimidos para uso oral, los vehículos que se emplean comúnmente incluyen lactosa y almidón de maíz. También se agregan típicamente agentes lubricantes, tales como estearato de magnesio. Para la administración oral en forma de cápsula, los diluyentes útiles incluyen lactosa y almidón de maíz seco. Cuando se administran las suspensiones acuosas oralmente, el componente activo se combina con agentes emulsionantes y de suspensión. Si se desea, se pueden agregar ciertos agentes edulcorantes y/o saborizantes y/o colorantes.

Otros vehículos o portadores para las formulaciones y composiciones mencionadas anteriormente se pueden encontrar en farmacéuticos estándar, por ejemplo, en "Remington's Pharmaceutical Sciences", The Science and Practice of Pharmacy, 19th Ed. Mack Publishing Company, Easton, Penn., (1995).

Los niveles de dosificación entre alrededor de 0,01 y alrededor de 100 mg/kg de peso corporal por día, preferentemente entre alrededor de 0,1 y alrededor de 50 mg/kg de

239
241

peso corporal por día del compuesto inhibidor de proteasa que se describe en la presente son útiles en una monoterapia para la prevención y tratamiento de la enfermedad mediada por el VHC. De manera típica, la composición farmacéutica de la presente invención se administrará de alrededor de 1 a alrededor de 5 veces por día o alternativamente, como una infusión continua. Tal administración se puede emplear como una terapia crónica o aguda. La cantidad de componente activo que se puede combinar con los materiales vehículo para producir una forma de dosificación simple variará dependiente del huésped que se somete a tratamiento y al modo en especial de administración. Una preparación típica contendrá de alrededor del 5% a alrededor del 95% de compuesto activo (*p/p*). Preferentemente, tales preparaciones contienen de alrededor del 20% a alrededor de 80% de compuesto activo.

Según apreciará el experto en la técnica, se podrán requerir dosificaciones inferiores o superiores a aquellas mencionadas anteriormente. Los regímenes específicos de dosificación y tratamiento para cualquier paciente en especial dependerá de una variedad de factores, incluyendo la actividad del compuesto específico empleado, la edad, peso corporal, estado general de salud, sexo, dieta, tiempo de administración, grado de excreción, combinación de fármacos, la gravedad y curso de la infección, la disposición del paciente a la infección y el criterio del médico tratante. En general, el tratamiento se inicia con pequeñas dosificaciones sustancialmente menos que la dosis óptima del péptido. Por lo tanto, la dosificación se incrementa mediante pequeños incrementos hasta que se alcanza el efecto óptimo según las circunstancias. En general, el compuesto se administra de manera más conveniente en un nivel de concentración que generalmente dará resultados efectivos antiviralmente sin causar ningún efecto secundario perjudicial o pernicioso.

Cuando la composición de la presente invención comprende una combinación de un compuesto de fórmula I y uno o más agentes terapéuticos o profilácticos adicionales, ambos el compuestos y el agente adicional se deben encontrar presentes en niveles de dosificación entre alrededor de 10 a 100% y más preferentemente entre alrededor de 10 y 80% de la dosificación administrada normalmente en un régimen de monoterapia.

Cuando estos compuestos, incluyendo sus sales y ésteres aceptables para uso farmacéutico, se formulan junto con un vehículo aceptable para uso farmacéutico, la composición resultante se puede administrar *in vivo* a mamíferos, tales como el hombre, para inhibir la proteasa NS3 del VHC o para tratar o prevenir la infección del virus de del VHC. Tal tratamiento también se puede lograr usando un compuesto de la presente invención en combinación con otro agente antiviral. Otros agentes antivirales preferidos

240
243

se describen en la sección de Definiciones y en la sección de composiciones farmacéuticas preferidas de acuerdo con la presente invención e incluyen, pero sin limitación, interferón α, β, δ, ω, γ o τ, ribavirin, amantadina; otros inhibidores de proteasa NS3 del VHC; inhibidores de la polimerasa del VHC; inhibidores de otros blancos en el ciclo de vida del VHC, que incluyen pero sin limitaciónn, helicasa, proteasa NS2/3, o sitio interno de entrada del ribosoma (IRES); o sus combinaciones. Los agentes adicionales se pueden combinar con compuestos de la presente invención para crear una forma de dosificación simple. De manera alternativa, estos agentes adicionales se pueden administrar por separado a un mamífero como parte de una forma de dosificación múltiple.

Por consiguiente, otra realización de la presente invención proporciona un método para inhibir la actividad de la proteasa NS3 del VHC en un mamífero administrando un compuesto de fórmula I, incluyendo una sal aceptable para uso farmacéutico o éster del mismo.

En una realización preferida, este método es útil para disminuir la actividad de proteasa NS3 del virus de la hepatitis C que infecta a un animal.

Según se discutió anteriormente, se considerá la terapia de combinación en la cual se co-administra un compuesto de fórmula (I), o una sal o éster aceptable para uso farmacéutico del mismo, con al menos un agente antiviral adicional. Los agentes antivirales preferidos se describieron anteriormente en la presente y ejemplos de tales agentes se proporcionan en la sección de Definiciones. Estos agentes adicionales se pueden combinar con los compuestos de la presente invención para crear una forma de dosificación farmacéutica única. De manera alternativa, estos agentes adicionales se pueden administrar por separado al paciente como parte de una forma de dosificación múltiple, por ejemplo, usando un kit. Tales agentes adicionales se pueden administrar a un paciente antes de, de manera concurrente con, o a continuación de la administración de un compuesto de fórmula (I), o una sal o éster aceptable para uso farmacéutico del mismo.

Un compuesto de fórmula (I), o una sal o éster aceptable para uso farmacéutico del mismo, expuesto en la presente también se puede emplear como un reactivo de laboratorio. Además, también se puede emplear un compuesto de la presente invención, incluyendo una sal o éster aceptable para uso farmacéutico del mismo, para tratar o evitar la contaminación viral de materiales y, por lo tanto, reducir el riesgo de infección viral del laboratorio o personal médico o pacientes en contacto con tales materiales (por

ej. sangre, tejido, instrumentos quirúrgicos y vestimenta, instrumentos y vestimenta de laboratorio y aparatos y materiales para la extracción de sangre).

Un compuesto de fórmula (I), incluyendo una sal o éster aceptable para uso farmacéutico del mismo, que se expone en la presente también se puede emplear como un reactivo de investigación. Un compuesto de fórmula (I), incluyendo una sal o éster aceptable para uso farmacéutico del mismo, también se puede emplear como control positivo para validar ensayos sustitutos de base celular o ensayos de replicación viral *in vitro* o *in vivo*.

Metodología

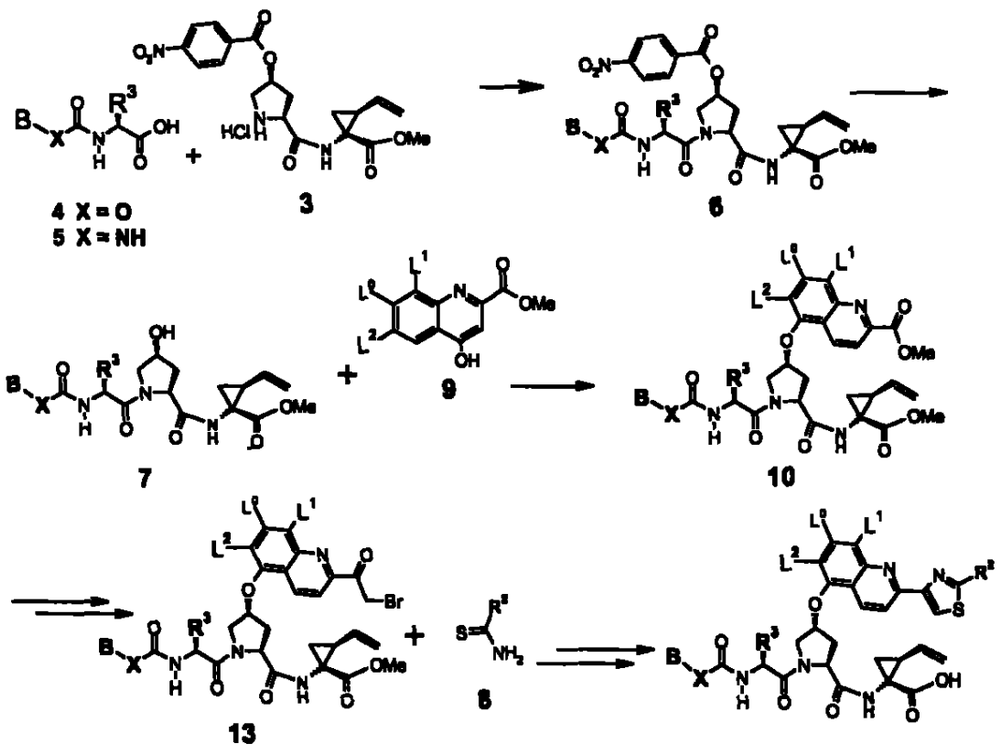
Se revelan diversas maneras de llevar a cabo la Síntesis de compuestos de fórmula I con diferentes derivados de quinolina en WO 00/09558. El dipéptido intermediario **15** (Esquema 2) y 2-carbometoxi-4-hidroxi-7-metoxiquinolina **9** (Esquema 1) se sintetizaron de acuerdo con los métodos generales descriptos en WO 00/09543.

Los compuestos de fórmula I en los cuales R^C es $NHSO_2R^8$ según se definió en la presente se preparar acoplando el ácido correspondiente de fórmula I (es decir, R^C es hidroxi) con una sulfonamida adecuada de fórmula $R^8SO_2NH_2$ en presencia de un agente de acoplamiento en condiciones estándar. Aunque se pueden emplear varios agentes de acoplamiento usados comúnmente, se descubrió que TBTU y HATU eran prácticos. Las sulfonamidas se encuentran disponibles comercialmente o se pueden preparar por métodos conocidos.

Los siguientes esquemas ilustran dos procesos convenientes empleando métodos conocidos para preparar los compuestos de fórmula 1 cuando R^1 es vinilo y R^C es OH.

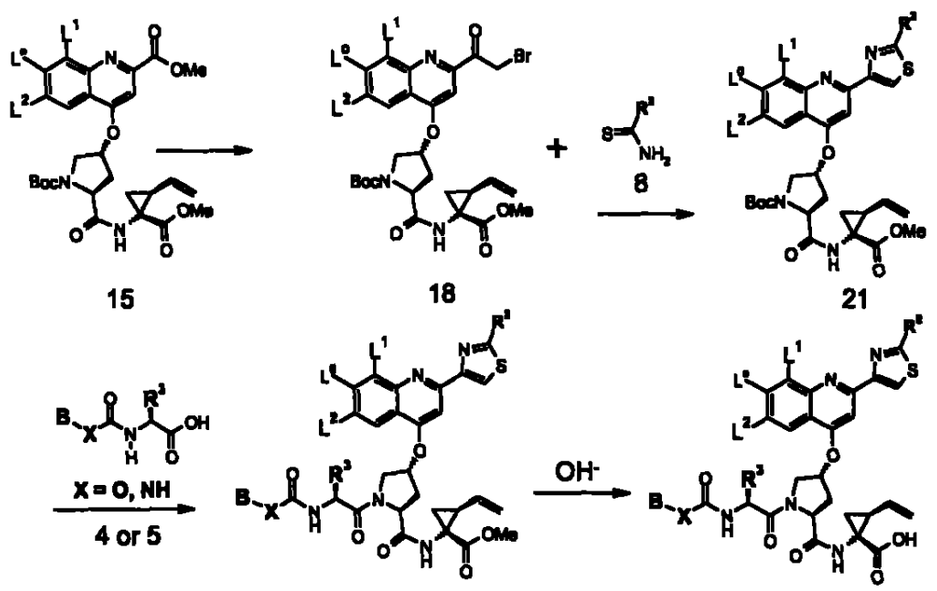
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Esquema 1



En resumen, la síntesis del dipéptido **3** se lleva a cabo acoplando el residuo P1 a la *trans*-hidroxi prolina protegida de manera adecuada bajo condiciones estándar. La estereoquímica del grupo hidroxilo se invirtió mediante la conocida reacción de Mitsunobu usando ácido *para*-nitrobenzoico. El acoplamiento del dipéptido con el resto P3 (preparado empleando metodología estándar y ejemplificado en la sección de ejemplos) dio el tripéptido **6**. La introducción del resto de quinolina al grupo hidroxilo del tripéptido **7** con la inversión de la estereoquímica se puede llevar a cabo usando o una reacción de Mitsunobu o convirtiendo el grupo hidroxilo libre en un buen grupo saliente (tal como un brosilato) y desplazándolo con el derivado de hidroxil quinolina **9**. Para la síntesis de los derivados de 2-(2-amino-4-tiazolilo), la quinolina empleada contiene un grupo 2-carbometoxi según se muestra en **9**. La conversión del grupo carboxilato al derivado aminotiazol se lleva a cabo mediante metodología de síntesis conocida y se describe y ejemplifica en WO 00/09543 y WO 00/09598. Finalmente, el éster de término C se hidroliza bajo condiciones acuosas básicas.

Esquema 2



El Esquema 2 describe otra secuencia de reacción para preparar compuestos de fórmula I. En este caso, el resto de quinolina se introduce al péptido de una manera similar a la descripta en el Esquema 1. Finalmente, el resto P3 se acopla bajo condiciones estándar al dipéptido **21**. La conversión del tripéptido resultante en el compuesto final se lleva a cabo según se describe en el Esquema 1.

SÍNTESIS DE FRAGMENTOS DE P1

Los restos P1 de los compuestos de fórmula (I) se prepararon usando los protocolos expuestos en WO 00/59929, publicado el 12 de Octubre de 2000 y WO 00/09543, publicada el 24 de febrero de 2000. En especial, se hace referencia a las páginas 33-35, Ejemplo 1 de WO00/59929 y Páginas 56-69, Ejemplo 9–20 de WO00/09543 para la preparación de restos P1 de ácido 1-aminociclopropancarboxílico.

SÍNTESIS DE SUSTITUYENTES P2

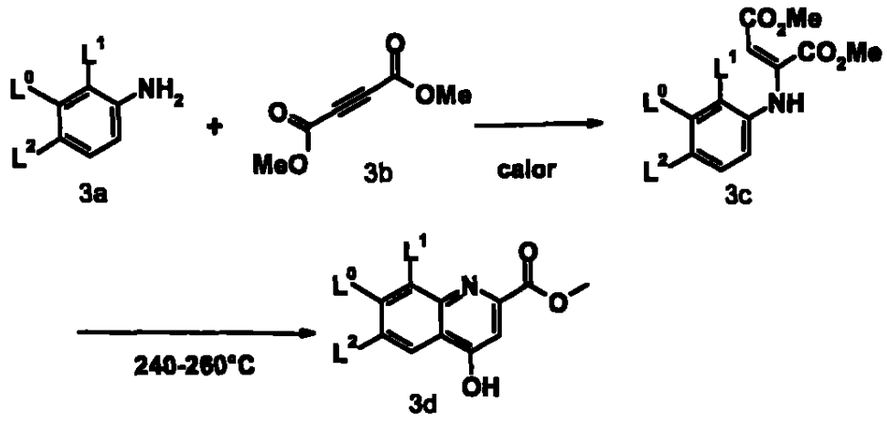
Los compuestos de fórmula **9** se pueden sintetizar a partir de materiales disponibles comercialmente empleando las técnicas descriptas en las Solicitudes Internacionales de Patente WO 00/59929, WO 00/09543, WO 00/09558 y Patente Estadounidense U.S. 6.323.180 B1.

Ejemplos de la síntesis de diferentes derivados de 2-carbometoxi-4-hidroxiquinolina se llevaron a cabo de la siguiente manera:

La síntesis de derivados de 2-carbometoxi-4-hidroxi-quinolina se llevó a cabo a partir de las anilinas correspondientes de acuerdo con el procedimiento de: Unangst,

P.C.; Connor, D.T. *J. Heterocyc. Chem.* **29**, *5*, **1992**, 1097-1100. El procedimiento se muestra en el esquema 3 a continuación:

Esquema 3



En resumen, se dejaron reaccionar las anilinas sustituidas de manera adecuada en la posición 2, 3 y/o 4 con dicarboxilato de dimetil acetileno y la enamina resultante se calentó a temperaturas elevadas para llevar a cabo la ciclación.

Las anilinas correspondientes se encuentran disponibles comercialmente o pueden requerir alguna transformación química conocida. Por ejemplo, puede ser que el nitro-compuesto se encuentre disponible comercialmente y que se convierta entonces en la amina correspondiente usando un agente reductor. Asimismo, cuando el ácido carboxílico se encuentra disponible comercialmente, se puede transformar en la amina correspondiente mediante un reordenamiento de Curtius.

Detalles adicionales de la invención se ilustran en los siguientes ejemplos que se entiende que no son limitativos con respecto a las reivindicaciones que se adjuntan. Otras maneras específicas de síntesis o resolución de los compuestos de la presente invención se pueden encontrar en WO 00/09543; WO 00/09558 & WO 00/59929 y en la solicitud pendiente de manera conjunta 09/368,670, la totalidad de las mismas se incorporan a la presente a modo de referencia.

EJEMPLOS

Las temperaturas se dan en grados Celsius. Los porcentajes de solución expresan una relación peso a volumen y las relaciones en solución expresan una relación volumen a volumen, salvo que se indique lo contrario. Los espectros de resonancia magnética nuclear (RMN) se registraron en un espectrómetro Bruker 400 MHz; los desplazamientos químicos (δ) se informan en partes por millón. La cromatografía flash se llevó a cabo sobre gel de sílice (SiO_2) de acuerdo con la técnica de cromatografía flash de Still (W.C. Still *et al.*, J. Org. Chem., (1978), 43, 2923).

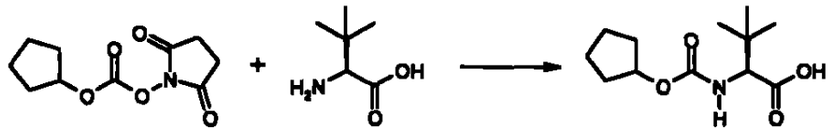
Las abreviaturas empleadas en los ejemplos incluyen:

BOC o Boc: *ter*-butiloxicarbonilo; DBU: 1,8-diazabiciclo[5,4,0]undec-7-eno; DCM: diclorometano; DIAD: azodicarboxilato de diisopropilo; DIEA: diisopropiletilamina; DIPEA: diisopropiletil amina; DMF: *N, N*-dimetilformamida; DMAP: 4-(dimetilamino)piridina; DMSO: dimetilsulfóxido; EtOAc: acetato de etilo; HATU: [hexafluorofosfato de O-7-azabenzotriazol-1-il)-1,1,3,3-tetrametiluronio]; HPLC: cromatografía líquida de alta resolución; MS: espectrometría de masa (MALDI-TOF: Ionización de desorción láser asistida por matriz - Tiempo de Vuelo, FAB: Bombardeo de Átomos Rápidos); Me: metilo; MeOH: metanol; Ph: fenilo; T.A.: temperatura ambiente (18 a 22°); *ter*-butilo o t-butilo: 1,1-dimetiletilo; Tbg: *ter*-butil glicina: *ter*-leucina; TBTU: tetrafluoroborato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametil uronio; TEA: trietilamina; TFA: ácido trifluoroacético; y THF: tetrahidrofurano.

Ejemplo 1

Síntesis de derivados de P3:

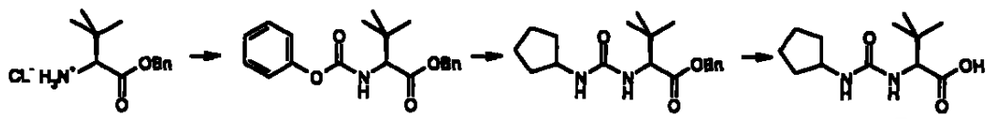
Síntesis del carbamato **4a**



4a

Se agregó THF (350 ml) a un matraz que contenía ciclopentil éster 2,5-dioxo-pirrolidin-1-il éster del ácido carbónico (9,00 g; 39,6 mmol) y *ter*-butil glicina (6,24 g; 47,5 mmol) que produce una suspensión. Se agregó agua destilada (100 ml) agitando de manera intensa. Una pequeña cantidad de sólido permaneció sin disolverse. Luego se agregó trietilamina (16,6 ml; 119 mmol) dando una solución homogénea que se agitó a T.A. Después de 2,5 h, el THF se evaporó y el residuo acuoso se diluyó con agua (100 ml). La reacción se convirtió en básica mediante la adición de NaOH 1 N (25 ml - pH final >10). La solución se lavó con EtOAc (2x 200 ml) y la fase acuosa se acidificó con HCl 1 N (ca. 70 ml - final pH <2). La solución turbia se extrajo con EtOAc (200 + 150 ml). El extracto se secó ($MgSO_4$) y se evaporó para dar carbamato **4a** como un sólido blanco (8,68 g).

Preparación de Ureas **5a**



5a

~~246~~
249

Una solución de hidrocloruro de *ter*-butil glicina bencil éster (2,55 g; 9,89 mmol) en THF (20 ml) y piridina (2,0 ml; 24,73 mmol) se enfrió a 0°C. Se agregó gota a gota cloroformiato de fenilo (1,30 ml; 10,19 mmol) a la solución fría. La suspensión resultante se agitó durante 5 min a 0°C, luego a T.A. durante 1,5 h. La mezcla de reacción se diluyó con EtOAc, se lavó con 10% de ácido cítrico (2x), agua (2x), $NaHCO_3$ saturado (2x), agua (2x) y salmuera (1x), se secó ($MgSO_4$), se filtró y se evaporó para obtener el compuesto bruto como un aceite casi incoloro (3,73 g; >100%; asume 9,89 mmol). El producto bruto (1,01 g; 2,97 mmol) se disolvió en DMSO (6,5 ml) y se agregó ciclopentilamina gota a gota. La mezcla de reacción se agitó a T.A. durante 45 min y luego se diluyó con EtOAc. La fase orgánica se lavó con 10% de ácido cítrico (2x), agua (2x), $NaHCO_3$ saturado (2x), agua (2x) y salmuera (1x), se secó ($MgSO_4$), se filtró y se evaporó para dar el producto bruto ciclopentil urea-Tbg-OBn como un aceite casi incoloro. El material bruto se purificó mediante cromatografía flash en columna con sílice empleando hexano:EtOAc 9:1 para eliminar las impurezas menos polares y 7:3 para eluir el producto el producto purificado como un aceite espeso incoloro (936 mg; 95%). El bencil éster producto (936 mg; 2,82 mmol) se desprotegió bajo un balón relleno con hidrógeno a T.A. en solución de etanol absoluto (15 ml) agitando la solución con Pd/C al 10% (93,6 mg) durante 5,5 h. La mezcla de reacción se filtró a través de un filtro de 0,45 micrones y se evaporó hasta sequedad para dar urea **5a** como un sólido blanco (669 mg; 98%)

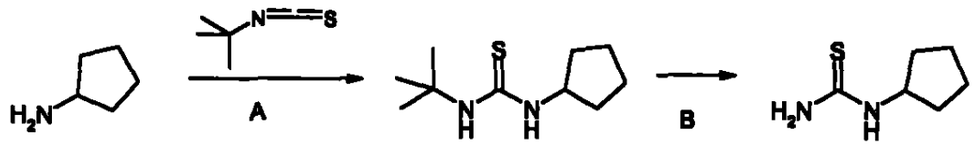
^{1}H RMN (400 MHz, DMSO-d_6): δ 12,39 (s, 1H), 6,09 (d, J = 7,4 Hz, 1H), 5,93 (d, J = 9,4 Hz, 1H), 3,90 (d, J = 9,4 Hz, 1H), 3,87-3,77 (m, 1H), 1,84-1,72 (m, 2H), 1,63-1,42 (m, 4H), 1,30-1,19 (m, 2H), 0,89 (s, 9H).

M.S. (electroaspersión) : 241,0 $(M-H)^-$ 243,0 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; CH_3CN : H_2O): 99%.

Ejemplo 2

Síntesis de Tiourea 8

Síntesis de tiourea 8a:



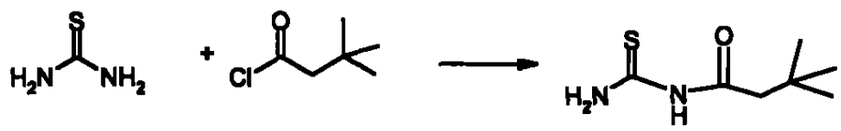
8a

A una solución de isotiocianato de *ter*-butilo (5,0 ml; 39,4 mmol) en DMC (200 ml) se agregó ciclopentilamina (4,67 ml; 47,3 mmol) seguida por DIPEA y la mezcla de reacción se agitó a T.A. durante 2 h. La mezcla se diluyó con EtOAc y se lavó con a 10% de solución acuosa de ácido cítrico (2x), $NaHCO_3$ saturado (2x), H_2O (2x) y salmuera

(1x). La capa orgánica se secó sobre $MgSO_4$ anhídrido, se filtró y se evaporó para dar *N-ter*-butil-*N'*-ciclopentiltiourea como un sólido blanco (3,70 g; 47% de rendimiento). Se disolvió *N-ter*-butil-*N'*-ciclopentiltiourea (3,70 g) en HCl concentrado (46 ml). La solución amarillo oscuro se calentó a reflujo leve. Después de 40 min, se permitió que la mezcla de reacción se enfríe a T.A. y después se enfrió en hielo y se basificó a pH 9,5 con sólido y una solución acuosa saturada de $NaHCO_3$. El producto se extrajo en EtOAc (3x). Los extractos de EtOAc combinados se lavaron con H_2O (2x) y salmuera (1x). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró para dar un sólido beige (2,46 g bruto). La trituración del material bruto en hexano/EtOAc 95/5 dio, después de la filtración, la *N*-ciclopentiltiourea **8a** como un sólido blanco (2,38 g; 90% de rendimiento).

^{1}H RMN (400 MHz, DMSO-d_6): δ 7,58 (bs, 1H), 7,19 (bs, 1H), 6,76 (bs, 1H), 4,34 (bs, 1H), 1,92-1,79 (m, 2H), 1,66-1,55 (m, 2H), 1,55-1,30 (m,4H). MS; es$^+$ 144,9 $(M + H)^+$, es$^-$: 142,8 $(M - H)^-$.

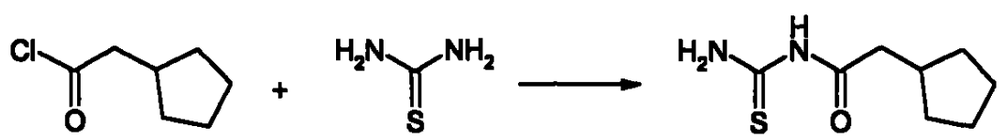
Preparación de Tiourea **8b**



8b

Se disolvió tiourea (5,0 g, 66 mmol) en tolueno (50 ml) y se agregó cloruro de *ter*-butilacetilo (8,88 g, 66 mmol). La mezcla se calentó a reflujo durante 14 h para dar una solución amarilla. La mezcla se concentró hasta sequedad y el residuo se dividió entre EtOAc y $NaHCO_3$ sat.. La fase orgánica amarilla se secó sobre $MgSO_4$, se filtró y se concentró para dar un sólido amarillo. El sólido se disolvió en una cantidad mínima de EtOAc y se trituró con hexano para dar **8b** como un sólido blanco (8,52 g; 75%). M.S. (electroaspersión): 173 $(M-H)^-$ 175 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06 % de TFA; CH_3CN : H_2O) : 99 %.

Preparación de Tiourea **8c**



8c

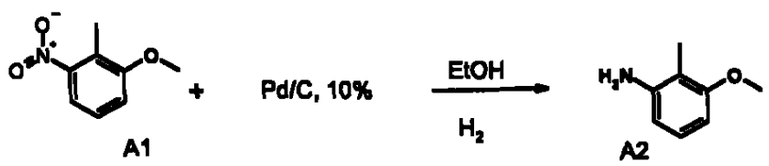
Empleando el procedimiento descripto anteriormente, pero usando cloruro de ciclopentil acetilo en lugar de cloruro de *ter*-butilacetilo, dio la tiourea **8c**.

Síntesis de derivados de 2-carbometoxi-4-hidroxi quinolina

Ejemplo 3A

Síntesis de 2-carbometoxi-4-hidroxi-7-metoxi-8-metilquinolina (A5)

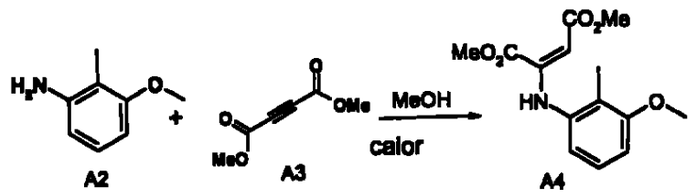
Paso A



A una solución de 2-metil-3-nitro anisol **A1** (5,1 g; 30,33 mmol; requiere ~30 min para que se disuelva) en etanol absoluto (85 ml) se agregó catalizador de Pd/C al 10% (500 mg). La solución se hidrogenó bajo un balón relleno con hidrógeno a presión atmosférica y temperatura ambiente durante 19 h. La mezcla de reacción se filtró a través de un lecho de Celite, se enjuagó y se evaporó hasta sequedad para obtener 2-metil-3-metoxianilina **A2** como un aceite color malva oscuro (4,1 g; 29,81 mmol; 98% de rendimiento).

MS 137 $(MH)^+$. Homogeneidad de HPLC de Fase Reversa @ 220 nm (0,06 % de TFA; $CH_3CN : H_2O$) : 99%.

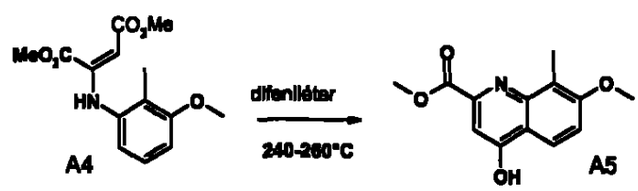
Paso B



Se agregó gota a gota dicarboxilato de dimetil acetileno **A3** (3,6 ml, 29,28 mmol) a una solución de 2-metil-3-metoxianilina **A2** (3,95 g, 28,79 mmol) en MeOH (100 ml) (la reacción es exotérmica). La mezcla se calentó a un reflujo suave durante 5 horas, se enfrió y se concentró en vacío. El material bruto se purificó mediante cromatografía flash en columna en gel de sílice con hexano:EtOAc (95 : 5) para dar, después de la evaporación de las fracciones puras, el producto **A4** (6,5 g; 23,27 mmol; 81% de rendimiento).

Homogeneidad de HPLC de Fase Reversa a 220 nm (0,06% de TFA; $CH_3CN:H_2O$): 95%.

Paso C

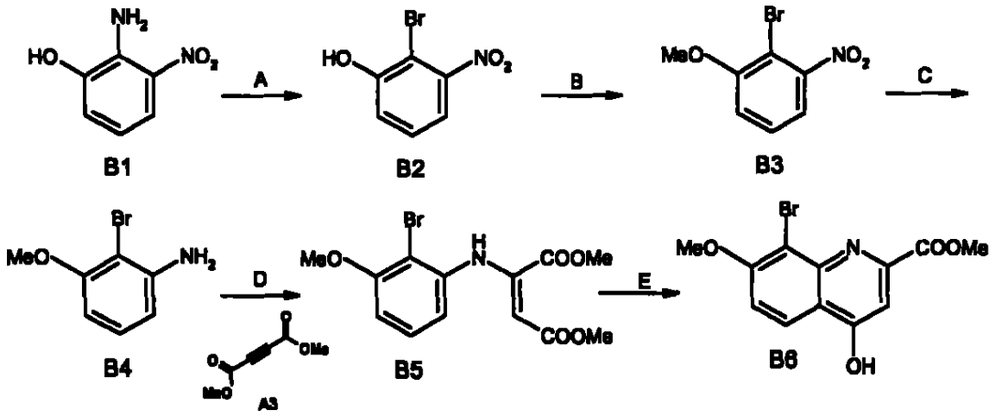


Se disolvió el diéster **A4** (6,5 g, 23,27 mmol) en difeniléter (12 ml) y la mezcla de reacción se colocó en un baño de arena pre-calentado a una temperatura de baño de 350-400°C. una vez que la mezcla de reacción alcanzó una temperatura interna de 240°C (observar la evolución de MeOH a 230-240°C) se inició un conteo de seis minutos antes de retirar el baño (punto final de temperatura: 262°C) y se dejó que la reacción se enfríe hasta temperatura ambiente. Se formó un sólido al enfriarse que se diluyó con éter, se filtró y se secó para dar un sólido color marrón tostado (3,48 g bruto). El material bruto se sometió a cromatografía sobre columna de gel de sílice con hexano:EtOAc 5:5 para eliminar impurezas, luego 2:8 y después 100% de EtOAc para completar la elución del producto para dar **A5**. Después de la evaporación, como un sólido amarillo pálido (2,1 g, 37% de rendimiento).

MS $(M + H)^+$; 246 y $(M - H)^-$; 248,1, Homogeneidad de HPLC de Fase Reversa a 220 nm (0,06% de TFA; CH_3CN:H_2O):99%.

Ejemplo 3B

Síntesis de 2-carbometoxi-8-bromo-4-hidroxi-7-metoxiquinolina (B6)



Paso A

Se disolvió 2-amino-3-nitrofenol **B1** (5 g; 32,4 mmol) en H_2O (29,5 ml) y 1,4-dioxano (14,7 ml). La mezcla se calentó a reflujo y se agregó ácido bromhídrico (48%; 16,7 ml; 147 mmol) gota a gota durante un período de 20 min. Una vez completada la adición, el reflujo se mantuvo 15 min adicionales. La reacción se enfrió a 0°C (baño de hielo) y se agregó nitrito de sodio (2,23 g; 32,3 mmol) en H_2O (20 ml) durante un período de 30 min. La agitación se continuó durante 15 min a 0°C, luego la mezcla se transfirió a un embudo de goteo con camisa (0°C) y se agregó gota a gota a una mezcla agitada de Cu(I)Br (5,34 g; 37,2 mmol) en H_2O (29,5 ml) y HBr (48%; 16,7 ml; 147 mmol) a 0°C. La reacción se agitó durante 15 min a 0°C, se calentó a 60°C, se agitó durante un adicional de 15 min, se enfrió hasta temperatura ambiente y se dejó en agitación hasta el día

siguiente. La mezcla de reacción se transfirió a un embudo de separación y se extrajo con éter (3x 150 ml). Las capas orgánicas se combinaron, se lavaron con salmuera (1X), se secaron (Na_2SO_4), se filtraron y se concentraron para dar el producto bruto (7,99 g) como un aceite rojo-amarronado. El material bruto se purificó mediante cromatografía flash en columna (1:25 gel de sílice ultra puro, malla de 230-400, 40-60 mm, 60 angstroms; CH_2Cl_2 como el solvente) para dar 2-bromo-3-nitrofenol puro **B2** (45%; 3,16 g) como un sólido marrón anaranjado.

MS 217,8 $(MH)^-$. Homogeneidad mediante HPLC (TFA) a 220 nm: 97%.

Paso B

El material de partida de nitrofenol **B2** (3,1 g; 14,2 mmol) se disolvió en DMF (20 ml) y a la solución se agregó carbonato de cesio de base (5,58 g; 17,1 mmol) seguido por MeI (2,6 ml; 42,5 mmol). La mezcla se agitó a temperatura ambiente hasta el día siguiente. El DMF se evaporó, el residuo se capturó en éter (1x 200 ml), se lavó con agua (1x 200 ml), salmuera (4x 100 ml), se secó ($MgSO_4$), se filtró y se evaporó para dar el 2-bromo-3-nitroanisol bruto **B3** (94%; 3,1 g) como un sólido anaranjado.

MS 234 $(M+2H)^+$; Homogeneidad mediante HPLC (TFA) a 220 nm: 98%.

Paso C

Se disolvió 2-bromo-3-nitroanisol **B3** (1,00 g; 4,31 mmol) en ácido acético glacial (11,0 ml) y etanol (11,0 ml). A esta solución se agregó polvo de hierro (0,98 g; 17,5 mmol). La mezcla se agitó a reflujo durante 3,5 h y se procesó. La mezcla de reacción se diluyó con agua (35 ml), se neutralizó con Na_2CO_3 sólido y el producto se extrajo con CH_2Cl_2(3X 50 ml). El extractos se secaron (Na_2SO_4), se filtraron y se concentraron *in vacuo* para dar el producto bruto, 2-bromo-3 metoxianilina **B4** (91%; 0,79 g) como un aceite amarillo pálido.

MS 201,8 $(MH)^+$; Homogeneidad mediante HPLC (TFA) a 220 nm: 95%.

Paso D

A una solución de 2-bromo-3-metoxianilina **B4** (0,79 g; 3,9 mmol) en MeOH (7,6 ml) se agregó dicarboxilato de dimetil acetileno **A3** (0,53 ml; 4,3 mmol) gota a gota a 0°C (advertencia: la reacción es exotérmical). La solución se calentó hasta el día siguiente a reflujo y se procesó. El MeOH se evaporó y el producto bruto se secó en alto vacío para dar una goma roja, se purificó mediante cromatografía flash en columna (1:30 gel de sílice ultra puro, malla de 230-400, 40-60 mm, 60 angstroms; hexano/EtOAc 4:1) para dar el aducto **B5** (86%; 1,16 g) como un sólido amarillo pálido.

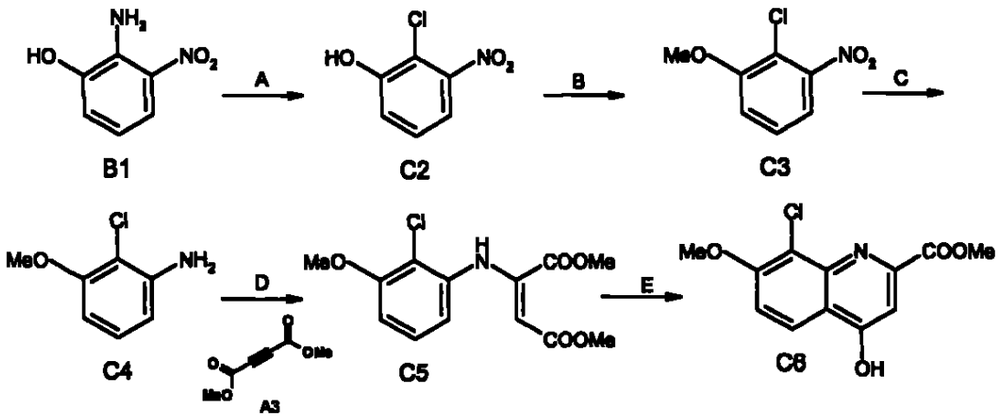
MS 344,0 $(MH)^+$; Homogeneidad mediante HPLC (TFA) a 220 nm: 72%.

Paso E

A un baño de arena pre-calentado a alrededor de 440°C (temperatura externa) se le colocó el aducto del diéster **B5** (1,1 g; 3,16 mmol) en difeniléter (3,6 ml). La reacción se agitó entre 230°C-245°C (temperatura interna; el MeOH comenzó a evaporarse a alrededor de 215°C) durante 7 min y posteriormente se enfrió hasta temperatura ambiente. A medida que la solución se enfrió, el producto se cristalizó a partir de la mezcla de reacción. El sólido marrón resultante se filtró, se lavó con éter y se secó en alto vacío para dar el producto bromoquinolina **B6** bruto (74%; 0,74 g) como un sólido marrón. La RMN reveló que este producto es una mezcla alrededor 1:1 de tautómeros. RMN (DMSO; 400 MHz) ok (mezcla 1:1 de tautómeros); MS 311,9 $(MH)^+$; Homogeneidad mediante HPLC (TFA) a 220 nm: 96%.

Ejemplo 3C

Síntesis de 2-carbometoxi-8-cloro-4-hidroxi-7-metoxiquinolina (C6)



Paso A

Se disolvió 2-amino-3-nitrofenol **B1** (5 g; 32,4 mmol) en HCl concentrado (75 ml) y 1,4-dioxano (14,7 ml). La mezcla se calentó a 70°C hasta que la mayoría de los sólidos se encontraron en solución. La mezcla de reacción se enfrió a 0°C (baño de hielo) y se agregó nitrito de sodio (2,23 g; 32,3 mmol) en H_2O (5,4 ml) durante un período de 3 horas a la solución marrón. La temperatura se mantuvo por debajo de 10°C durante la adición y se continuó la agitación durante un adicional de 15 min a 0°C. Este intermediario de diazonio se vertió en una solución de Cu(I)Cl (3,8 g; 38,9 mmol) en H_2O (18,5 ml) y HCl conc. (18,5 ml) a 0°C. La reacción se agitó durante 15 min a 0°C, se calentó a 60°C y se agitó durante un adicional de 15 min. La mezcla de reacción se llevó entonces hasta temperatura ambiente y se dejó en agitación hasta el día siguiente. La mezcla de reacción se transfirió a un embudo de separación y se extrajo con éter (3X 150 ml). Las capas orgánicas se combinaron, se lavaron con salmuera (1X), se secaron (Na_2SO_4), se filtraron y se concentraron para dar el producto bruto (5,83 g) como un sólido rojo

amarronado. El material bruto se purificó mediante cromatografía flash en columna (1:25 gel de sílice ultra puro, malla de 230-400, 40-60 mm, 60 angstroms; hexano/EtOAc 3:1 como solvente) para dar 2-cloro-3-nitrofenol puro **C2** (48%; 2,7 g) como un sólido anaranjado.

MS 171,8 $(MH)^-$: Homogeneidad mediante HPLC (TFA) a 220 nm: 96%.

Literatura relevante para la Reacción de Sandmeyer: *J. Med. Chem*, **1982**, 25(4), 446-451.

Paso B

El material de partida, nitrofenol **C2** (1,3 g; 7,49 mmol), se disolvió en DMF (10 ml) y a esta solución se agregó carbonato de cesio molido (2,92 g; 8,96 mmol), seguido por MeI (1,4 ml; 22,5 mmol). La mezcla se agitó a temperatura ambiente hasta el día siguiente. El DMF se evaporó in *vacuo* y el residuo se tomó en éter (150 ml), se lavó con agua (150 ml), salmuera (4x 100 ml) y luego se secó sobre ($MgSO_4$). La fase orgánica se filtró y se evaporó para dar el 2-cloro-3-nitroanisol bruto **C3** (98%; 1,38 g) como un sólido anaranjado.

Homogeneidad mediante HPLC (TFA) a 220 nm: 93%.

Paso C

Se disolvió 2-cloro-3-nitroanisol **C3** (1,38 g; 7,36 mmol) en una mezcla de ácido acético glacial (19 ml)/etanol (19 ml). A esta solución se agregó hierro en polvo (1,64 g; 29,4 mmol). La mezcla se agitó a reflujo durante 3,5 hr y se procesó. La mezcla de reacción se diluyó con agua (70 ml), se neutralizó con Na_2CO_3 sólido y el producto se extrajo con CH_2Cl_2 (3X 150 ml). El extractos se combinaron y se lavaron con salmuera saturada y luego se secaron sobre (Na_2SO_4), se filtraron y se concentraron in *vacuo* para dar el producto bruto, 2-cloro-3-metoxianilina **C4** (100%; 1,2 g) como un aceite amarillo. Este material se empleó como tal en los siguientes pasos.

MS 157,9 $(MH)^+$; Homogeneidad mediante HPLC (TFA) a 220 nm: 86%.

Paso D

A una solución de 2-cloro-3-metoxianilina **C4** (1,2 g; 7,61 mmol) en MeOH (15 ml) se agregó dicarboxilato de dimetil acetileno **A3** (1,0 ml; 8,4 mmol) gota a gota a 0°C (advertencia: la reacción es exotérmica!). La solución se calentó hasta el día siguiente a reflujo y se procesó. El MeOH se evaporó y el producto bruto se secó en alto vacío para dar una goma roja que se purificó mediante cromatografía flash en columna (1:30 de gel de sílice ultra puro, malla de 230-400, 40-60 mm, 60 angstroms; hexano/EtOAc 4:1) para dar el aducto **C5** (74 %; 1,68 g) como un sólido amarillo.

MS 300 $(MH)^+$; Homogeneidad mediante HPLC (TFA) @ 220 nm: 90%.

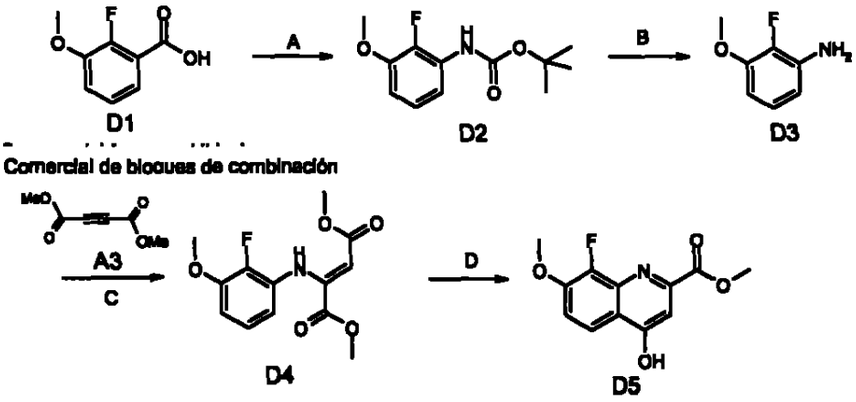
Paso E

A un baño de arena pre-calentado a alrededor de 440°C (temperatura externa) se colocó el aducto de diéster C5 (1,68 g; 5,6 mmol) en difeniléter (6,3 ml). La reacción se agitó entre 230°C-245°C (temperatura interna; el MeOH comenzó a evaporarse a alrededor de 215°C) durante 7 min y posteriormente se enfrió hasta temperatura ambiente. A medida que la solución se enfrió, el producto se cristalizó a partir de la mezcla de reacción. El sólido amarronado resultante se filtró, se lavó con éter y se secó en alto vacío para dar la quinolina C6 (83%; 1,25 g) como un sólido de color beige. La RMN reveló que este producto es una mezcla alrededor 1:1 de tautómeros (formas ceto/fenol).

MS 267,9 $(MH)^+$; Homogeneidad mediante HPLC (TFA) a 220 nm: 92%.

Ejemplo 3D

Síntesis de 2-carbometoxi-8-fluoro-4-hidroxi-7-metoxiquinolina (D5)



Paso A

Se agitaron una solución de ácido 2-fluoro-3-metoxi benzoico D1 (1,68 g, 9,87 mmol) y DIPEA (2,07 ml, 11,85 mmol, 1,2 equiv.) en una mezcla de tolueno (8 ml) y t-BuOH (8 ml) sobre tamices moleculares 4A activados durante 1 h seguido del agregado de difenil dosforil azida (DPPA, 2,55 ml, 11,85 mmol) y esta mezcla se reflujó hasta el día siguiente. La mezcla de reacción se filtró y el filtrado se concentró *in vacuo*, el residuo se capturó en EtOAc (50 ml), se lavó con H_2O (2x 30 ml) y salmuera (1x 30 ml). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró a presión reducida. El producto bruto D2 (2,38 g, 96%) se empleó tal cual en el paso siguiente. El análisis de MS muestra la pérdida del grupo Boc: 141,9 $((M+H)-Boc)^+$, 139,9 $((M-H)-Boc)^-$.

Paso B

Se trató el compuesto D2 (2,28 g, 9,45 mmol) con solución de HCl 4 N/dioxano (de Aldrich) (10 ml, 40 mmol) durante 60 min y el análisis de HPLC mostró que el material

de partida se consumió completamente. La mezcla de reacción se concentró in *vacuo*, se redisolvió en EtOAc y se lavó con agua, $NaHCO_3$ saturado (ac.) y salmuera saturada. La fase orgánica se secó ($MgSO_4$), se filtró y se concentró para dar 1,18 g (88%) de **D3** como un aceite marrón, que se empleó según se hace en el paso siguiente. MS: 141,9 $(M+H)^+$, 139,9 $(M-H)^-$.

Paso C

Se combinó la anilina **D3** (1,18 g, 8,36 mmol) con dicarboxilato de dimetilacetileno **A3** (1,45 ml, 10,0 mmol) en metanol (25 ml). La reacción se reflujó durante 2 horas antes de que se concentre hasta sequedad. El material bruto se purificó mediante cromatografía flash eluyendo con 9/1 (hexano/EtOAc) para dar el aducto Michael **D4** como un aceite amarillo, (1,27 g, 54%).

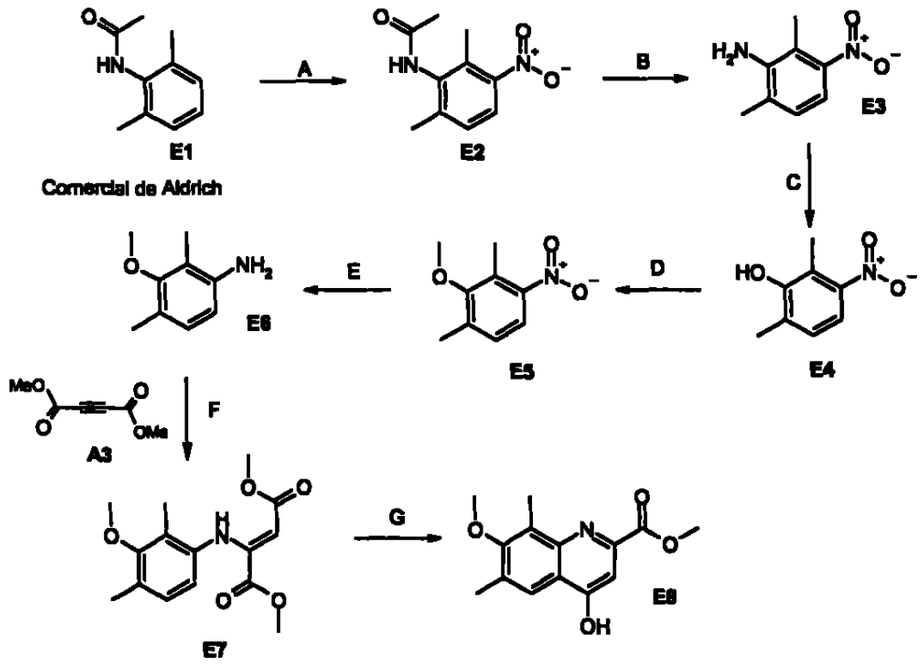
Paso D

El aducto de Michael **D4** se disolvió en difeniléter caliente (6 ml) y se colocó en un baño de arena previamente calentado a ~350°C. La temperatura interna de la reacción se monitoreó y se mantuvo a ~245°C durante alrededor de 5 minutos (la solución se tornó de color marrón). Después de enfriarse a T.A., la 4-hidroxiquinolina deseada precipitó de la solución. El sólido marrón se filtró y se lavó varias veces con dietiléter para dar, una vez seco, quinolina **D5** como un sólido marrón (0,51 g, 45%). MS: 252 $(M+H)^+$, 249,9 $(M-H)^-$. Mezcla de tautómeros 1:1, ^{1}H-RMN (DMSO-d6, 400 MHz) 12,04 (s, 1H), 11,02 (s. 1H), 8,0 (d, 1H), 7,88 (d, 1H), 7,65 (m, 1H), 7,39 (s, 1H), 7,32 (m, 1H), 6,5 (s, 1H), 4,0 (s, 3H), 3,98 (s, 3H), 3,95 (s, 3H), 3,91 (s, 3H).

EFT 258

Ejemplo 3E

Síntesis de 2-carbometoxi-6,8-dimetil-4-hidroxi-7-metoxiquinolina (E8)



Paso A

La amida E1 (5,0 g, 30,63 mmol) se disolvió en una mezcla de ácido acético (5 ml) y ácido sulfúrico (10 ml) y se enfrió a 0°C. Se agregó una mezcla de ácido nítrico (70%, 3 ml) y ácido sulfúrico (2 ml) gota a gota después de lo cual la solución se calentó a T.A. y se agitó durante 1 h. La mezcla de reacción se vertió luego sobre hielo triturado y se filtró (después que fundió el hielo, pero cuando la solución aún se encontraba fría) para dar el compuesto deseado E2 (5,8 g, 91%) que se continuó en la siguiente reacción sin purificación adicional. MS ES^+ = 209,0, ES^- = 206,9, *(Ref: Giumenini, A.G.; Verardo, G.; Polana, M. J. Prak. Chem. 1988, 181).*

Paso B

El compuesto E2 (5,8 g, 27,86 mmol) se trató con solución HCl 6M (5 ml) en MeOH (10 ml) y se calentó a reflujo durante 48 h para dar el producto deseado E3 (4,6 g, 99 %). La RP-HPLC indica el consumo total del material de partida (R_t (E2) = 2,6 min.; R_t (E3)= 3,9 min.). La mezcla se concentró y se empleó en la posterior reacción sin purificación adicional.

Paso C

Se agregó ácido sulfúrico (18 ml) a la solución de la anilina E3 (4,20 g, 25,27 mmol) en agua (36 ml) a 0°C, seguido por la adición de nitrito de sodio (2,3 g, 33,33 mmol en agua (6 ml). en un matraz separado, se colocó una mezcla de agua (14 ml) y ácido

sulfúrico (1,5 ml). Esta solución se llevó hasta reflujo y luego se agregó la solución inicial gota a gota mientras se mantuvo el hervor. Una vez completada la adición, se continuó el hervor durante 5 min y luego se vertió la mezcla sobre mezcla de hielo/carbonato de sodio mientras se enfrió en un baño de hielo. El producto se extrajo con EtOAc acuoso y se concentró para dar un líquido marrón oscuro viscoso **E4** (2,00 g, 47 %) que se empleó en la reacción posterior sin purificación adicional. MS ES^- = 210,9.

Paso D

Se agregó MeI (1,42 ml, 22,74 mmol) a una solución del fenol de partida **E4** (1,9 g, 11,37 mmol) y carbonato de potasio (2 g) en DMF (25 ml) a T.A. La mezcla se calentó a 50°C durante 2 h y luego se enfrió a T.A. Se agregó EtOAc y la solución se lavó con agua (3x) y luego la capa acuosa se extrajo con EtOAc. Las capas orgánicas combinadas se secaron, se filtraron y se concentraron para dar el metil éter deseado **E5** (2,0 g, 97%). ^{1}H-RMN ($CDCl_3$, 400 MHz) 7,62 (d, J = 8,4 Hz, 1H), 7,13 (d, J = 8,4 Hz, 1H), 3,74 (s. 3H), 2,48 (s, 3H), 2,36 (s, 3H).

Paso E

Se agregó Pd/C diez por ciento (10%) (200 mg) a una solución del material de partida, el nitro-compuesto **E5** (2,0 g, 11,04 mmol), en EtOH y se colocó en un agitador Parr bajo una atmósfera de H_2 de 40 psi durante 2 h. La solución se filtró a través de un lecho de sílice/Celite, se enjuagó con MeOH y se concentró para dar la anilina deseada **E6** (1,5 g, 90 %) que se empleó sin purificación adicional.

Paso F

Se combinó la anilina **E6** (1,9 g, 12,65 mmol) con dicarboxilato de dimetilacetileno **A3** (2,32 ml, 18,85 mmol) en metanol (3 ml). La reacción se calentó a reflujo durante 2 h antes de concentrarse hasta sequedad. El material bruto se purificó mediante cromatografía flash (9:1 hexano/EtOAc) para dar el aducto de Michael **E7** como un aceite amarillo (2,8 g, 76%). ^{1}H-RMN ($CDCl_3$, 400 MHz) 9,48, (s, br, 1H), 6,89 (d, J = 7,9 Hz, 1H), 6,47 (d, J = 7,9 Hz, 1H), 5,35 (s, 1H), 3,74 (s. 3H), 3,70 (s, 3H), 3,65 (s, 3H) 2,27 (s, 3H), 2,24 (s, 3H).

Paso G

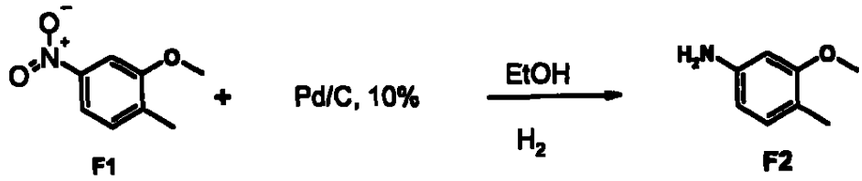
El aducto de Michael **E7** se disolvió en difenil éter caliente (10 ml) y se colocó en un baño de arena calentado previamente a ~350°C. La temperatura interna de la reacción se monitoreó, se mantuvo a ~245°C durante alrededor de 5 minutos (la solución se tornó marrón) y se enfrió a T.A. en dicho momento la 4-hidroxiquinolina deseada se precipitó fuera de la solución. El sólido marrón se filtró y se lavó varias veces con dietiléter para dar quinolina **E8** como un sólido amarillo-amarronado después del secado (1,10 g, 88 %).

^{1}H-RMN ($CHCl_3$, 400 MHz) 8,80, (s, br, 1H), 8,06 (s, 1H), 7,26 (s, 1H), 6,93 (s, 1H), 4,04 (s. 3H), 3,80 (s, 3H), 2,45 (s, 3H) 2,39 (s, 3H).

Ejemplo 3F

Síntesis de 2-carbometoxi-4-hidroxi-7-metoxi-8-metilquinolina (F4):

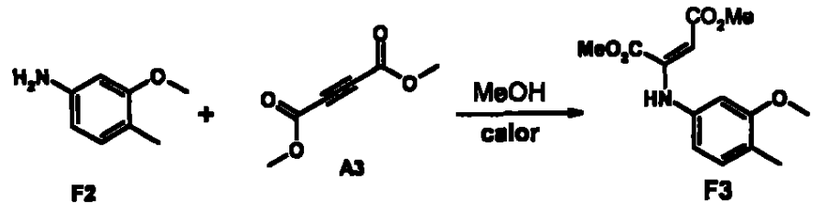
Paso A



F1 F2

A una suspensión de 2-metil-5-nitroanisol F1 (1,54 g; 9,21 mmol) en etanol absoluto (15 ml) se agregó 10% de catalizador Pd/C (249 mg). La suspensión se hidrogenó bajo un balón relleno con hidrógeno a presión atmosférica y a temperatura ambiente durante 6,5 h. La mezcla de reacción se filtró a través de un filtro Millex de 0,45 micrones y se evaporó hasta sequedad para dar 4-metil-*m*-anisidina F2 (1,22 g; 8,89 mmol; 97% de rendimiento)

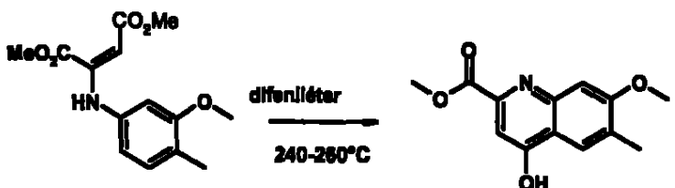
Paso B



F2 A3 F3

Se agregó dicarboxilato de dimetil acetileno A3 (1,1 ml, 8,95 mmol) gota a gota a una solución de 4-metil-*m*-anisidina F2 (1,22 g, 8,89 mmol) en MeOH (20 ml). Advertencia: la reacción es exotérmica. La mezcla se calentó a reflujo leve durante 4 horas, se enfrió y se concentró en vacío. El material bruto se purificó mediante cromatografía flash en columna sobre gel de sílice con hexano:EtOAc (92,5:7,5) para dar, después de la evaporación de las fracciones puras, el aducto de diéster F3 (1,8 g; 6,44 mmol; 73% de rendimiento).

Paso C



F3 F4

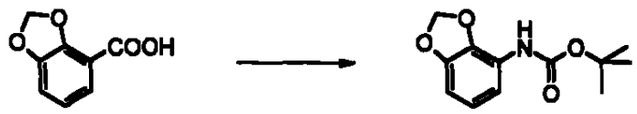
El diéster F3 (1,8 g, 6,44 mmol) se disolvió en difeniléter (5 ml) y la mezcla de reacción se colocó en un baño de arena pre-calentado a una temperatura de baño de 350-400°C. Una vez que la mezcla de reacción llegó a una temperatura interna de 240°C, comenzó un conteo de cinco minutos antes de retirar el baño y se dejó que la reacción se enfríe hasta temperatura ambiente hasta el día siguiente. Se formó un sólido al enfriarse que se diluyó con éter, se filtró y se secó para dar un sólido marrón (0,97 g bruto) que contenía ambos regioisómeros en proporciones casi iguales. El material bruto se trituró con MeOH y EtOAc, se filtró y se secó para dar el regioisómero correcto del producto de metilquinolina F4 como un sólido amarillo (245 mg, 15% de rendimiento).

Homogeneidad mediante HPLC (TFA) a 220 nm: 90%.

Ejemplo 3G

Síntesis de 2-carbometoxi-4-hidroxi-[1,3]dioxolo[4,5-h]quinolina (G5):

Paso A



G1 G2

A una solución a reflujo de ácido 2,3-metilendioxibenzoico disponible comercialmente G1 (485 mg; 2,92 mmol) en 1,4-dioxano (8,0 ml) y t-butanol (2,5 ml) se agregó TEA (430 µl; 3,08 mmol) y difenilfosforil azida (DPPA, 630 µl; 2,92 mmol) y se reflujó durante 10 h. La mezcla se evaporó, se diluyó con cloroformo, se lavó con ácido cítrico 5% (3x), agua, bicarbonato de sodio saturado y salmuera, se secó ($MgSO_4$), se filtró y se evaporó para dar el producto bruto. Purificación flash en columna sobre gel de sílice con hexano:EtOAc (75:25) dio el compuesto Boc-amino puro G2 (257 mg; 37%).

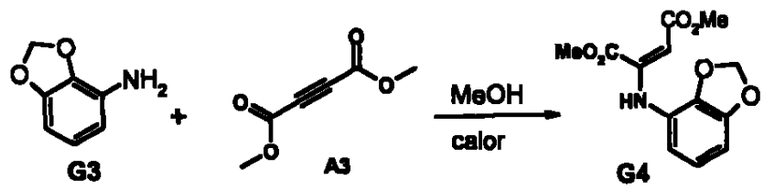
Paso B



G2 G3

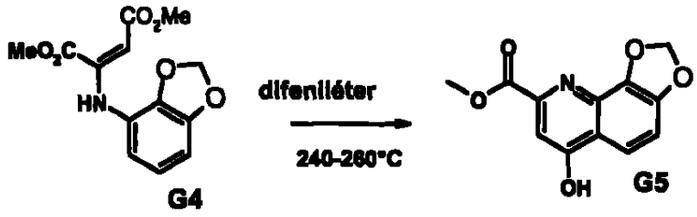
El material de partida de Boc G2 (257 mg; 1,08 mmol) se disolvió en HCl 4M /dioxano (5,0 ml) y se agitó a temperatura ambiente durante 1 hr. El solvente se evaporó y el residuo se diluyó con bicarbonato de sodio saturado (algunos ml) y NaOH 1 M (1 ml), se extrajo con EtOAc (2x), se secó ($MgSO_4$), se filtró y se evaporó hasta sequedad para dar la 2,3-metilendioxianilina bruta G3 (158 mg; 106%).

Paso C



Se agregó dicarboxilato de dimetil acetileno **A3** (130 µl, 1,06 mmol) gota a gota a una solución de 2,3-metilendioxianilina bruta **G3** (148 mg, 1,08 mmol) en MeOH (2,5 ml). Advertencia: la reacción es exotérmica. La mezcla se calentó a reflujo leve durante 3 horas, se enfrió y se concentró en vacío. El material bruto se purificó mediante cromatografía flash en columna en gel de sílice con hexano:EtOAc (9:1) para dar, después de la evaporación de las fracciones puras, el aducto de diéster **G4** (185 mg; 0,662 mmol; 61% de rendimiento).

Paso D



El diéster **G4** (180 mg, 0,645 mmol) se disolvió en difeniléter (2,5 ml) y la mezcla de reacción se colocó en un baño de arena pre-calentado a una temperatura de baño de 350-400°C. Una vez que la mezcla de reacción alcanzó una temperatura interna de 250°C (observar la evolución del MeOH a 220-230°C) se comenzó un conteo de seis minutos antes de retirara el baño (punto final de temperatura: 262°C) y se dejó que la reacción se enfríe hasta temperatura ambiente. Al enfriarse se formó un sólido que se diluyó con éter, se filtró y se secó para dar la dioxiquinolina bruta **G5** (125 mg; 78 %). No se requirió la purificación y el material se empleó como tal en las siguientes reacciones.

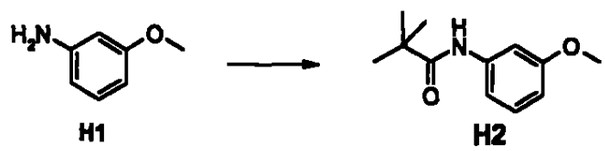
MS $(M+H)^+$; 246 y $(M-H)^-$; 248,1.

Homogeneidad mediante HPLC (TFA) a 220 nm :88%.

Ejemplo 3H

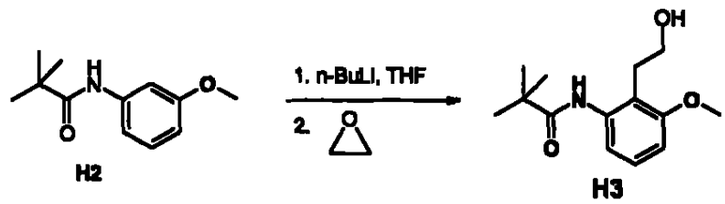
Síntesis de 2-carbometoxi-4-hidroxi-8,9-dihidro-furo[2,3-h]quinolina (H7):

Paso A



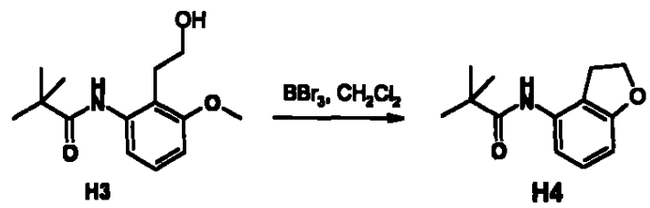
Se agregó trietilamina (5,0 ml, 35,6 mmol) a un matraz que contenía la amina H1 (2,0 ml, 17,8 mmol) y diclorometano (100 ml) bajo una atmósfera de nitrógeno. Los contenidos se enfriaron en un baño de hielo y se agregó cloruro de trimetilacetilo (3,3 ml, 26,7 mmol) gota a gota. Se permitió que la reacción se caliente lentamente a T.A. y se agitó durante 14 h. a esta temperatura. La reacción se desactivó con solución de $NaHCO_3$ saturado y se extrajo con EtOAc. Las capas orgánicas combinadas se secaron, se filtraron y se concentraron seguidas por cromatografía flash en columna (hexano:EtOAc 4:1 a 1:1) para dar el producto deseado H2 como un sólido blancuzco (3,7 g, 97% de rendimiento).

Paso B



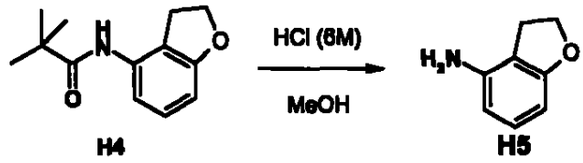
Se agregó n-BuLi (15,9 ml, 1,6M, 25,5 mmol) gota a gota un matraz secado a la llama que contenía una solución de la amida de partida H2 (1,6 g, 7,72 mmol) en THF a 0°C bajo argón. La solución se tornó levemente amarilla/naranja en color cuando se agregó n-BuLi. Se permitió que la solución se caliente lentamente a T.A. y se agitó durante 24 h. La solución se enfrió nuevamente hasta 0°C y se agregó óxido de etileno (0,46 ml, 9,26 mmol) gota a gota. Se permitió que la solución se caliente lentamente a 23°C, se desactivó con solución de $NaHCO_3$ saturado, se extrajo con EtOAc, se secó, se filtró y se concentró seguido por cromatografía flash en columna (hexano:acetato de etilo 4:1 a 1:1) para obtener el producto deseado H3 (1,94 g, 5,01 mmol, 65% de rendimiento). Homogeneidad mediante HPLC (TFA) a 220 nm : 99%.

Paso C



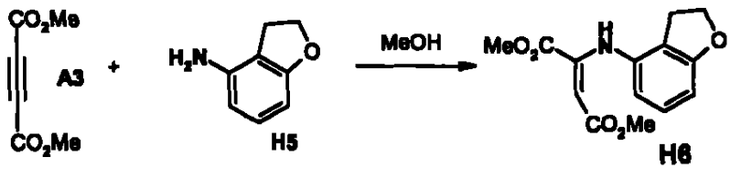
Se agregó una solución de BBr_3 (26 ml, 1,0 M, 26,0 mmol) gota a gota al metil-éter H3 en CH_2Cl_2 a 0°C. La solución se calentó lentamente a 23°C y se agitó durante 14 h a T.A.. La reacción se desactivó con solución de NaOH 1M y se extrajo con EtOAc y CH_2Cl_2 para obtener una mezcla del producto deseado H4 y un poco de diol no ciclado. Homogeneidad mediante HPLC (TFA) a 220 nm: 99%.

Paso D



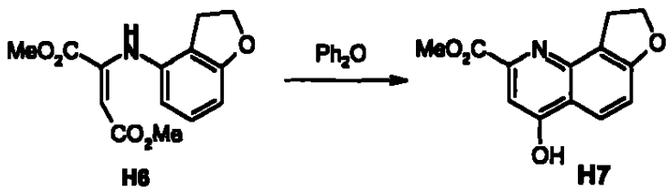
Se agregó HCl (4,0 ml, 6,0M) a una solución de amida **H4** (0,27 g, 1,22 mmol) en MeOH (4,0 ml) a 23°C. La reacción se calentó entonces a reflujo durante 48 h, se agregó $NaHCO_3$ (saturado, ac.) y se extrajo con EtOAc. Las capas orgánicas combinadas se secaron, se filtraron y se concentraron para obtener la anilina deseada **H5** que fue de pureza suficiente para emplearla en otras transformaciones.

Paso E



Se agregó dicarboxilato de dimetil acetileno **A3** (0,16 ml, 1,33 mmol) a una solución de la anilina **H5** (0,18 g, 1,33 mmol) en MeOH (3,0 ml) a T.A. La solución se calentó a reflujo durante 3 h., se enfrió a T.A. y se agregó una solución de NaCl saturado. La mezcla se extrajo con EtOAc (3x) y luego las capas orgánicas combinadas se secaron, se filtraron y se concentraron seguido por purificación mediante cromatografía flash en columna (hex:EtOAc 9:1 a 1:1) para dar la olefina deseada **H6** (0,29 g, 78%).

Paso F



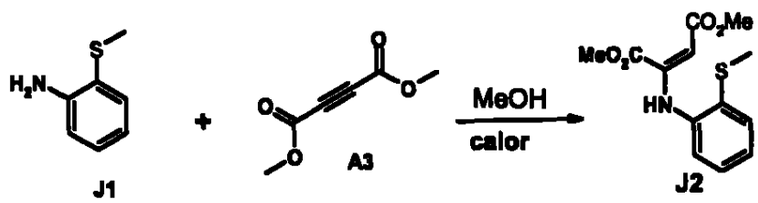
Un matraz que contenía la olefina de partida **H6** (0,29 g, 1,04 mmol) en difeniléter (2,0 ml) se introdujo en un baño de arena pre-calentado (350°C). Cuando la temperatura interna de la reacción alcanzó 225°C, el matraz se calentó durante 6-7 minutos, tiempo durante el cual la temperatura interna se elevó a 240°C. La mezcla de reacción se retiró entonces del baño de arena y se permitió que se enfríe lentamente hasta T.A. Al dejar en reposo se formó un precipitado. Se agregó dietiléter y la solución se filtró y se enjuagó con dietiléter adicional para dar un sólido marrón claro **H7** (0,20 g, 77%). MS 246,0 $(MH)^+$.

262
265

Ejemplo 3J

Síntesis de 2-carbometoxi-4-hidroxi-8-metiltioquinolina (J3):

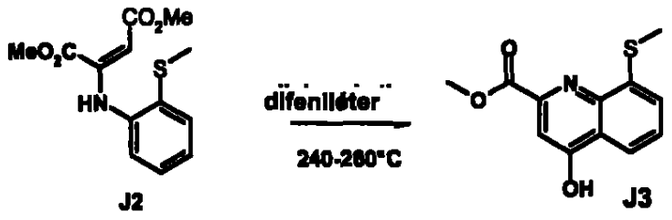
Paso A



Se agregó dicarboxilato de dimetil acetileno **A3** (5,21 ml, 35,91 mmol) gota a gota a una solución de 2-metilmercaptoanilina **J1** (5,0 g, 35,91 mmol) en MeOH (100 ml). Advertencia: la reacción es exotérmica. La mezcla se calentó a un reflujo leve durante 2 horas, se enfrió y se concentró al vacío. El material bruto se purificó mediante cromatografía flash en columna con hexano:EtOAc (90:10) para dar, después de la evaporación de las fracciones puras, el aducto de diéster **J2** (10,53 g; 37,43 mmol; 99% de rendimiento).

Homogeneidad mediante HPLC (TFA) a 220 nm : 85%.

Paso B

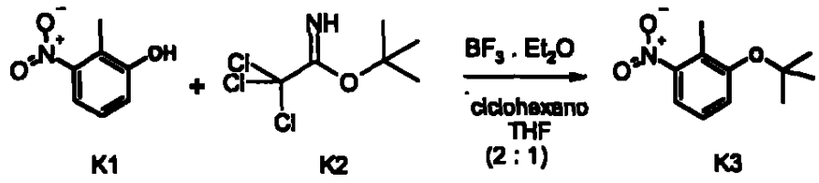


Se disolvió el diéster **J2** (10,53 g, 37,43 mmol) en difeniléter (35 ml) y la mezcla de reacción se colocó en un baño de arena pre-calentado a una temperatura de baño de 350-400°C. Una vez que la mezcla de reacción alcanzó una temperatura interna de 245°C, se comenzó un conteo de seis minutos antes de retirar el baño y se dejó que la reacción se enfríe hasta temperatura ambiente. Se formó un precipitado, que se suspendió en éter, se filtró y se lavó nuevamente con éter para dar el producto de quinolina C8-SMe **J3** (6,15 g; 66%). MS $(M+H)^+$; 250 Homogeneidad mediante HPLC (TFA) a 220 nm: 99%.

Ejemplo 3K

Síntesis de 7-*ter*-butiloxi-2-carbometoxi-4-hidroxi-8-metilquinolina (K6)

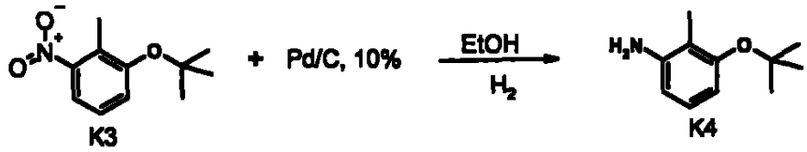
Paso 1:



K1 K2 K3

A una solución de 2-metil-3-nitrofenol **K1** (1,1 g ; 7,18 mmol) en THF (13 ml) se agregó ciclohexano (27 ml; se mantuvo una solución). Se agregó tricloroacetimidato de *ter*-butilo **K2** (5,36 ml ; 28,73 mmol) seguido de una cantidad catalítica de trifloruro de boro eterato (143,8 µl; 1,14 mmol) y la reacción se agitó a temperatura ambiente durante 15 h. La reacción fue incompleta (mediante HPLC analítica) y se agregó una cantidad adicional de tricloroacetimidato de *ter*-butilo (1,4 ml ; 7,51 mmol) (la reacción permaneció en solución). La reacción se completó después de agitar a temperatura ambiente durante 5 h. Se agregó bicarbonato de sodio sólido y la mezcla se filtró, se enjuagó con diclorometano y se evaporó hasta sequedad para dar un sólido blanco. El sólido se trituró con diclorometano, el sólido blanco se filtró y se desechó (= tricloroacetimida). El filtrado se concentró y se cargó en una columna flash para purificación (hexano:EtOAc 9:1) para dar el 2-metil-3-*ter*-butoxinitrobenceno puro **K3** (1,17 g; 78%). Homogeneidad mediante HPLC (TFA) a 220nm: 96%

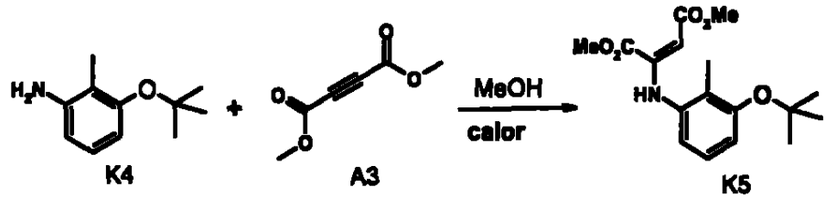
Paso 2:



K3 K4

A una solución de 2-metil-3-*ter*-butoxinitrobenceno **K3** (1,31 g; 6,26 mmol) en etanol absoluto (30 ml) se agregó catalizador de Pd/C 10% (130 mg) . La solución se hidrogenó bajo un balón relleno con hidrógeno a presión atmosférica y a temperatura ambiente durante 63 h. La mezcla de reacción se filtró a través de un lecho de Celite, se enjuagó con EtOH absoluto y se evaporó hasta sequedad para dar 2-metil-3-*ter*-butoxianilina **K4** (1,1 g; 6,14 mmol; 98% de rendimiento). M.S. 180 (M+H)+ . Homogeneidad mediante HPLC (TFA) a 220nm: 96%

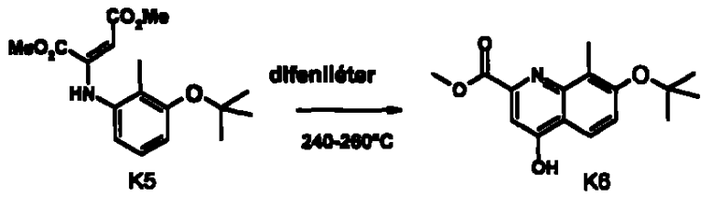
Paso 3:



K4 A3 K5

Se agregó dicarboxilato de dimetil acetileno **A3** (749 µl, 5,97 mmol) gota a gota a una solución de 2-metil-3-*ter*-butoxianilina **K4** (1,07, 5,97 mmol) en MeOH (14 ml). La mezcla se calentó a un reflujo suave durante 2 horas, se enfrió y se concentró en vacío. El material bruto se purificó mediante cromatografía flash en columna con hexano:EtOAc (95:5) para dar, después de la evaporación de las fracciones puras, el aducto de diéster (1,13 g; 3,52 mmol; 59% de rendimiento). M.S. 320,0 $(M-H)^-$ 322,1 $(M+H)^+$. Homogeneidad mediante HPLC (TFA) a 220 nm : 92%.

Paso 4:



K5 K6

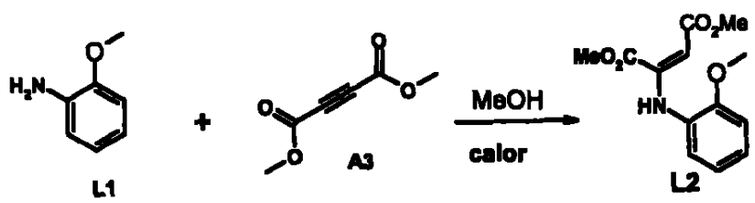
Se disolvió el diéster **K5** (1,13 g, 3,52 mmol) en difeniléter (3,0 ml) y la mezcla de reacción se colocó en un baño de arena pre-calentado a una temperatura de baño de 400-440°C. Una vez que la mezcla de réacción alcanzó una temperatura interna de 230°C (observar la evolución de MeOH a 220°C) se comenzó un conteo de seis minutos antes de retirar el baño (punto final de temperatura: 242°C) y se dejó que la reacción se enfríe hasta temperatura ambiente. No se formó sólido al enfriarse, por lo tanto, la mezcla bruta se purificó flash con hexano:EtOAc (8:2 para eliminar el difenil éter, luego, 4:6 para completar la elución del producto) para dar la quinolina C7-O-*ter*-Bu,C8-Me **K6** como un sólido de color beige (838 mg; 82%). MS 288,0 $(M-H)^-$ 290,0 $(M+H)^+$ .Homogeneidad mediante HPLC (TFA) a 220 nm : 99%.

Este resto de quinolina se empleó para la síntesis de los compuestos 1032 y 1033 de la tabla 1. Para la síntesis del compuestos 1034, 1035, 1057 y 1058, también de la tabla 1, se empleó la quinolina **K6**. La conversión del grupo C7-*ter*-butil-éter a un grupo hidroxilo se llevó a cabo mediante el tratamiento del compuesto final con TFA 50% en diclorometano durante 30 min. a 0°C , luego durante 30 min. a T.A., se evaporó hasta sequedad, se diluyó con agua y liofilizó.

Ejemplo 3L

Síntesis de 2-carbometoxi-4-hidroxi-8-metoxiquinolina (L3):

Paso A



Se agregó dicarboxilato de dimetil acetileno **A3** (5,5 ml, 44,74 mmol) gota a gota a una solución de *o*-anisidina **L1** (5,0 ml, 44,33 mmol) en MeOH (100 ml). Advertencia: la reacción es exotérmica. La mezcla se calentó a un reflujo suave durante 5 horas, se enfrió y se concentró al vacío. El material bruto se purificó mediante cromatografía flash en columna con hexano:EtOAc (95:5 a 90:10) para dar, después de la evaporación de las fracciones puras, el aducto de diéster **L2** (10 g; 37,70 mmol; 85% de rendimiento). Homogeneidad mediante HPLC (TFA) a 220 nm: 82%.

Paso B

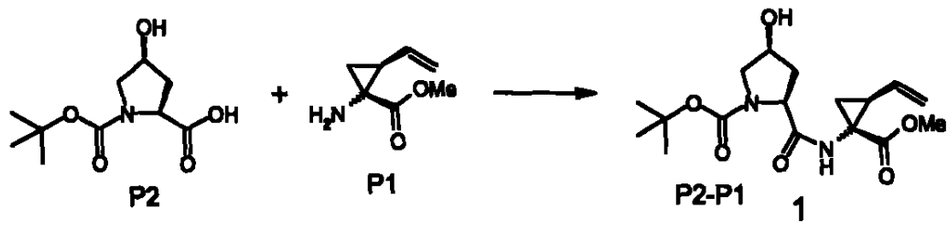


Se disolvió el diéster **L2** (10 g, 37,70 mmol) en difeniléter (15 ml) y la mezcla de reacción se colocó en un baño de arena pre-calentado a una temperatura de baño de 350-400°C. Una vez que la mezcla de reacción alcanzó una temperatura interna de 240°C, se comenzó un conteo de seis minutos antes de retirar el baño y se dejó que la reacción se enfríe hasta temperatura ambiente. No se formó un sólido al enfriarse, por lo tanto, la mezcla bruta se purificó mediante columna flash con hexano:EtOAc (6:4 a 5:5 para eliminar impurezas, luego 2:8 para completar la elución) para dar el producto quinolina C8-OMe **L3** (4,56 g; 52%). MS $(M-H)^-$; 231,9 Homogeneidad mediante HPLC (TFA) a 220 nm: 99%.

Ejemplo 4

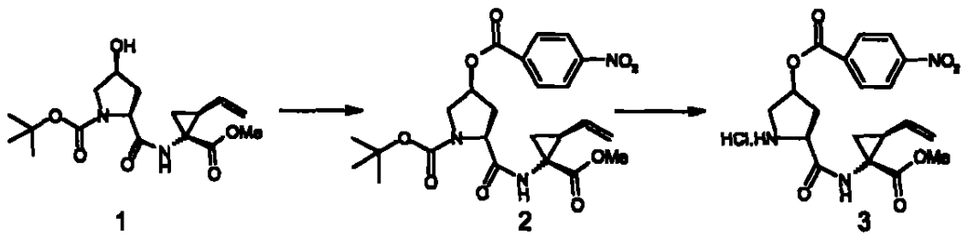
Preparación de Dipéptidos

Síntesis del dipéptido 1



Se agitó una mezcla de Boc-hidroxiprolina **P2** (50,0 g, 216 mmol), vinil-ACCA metil éster **P1** (42,25 g, 238 mmol, 1,1 equiv.), TBTU (76,36 g, 238 mmol, 1,1 equiv.) y DIPEA (113 ml, 649 mmol, 3 equiv.) en DMF (800 ml) a T.A. bajo una atmósfera de nitrógeno. Después de 3,5 h, el solvente se evaporó y el residuo se extrajo con EtOAc. El extracto se lavó con ácido clorhídrico (10%), bicarbonato de sodio saturado y salmuera. La fase orgánica se secó luego sobre sulfato de magnesio, se filtró y se evaporó para dar un aceite. Después de secarse hasta el día siguiente en alto vacío, se obtuvo el dipéptido **1** como una espuma amarilla (72,0 g, 94%, pureza >95% mediante HPLC).

Preparación del dipéptido 3



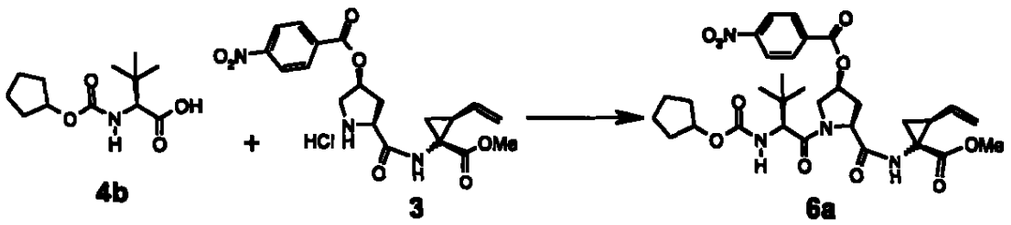
1 2 3

Se disolvieron dipéptido **1** (72,0 g, 203 mmol), trifenilfosfina (63,94 g, 243,8 mmol, 1,2 equiv.) y ácido 4-nitrobenzoico (41,08 g, 245,8 mmol, 1,2 equiv) en THF seco (1,4 l). La solución agitada se enfrió a 0°C bajo una atmósfera de nitrógeno. Luego se agregó dietil azodicarboxilato (38,4 ml, 244 mmol, 1,2 equiv.) gota a gota durante 45 min y se permitió que la reacción se caliente a T.A. Después de 4 h, el solvente se evaporó. El residuo se dividió en cuatro partes. Cada una de estas se purificó mediante cromatografía sobre gel de sílice fino (malla de 10-40 µm, diámetro de columna de 12 cm, extensión de columna de 16 cm) empleando un gradiente de hexano/EtOAc 2:1 a hexano/EtOAc 1:1 hasta EtOAc puro. De esta manera, el éster Boc-dipéptido **2** se obtuvo como un sólido blanco amorfo después de la evaporación de los solventes y secando los residuos con alto vacío a 70°C durante 1 h (108,1 g, cuantitativo). Se agregó una solución de cloruro de hidrógeno 4N en dioxano al éster Boc-dipéptido **2** (108 g, 243 mmol) dando una solución incolora. La solución se agitó a T.A. durante 1 h. El solvente se evaporó y el residuo se colocó en alto vacío durante 3 h dando la sal hidrocloruro del compuesto **3** como un sólido amorfo. El sólido se empleó como tal.

Ejemplo 5

Preparación de Tripéptidos

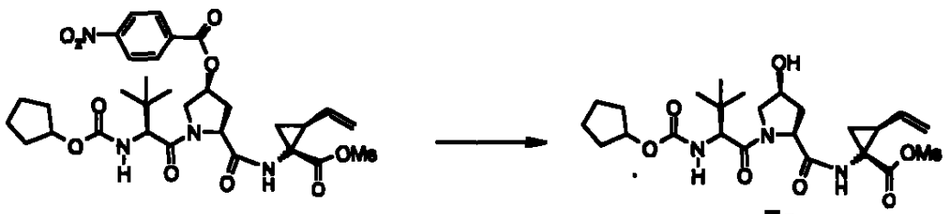
Síntesis del tripéptido 6a



4b 3 6a

Se suspendieron carbamato **4b** (6,15 g, 22,5 mmol) y TBTU (7,72 g, 24,7 mmol) en DMC y la suspensión se agitó rápidamente. Se agregó DIPEA (3,92 ml, 22,5 mmol) a T.A. y después de 10 min, la reacción fue casi homogénea. Luego, se vertió en la reacción una solución de dipéptido **3** (10,39 g, 23,6 mmol) en DCM anhidrido (100 ml) que contiene DIPEA (4,11 ml, 23,62 mmol). Se permitió que la solución amarilla resultante se agite durante 14 h. El solvente se evaporó entonces dando un jarabe amarilla que se extrajo con EtOAc (300 + 150 ml) y se lavó con HCl 0,05N (2x 200 ml), Na_2CO_3 saturado (300 ml) y salmuera (150 ml). Los extractos combinados se secaron sobre $MgSO_4$ y se evaporó para dar el tripéptido **6a** como una espuma de color amarillo pálido(15,68 g, cuantitativo).

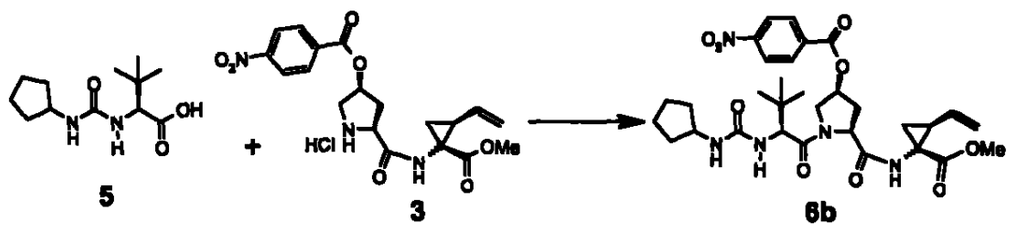
Síntesis del tripéptido 7a:



6a 7a

Se disolvió el tripéptido **6a** (15,68 g) en THF (200 ml) y se agregó agua (30 ml). La solución resultante se enfrió a 0°C y se agregó una solución de monohidrato de hidróxido de litio (1,18 g, 28,12 mmol) durante 3 min agitando intensamente. Después de 3 h a 0°C, la base en exceso se neutralizó con HCl 1N (pH final *ca.* 6) y el THF se evaporó, dando una suspensión acuosa (goma amarilla). La mezcla se extrajo con EtOAc (2x 200 ml) y se lavó con $NaHCO_3$ saturado (2x 300 ml). Los extractos combinados se secaron sobre $MgSO_4$ y se evaporó para dar una espuma amarilla pálida. La cromatografía flash de la espuma sobre gel de sílice empleando EtOAc como eluyente dio **7a** como un sólido blanco amorfo (9,77 g, 91%).

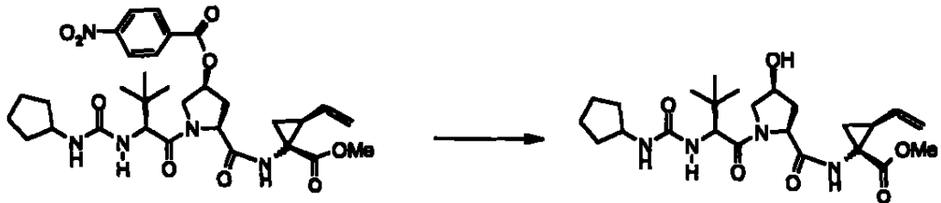
Síntesis del tripéptido 6b



5 3 6b

Se disolvieron/suspendieron la ciclopentilurea-Tbg **5** (2,21 g, 9,10 mmol) y TBTU (3,12 g, 10,0 mmol) en diclorometano anhídrido (40 ml) y se agregó DIPEA (1 equiv.). La reacción se agitó a temperatura ambiente bajo una atmósfera de nitrógeno hasta que la solución se tomó casi homogénea (ca. 10 min). Luego se agregó una solución de dipéptido P1-P2 (4,20 g, 9,56 mmol) en diclorometano anhidro (35 ml que contienen DIPEA 1 equiv.) a la reacción y se dejó en agitación la solución amarilla resultante durante 14 h después de que la reacción se basificó mediante la adición de DIPEA (ca. 1,5 ml). El solvente se evaporó dando una jalea amarilla que se extrajo con acetato de etilo (150 + 50 ml) y se lavó con HCl 0,1N (150 ml), agua (100 ml, la emulsión se interrumpió con salmuera), Na_2CO_3 saturado (150 ml) y salmuera (100 ml). Luego, los extractos combinados se secaron sobre $MgSO_4$ y se evaporaron a un sólido amarillo pálido **6b** (6,21 g, 95% de pureza por HPLC).

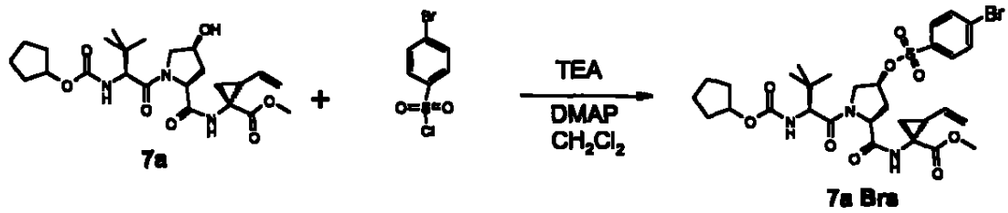
Síntesis del tripéptido 7b



6b **7b**

El éster pNBz bruto **6b** preparado anteriormente se disolvió en THF (90 ml) y se agregó metanol (40 ml). Luego se agregó solución 1,0N de hidróxido de sodio (12,0 ml; 12,0 mmol) agitando intensamente durante 10 min (embudo de goteo) y se permitió que continúe la hidrólisis a temperatura ambiente. Después de 2 h, la base en exceso se neutralizó mediante la adición cuidadosa de HCl 1 N (aprox. 1,5 ml, agregado gota a gota hasta que desapareció el color amarillo; pH final aprox. 6). Los solventes orgánicos se evaporaron y el residuo acuoso se extrajo con acetato de etilo (150 + 50 ml) y se lavó con bicarbonato de sodio saturado (3x 150 ml) y salmuera (100 ml). Los extractos combinados se secaron sobre $MgSO_4$ y se evaporaron hasta un sólido amorfo amarillo pálido que se secó en alto vacío **7b** (4,11 g, 87% de P3-urea, 93% de pureza por HPLC).

Síntesis del derivado Brosilato 7aBrs



7a 7a Brs

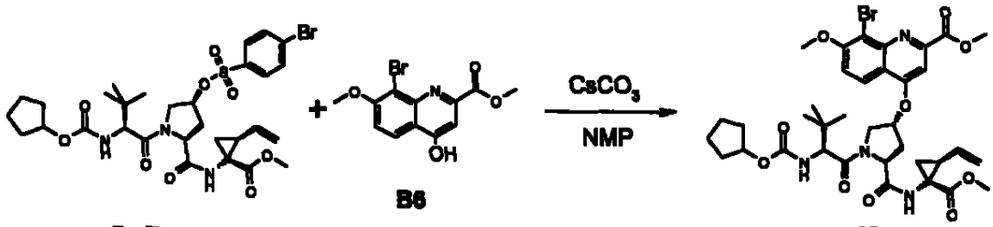
A una solución fría (0°C) del tripéptido (10 g; 20,85 mmol), se agregó cloruro de brosilo gota a gota (11,19 g; 43,79 mmol) y dimetilaminopiridina (254 mg; 2,09 mmol) disuelta en diclorometano (75 ml), trietilamina (10,2 ml; 72,98 mmol). La solución amarilla se agitó 1 hora a 0°C, luego se dejó que se caliente lentamente hasta temperatura ambiente y se agitó 60 horas a temperatura ambiente. La mezcla de reacción se concentró hasta sequedad, se diluyó con EtOAc, se lavó con solución de bicarbonato de sodio saturado, agua y salmuera, se secó ($MgSO_4$), se filtró y se evaporó hasta sequedad para obtener el producto bruto. El material bruto se purificó mediante cromatografía flash en columna con hexano:EtOAc; 60:40 a 50:50 para dar el producto puro **7aBrs** como una espuma blanca (11,66 g; 80%).

M.S. 698 $(M+H)^+$; 700,2 $(MH+2)^+$. Homogeneidad mediante HPLC (TFA) a 220 nm: 99%.

Ejemplo 6

Introducción de restos quinolina en los tripéptidos:

Síntesis del Intermediario 10a mediante el desplazamiento de brosilato:

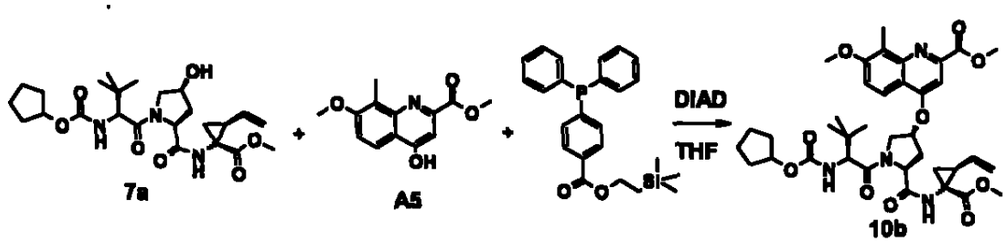


7a Brs B6 10a

Se disolvieron el brosilato **7aBrs** (0,5 g; 0,71 mmol), bromoquinolina **B6** (234 mg; 0,75 mmol) y carbonato de cesio molido (56 mg; 0,78 mmol) en 1-metil-2-pirrolidinona (7,6 ml) y la solución se calentó a 70°C y se agitó durante 7 h. La solución posteriormente se enfrió hasta la temperatura ambiente y se procesó. La mezcla de reacción se vertió en EtOAc, se lavó con H_2O (1X), $NaHCO_3$ (saturado; 2X), salmuera (5X), se secó, se filtró y se concentró para dar el producto bruto (0,565 g) como un sólido blancuzco. La purificación mediante cromatografía flash (gel de sílice 1:30; EtOAc/hexano 7:3) dio el producto puro **10a** (77%; 0,429 g) como un sólido blanco.

MS 775,2 $(M+2H)^+$. Homogeneidad mediante HPLC (TFA) a 220 nm: 96%.

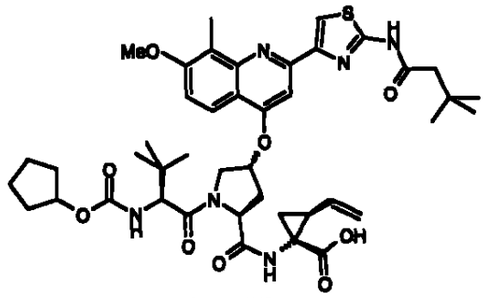
Síntesis del Intermediario 10b *mediante* reacción de Mitsunobu:



Al tripéptido **7a** (1,55 g; 3,23 mmol) disuelto en THF (30 ml), se agregó la hidroxiquinolina **A5** (1,08 g; 4,37 mmol) seguido de silil éster de trifenilfosfina 0,5 M en THF (13 ml; 6,46 mmol). A la suspensión amarilla, se agregó gota a gota el reactivo DIAD (1,27 ml; 6,46 mmol) y se agitó a temperatura ambiente durante 2 horas, se procesó mediante la adición gota a gota de solución de TBAF1M/THF (11,3 ml; 11,31 mmol) y se agitó a temperatura ambiente hasta el día siguiente. Mediante HPLC analítica, es evidente que se completó la escisión del subproducto derivado óxido de fosfina formado (a un resto soluble en agua). La reacción se diluyó con EtOAc, se lavó con solución saturada de bicarbonato de sodio (2x), agua (2x), NaOH 1N frío (2x; elimina el exceso de quinolina), agua (2x) y salmuera (1x), se secó ($MgSO_4$), se filtró y se evaporó para obtener un sólido beige . El material bruto se purificó mediante cromatografía flash con hexano:EtOAc (8:2) para obtener el producto **10b** como un sólido marfil (1,92 g; 84%).
M.S. 707,4 $(M-H)^-$ 709,4 $(M+H)^+$. Homogeneidad mediante HPLC (TFA) a 220 nm : 94%.

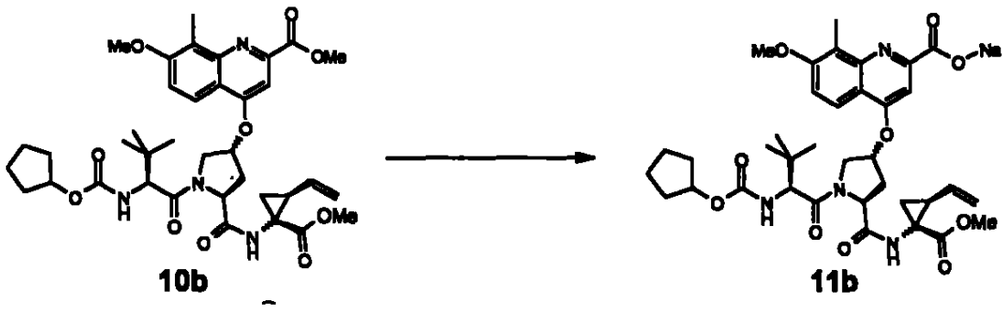
Ejemplo 7

Síntesis del compuesto 1007:



Compuesto 1007

<u>Paso 1 : Monohidrólisis selectiva del éster 10b:</u>

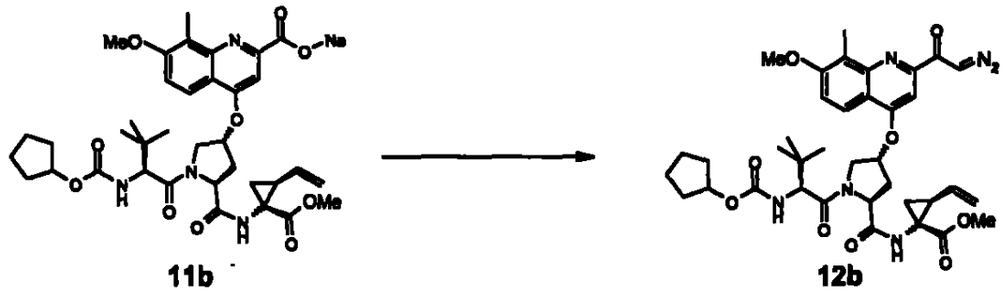


10b 11b

Se enfrió tripéptido **10b** (149 mg, 0,210 mmol), en 5 ml de una mezcla 1:1 de THF-MeOH, a 0°C para la adición de una solución de NaOH 1N acuoso (0,24 ml, 0,240 mmol). La solución resultante se agitó 15 min a 0°C, 1,5 h a T.A. y se descubrió que la reacción era incompleta mediante HPLC analítica. Se agregó NaOH 1N adicional (0,05 ml, 0,05 mmol) y la reacción se agitó durante una hora adicional. La mezcla se desactivó con HCl 1 M, se evaporó hasta casi sequedad, se diluyó con agua, se congeló y se liofilizó para dar el ácido **11b** (material bruto empleado para el siguiente paso; suponer 0,210 mmol).

Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 89%.

Paso 2 : Síntesis de la diazocetona 12b:

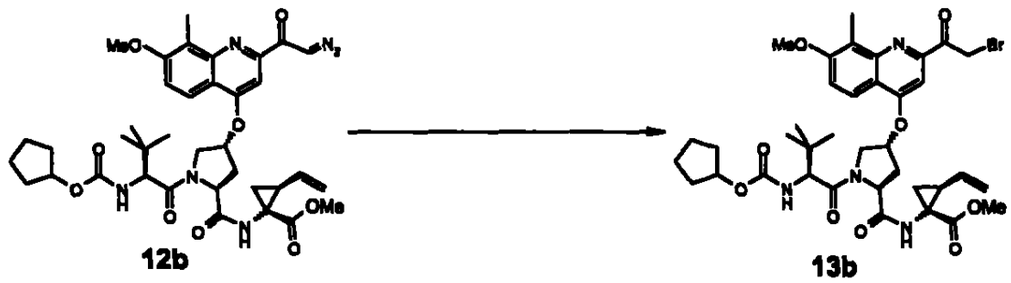


11b 12b

Se disolvió la sal sódica **11b** (asumir 0,210 mmol) en THF (5 ml), se agregó trietilamina (75 µl; 0,538 mmol) y la solución se enfrió a 0°C. Se agregó gota a gota isobutilcloroformiato (45 µl; 0,346 mmol) y la suspensión blanca se agitó a 0°C durante 1 hora, seguida por la adición de una solución de diazometano (1M en dietil éter; 1 ml; 0,999 mmol). La mezcla de reacción se agitó 15 min a 0°C, 1 hora a T.A. y se evaporó para dar una suspensión espesa. Esta suspensión se disolvió en EtOAc, se lavó con saturado $NaHCO_3$ (2x), salmuera (1x), se secó ($MgSO_4$), se filtró y se evaporó para dar el producto bruto diazocetona **12b** (145 mg, 95%).

M.S. (electroaspersión) : 717,4 $(M-H)^-$ 719,4 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 85%.

Paso 3: Síntesis de la bromocetona 13b:

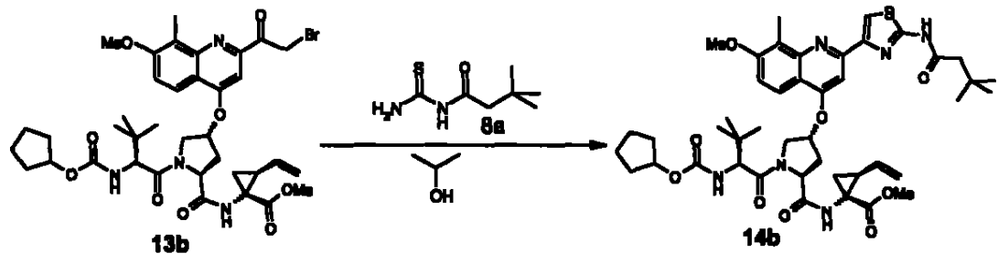


12b 13b

A 0°C, a una solución de diazocetona **12b** (145 mg, 0,201 mmol) en THF (4 ml) se agregó gota a gota una solución de HBr (48% ac., 0,1 ml) y la mezcla se agitó durante 1,25 h. La mezcla se desactivó con una solución de $NaHCO_3$ saturado, luego el THF se evaporó. El residuo se diluyó con EtOAc, se lavó con una solución de $NaHCO_3$ saturado (2x), salmuera (1x), se secó ($MgSO_4$), se filtró y se evaporó para dar la bromocetona bruta **13b** (139 mg, 89%).

M.S. (electroaspersión) : 773,3 $(MH+2)^+$ 771,3 $(M+H)^+$ 769 $(M-H)^-$.

Paso 4: Síntesis del tiazolil tripéptido 14b:



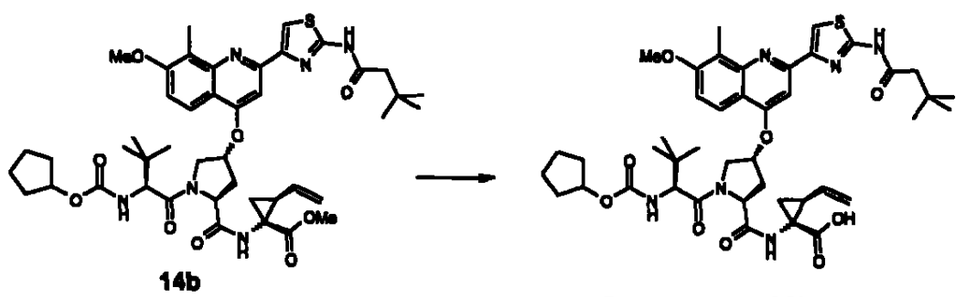
13b 8a 14b

Se disolvieron α-bromocetona **13b** (49 mg, 0,0635 mmol) y *N*-neopentiltiourea **8a** (12 mg; 0,0688 mmol) en isopropanol (3 ml) y la solución amarilla se calentó a 75°C durante 1 hora. Se dejó que la solución se enfríe a T.A. y se evaporó hasta sequedad. Este material bruto **14b** se empleó para el paso siguiente (asumir 0,0635 mmol).

M.S. (electroaspersión) : 845,5 $(M-H)^-$ 847,5 $(M+H)^+$.

Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; CH_3CN : H_2O) : 69% (contiene 16% de tiourea de partida).

Paso 5: Hidrólisis del éster 14b:



14b

Compuesto 1007

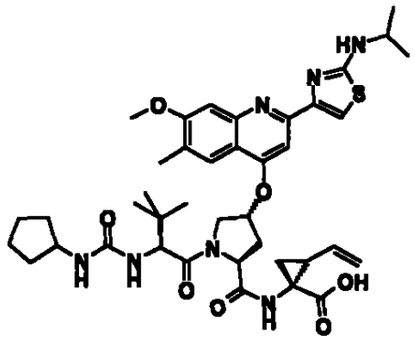
A una solución del metil éster **14b** (53 mg, 0,0626 mmol), en una mezcla de 3,5 ml de THF:H_2O (2,5:1), se agregó LiOH-monohidrato sólido (27 mg, 0,643 mmol). Se requirió 0,5 ml de MeOH para obtener una solución homogénea. La reacción resultante se agitó a temperatura ambiente hasta el día siguiente. La solución orgánica se desactivó con ácido acético y se concentró para dar una suspensión blancuzca. El material bruto se purificó mediante HPLC preparativa (YMC Combiscreen ODS-AQ, 50 x 20 mm DI S-5 micrones,120 A; 220 nm) empleando un gradiente lineal y 0,06% de TFA en CH_3CN/H_2O. Las fracciones puras se combinaron, se concentraron y se liofilizaron para dar el producto **1007** como sal del TFA (21 mg; 40% de rendimiento).

^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, <u>descripción del rotámero principal</u>; δ 12,31 (br s, 1H), 8,56 (s, 1H), 8,20-8,08 (m, 1H), 8,05 (d, J = 9,2 Hz, 1H), 7,46 (br s, 1H), 7,30 (d, J = 9,0 Hz, 1H), 6,99 (d, J = 8,6 Hz, 1H), 5,79-5,66 (m, 1H), 5,50-5,40 (m, 1H), 5,23-5,14 (m, 1H), 5,10-5,02 (m, 1H), 4,70-4,61 (m, 1H), 4,48-4,33 (m, 2H), 4,16-4,08 (m, 1H), 4,04-3,93 (m, 1H), 3,95 (s, 3H), 2,60 (s, 3H), 2,58-2,49 (m, 1H), 2,40 (br s, 2H), 2,32-2,21 (m, 1H), 2,08-1,98 (m, 1H), 1,80-1,22 (m, 10H), 1,04 (m, 9H), 0,97 (s, 9H).

M.S. (electroaspersión) : 831,5 $(M-H)^-$ 833,5 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 99%.

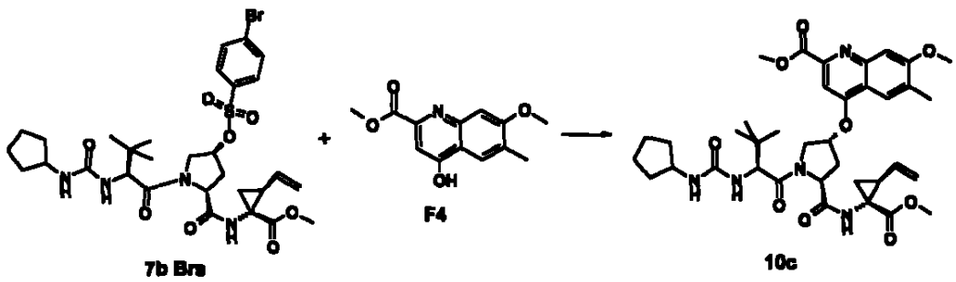
Ejemplo 8

Síntesis del compuesto 5005



Compuesto 5005

<u>Paso 1:</u>



7b Brs 10c

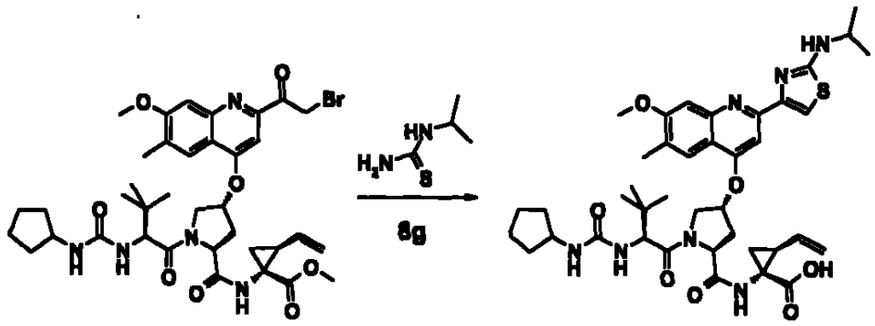
A una solución del brosilato **7b Brs** (1,89 g, 2,71 mmol) y la quinolina **F4** (670 mg, 2,71 mmol) en 1-metil-2-pirrolidinona (26 ml) se agregó carbonato de cesio (971 mg, 2,98 mmol) a temperatura ambiente. La mezcla de reacción se calentó a 70°C durante 12 horas, se enfrió hasta temperatura ambiente y se diluyó con EtOAc (100 ml), se lavó con agua (2x 50 ml), solución de $NaHCO_3$ saturado que contiene NaOH 1M (1/5 del volumen) (50 ml) y salmuera (50 ml). La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró para dar el producto bruto como un aceite amarillo, que se purificó mediante cromatografía flash sobre una columna de gel de sílice (malla 250-400), eluyendo con EtOAc/hexanos (13:7), para dar 1,27 g de un sólido pálido (contaminado con 20% de quinolina de partida). El sólido se disolvió en THF (15 ml) y la suspensión se trató con CH_2N_2 (5 ml) a T.A. durante 12 horas, luego se concentró. El residuo se purificó mediante cromatografía flash sobre una columna de gel de sílice (malla de 250-400) eluyendo con EtOAc/$CHCl_3$ (12:6) para dar 0,9 g de **10c** puro como una espuma de color amarillo pálido (48%).

Paso 2:

La conversión del grupo 2-carbometoxi de **10c** en el grupo 2-(1-oxo-2-bromo)etilo de **13c** se llevó a cabo empleando la secuencia de reacciones descripta en el ejemplo 7, pasos 1, 2 y 3.

Paso 3:

Reacción con derivado de tiourea e hidrólisis final:



13c Compuesto 5005

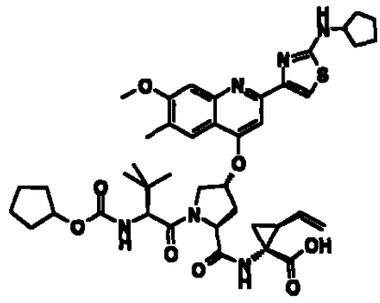
278

A la solución de 13c (50 mg, 0,065 mmol) en isopropanol (3 ml) se agregó isopropiltiourea 8g (10 mg, 0,085 mmol). La mezcla de reacción se agitó a 70°C durante 45 minutos. La HPLC reveló el consumo total del material de partida. Se enfrió hasta temperatura ambiente y se diluyó con THF (2 ml) y solución 1,0N de hidróxido de sodio (0,325 ml). Se agitó a temperatura ambiente durante 12 horas, la mezcla de reacción se concentró hasta sequedad. El residuo se disolvió en DMSO (2 ml) y la solución se inyectó sobre una columna de HPLC Combi-Prep. Las fracciones puras se combinaron y se liofilizaron para dar 26,1 mg del Compuesto 5005 como un sólido amarillo amorfo (sal trifluoroacetato) (50% de rendimiento).

^{1}H-RMN (400 MHz, DMSO-d_6): δ 8,60 y 8,82 (dos s, 1H), 8,01-8,11 (m, 1H), 7,98 (s, 1H), 7,86 (s, 1H), 7,72 y 7,75 (dos s, 1H), 5,90-6,03 (m, 1H), 5,80-5,90 (d, J= 16 Hz, 1H), 5,62-5,79 (m, 2H), 5,15-5,26 (m, 1H), 4,96-5,13 (m, 1H), 4,44-4,61 (m, 2H), 4,16-4,23 (m, 2H), 4,08-4,13 (m, 2H), 3,98-4,01 (dos s, 6H), 3,27 -3,38 (m, 1H), 2,53-2,70 (m, 1H), 2,32 y 2,36 (dos s, 3H), 1,96-2,09 (q, J = 9 Hz, 17 Hz, 1H), 1,31-1,67 (m, 7H), 1,23-1,30 (m, 7H), 1,02-1,13 (m, 1H), 0,87 y 0,94 (dos s, 9H).

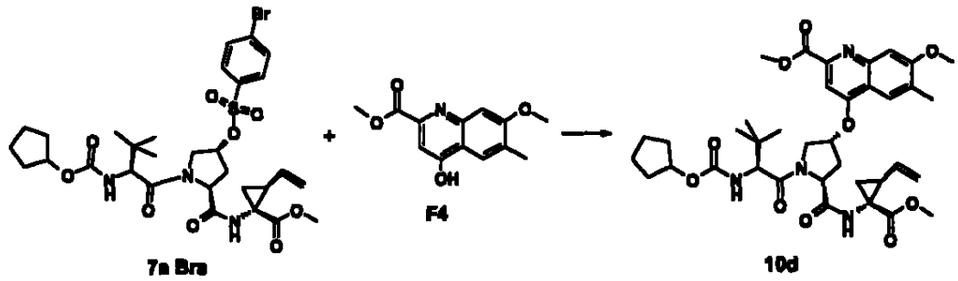
Ejemplo 9

Síntesis del compuesto 4004



Compuesto 4004

Paso 1:



7a Brs 10d

A una solución del brosilato 7a Brs (0,14 g, 0,20 mmol) y F4 (0,06 g, 0,24 mmol) en 1-metil-2-pirrolidinona (4 ml) se agregó carbonato de cesio (0,08 g, 0,26 mmol). La mezcla se calentó a 70°C y se agitó durante 7 hr. La mezcla de reacción se enfrió, se

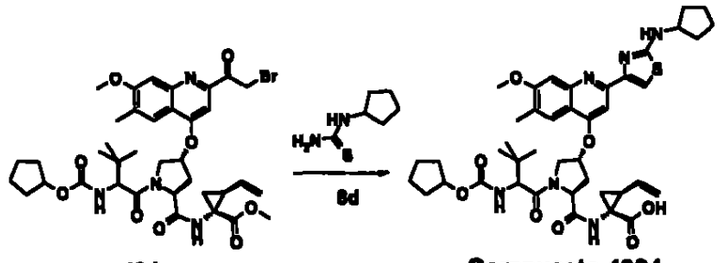
vertió en EtOAc (30 ml), se lavó con H_2O (2X 50 ml), $NaHCO_3$ sat. (2X 50 ml) y salmuera (3X 50 ml). La fase orgánica se secó, se filtró y se concentró a un aceite amarillo. Este material se purificó mediante cromatografía flash sobre una columna de gel de sílice (malla de 250-400) eluyendo con EtOAc/hexano (2:8), para dar 56 mg (40% de rendimiento) del producto **10d** como un semi-sólido amarillo pálido.

Paso 2:

La conversión del grupo 2-carbometoxi de **10d** en el grupo 2-(1-oxo-2-bromo)etilo de **13d** se llevó a cabo empleando la secuencia de reacciones descripta en el ejemplo 7, pasos 1, 2 y 3.

Paso 3:

Reacción con derivado de tiourea e hidrólisis final:



13d **Compuesto 4004**

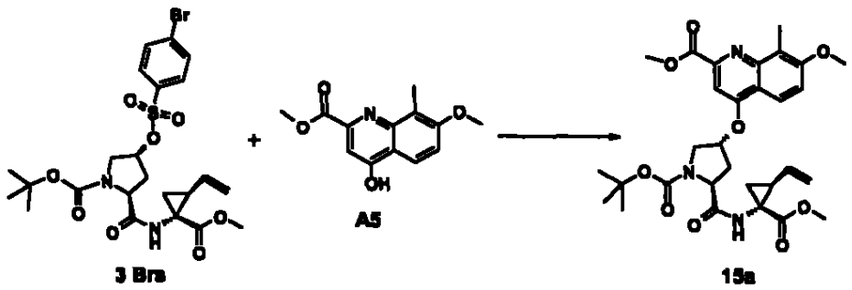
A una solución de la bromocetona **13d** (34 mg, 0,045 mmol) en isopropanol (2 ml) se agregó ciclopentiltiourea **8d** (8,4 mg, 0,06 mmol). La mezcla de reacción se agitó a 70°C durante 45 min, luego se concentró hasta sequedad y el residuo se disolvió en una mezcla de THF (1,5 ml) y metanol (0,3 ml). Se agregó lentamente agua (0,45 ml) a esta solución agitando, seguido por LiOH (10,3 mg, 0,24 mmol). La mezcla de reacción se agitó a T.A. durante 16 h. La HPLC reveló que la reacción se completó. La mezcla de reacción se concentró, el residuo se disolvió en DMSO y la solución se inyectó en una columna de HPLC Combi-prep. Las fracciones puras se combinaron y se liofilizaron para dar 16,5 mg (42% de rendimiento) de compuesto **4004** como un sólido blanco amorfo (sal del ácido trifluoroacético).

^{1}H RMN (400 MHz, DMSO-d_6) (mezcla de rotámeros; 8:2): δ 8,59 y 8,71 (2s,1H), 8,13 (m, 2H), 7,83-7,69 (m, 2H), 7,1 (d, J= 8,2Hz, 0,8H), 6,46 (d, J=8,2 Hz, 0,2H), 5,76-5,67 (m, 2H), 5,21 y 5,17 (2s, 1H). 5,05 (d, J=11Hz, 1H), 4,53-4,49 (m, 2H), 4,25 (br.s, 1H), 4,04-3,99 (m, 5H), 2,66-2,53 (m, 1H), 2,34 (s, 4H), 2,07-1,98 (m, 3H), 1,76-1,25 (m, 16H), 0,95 y 0,87 (2s, 9H).

Ejemplo 10

Preparación de Dipéptidos:

Síntesis del Dipéptido 3:

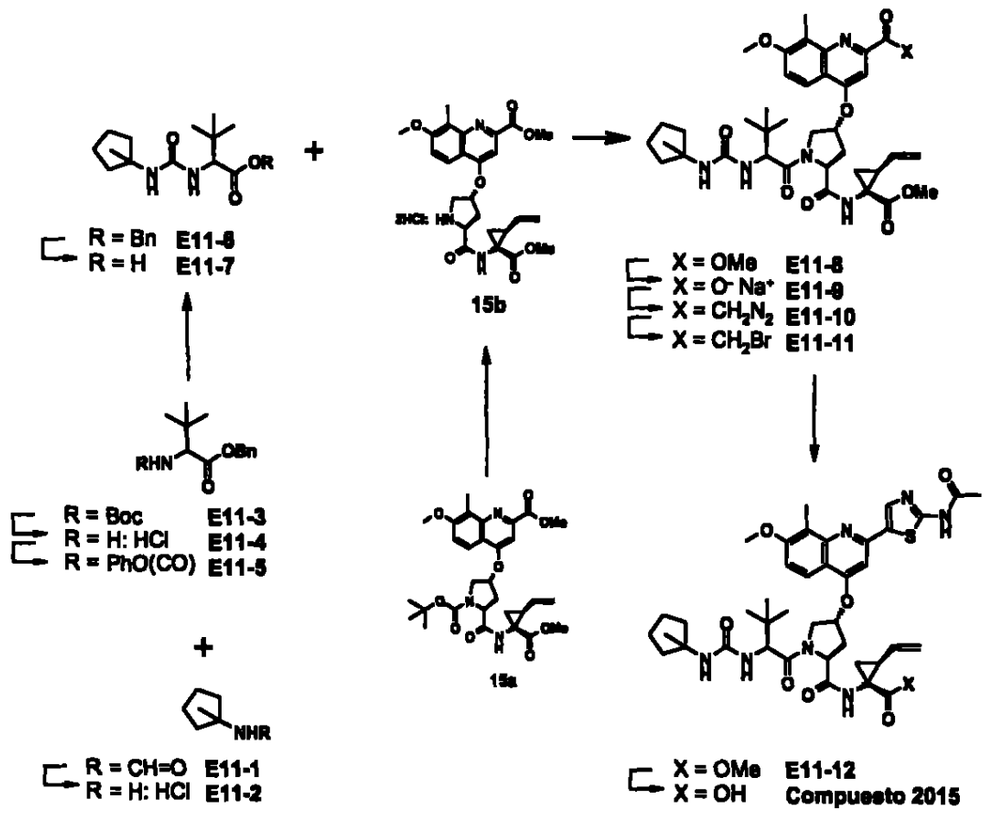


A una solución del brosilato **3 Brs**(4,2 g, 7,32 mmol) y la quinolina **A5** (1,45 g, 5,86 mmol) en 1-metil-2-pirrolidinona (25 ml) se agregó carbonato de cesio (3,1 g, 9,5 mmol). La mezcla se calentó a 70°C durante 12 h. La mezcla de reacción se vertió en EtOAc (150 ml), se lavó con H_2O (2X 150 ml), solución de $NaHCO_3$ saturado (2X 150 ml) y salmuera (2X 150 ml). La fase orgánica se separó, se secó sobre Na_2SO_4, se filtró y se concentró para dar el producto bruto como un aceite amarillo. Este material se purificó mediante cromatografía flash sobre una columna de gel de sílice (malla de 250-400) eluyendo con EtOAc 65% en hexano para dar **15a** (1,8 g, 42%) como un sólido blanco.

Ejemplo 11

Síntesis del compuesto 2015

La síntesis se llevó a cabo de acuerdo con la siguiente secuencia:



E11-1: Se agregó cianuro de potasio (1,43 g, 22,0 mmol) a una solución agitada de metilciclopentanol (2,00 g, 20,0 mmol) en ácido acético glacial (1,00 ml) dando una suspensión espesa. A esta se agregó, gota a gota, ácido sulfúrico (3 ml, advertencia: exotérmica) en un grado que la temperatura se mantuvo a 30-35°C ca.. Se agregó ácido acético adicional (1 ml) para facilitar la agitación de la pasta espesa. La mezcla se calentó entonces a 55-60°C durante 30 min seguido por agitación a temperatura ambiente durante 16 h. Luego se agregó agua helada (35 ml), la mezcla se extrajo con etil éter (2x 40 ml) y las fases orgánicas combinadas se lavaron con $NaHCO_3$ 5% (5x 30 ml), se secaron sobre $MgSO_4$ y el solvente se evaporó para dar un aceite marrón pálido (1,16 g). El pH de los lavados acuosos combinados se elevó a 11 mediante la adición de K_2CO_3 sólido y los sólidos resultantes se filtraron y se lavaron con etiléter (3x 40 ml). El filtrado se extrajo con etil éter (2x 40 ml), los extractos combinados se secaron sobre $MgSO_4$ y el solvente se evaporó para dar producto adicional (0,355 g) que se combinó con el aceite obtenido anteriormente (1,52 g, 60 %).

E11-2: Se agregó ácido clorhídrico 5N (8 ml) a una solución de E11-1 (1,50 g, 11,8 mmol) en dioxano (8,0 ml) dando alguna precipitación. Luego se agregó etanol (4 ml) y la solución se calentó a reflujo durante 4 h. Luego, la reacción se enfrió, los solventes orgánicos se evaporaron y el residuo acuoso se lavó con hexano (40 ml). La capa acuosa se evaporó entonces hasta sequedad (se empleó etanol para destilar azeotrópicamente las últimas trazas de agua) y el sólido resultante se secó con alto vacío para dar el hidrocloruro de metilciclopentilamina como un sólido de color beige (1,38 g, 86%).

E11-3: A una solución agitada, helada de Boc-Tbg-OH (5,00 g, 21,6 mmol) en acetonitrilo (75 ml) se agregó bromuro de bencilo (2,83 ml, 23,8 mmol) bajo una atmósfera de argón. Luego se agregó DBU (3,88 ml, 25,9 mmol) en pequeñas partes durante aproximadamente 5 min. La suspensión resultante se agitó a 0°C durante 30 min adicionales, luego se dejó calentar a temperatura ambiente. Después de 3 h, el solvente se evaporó y el residuo se extrajo con acetato de etilo (50 ml), se lavó con HCl 1N (2x 25 ml), $NaHCO_3$ ac. 5% (3x 25 ml) y salmuera (25 ml) y luego se secó sobre $MgSO_4$ y el solvente se evaporó para dar el bencil éster como un aceite incoloro (6,83 g, 98%).

E11-4: El E11-3 (6,80 g, 21,2 mmol) se disolvió en dioxano (4 ml) y se agregó una solución de HCl 4N en dioxano (30 ml, 120 mmol). Después de agitar a temperatura ambiente durante 2 h, el solvente se evaporó y se dejó en reposo el residuo bajo una corriente de nitrógeno dando una solidificación lenta. Luego, este material se trituró con

hexano (2x 50 ml), se filtró, se secó con aire durante 30 min y luego se colocó en alto vacío durante 5 días para dar la sal hidrocloruro como un sólido blanco (4,86 g, 89%).

E11-5: A una solución helada, agitada de E11-4 (4,85 g, 18,8 mmol) en tetrahidrofurano (75 ml) se agregó diisopropiletilamina (8,20 ml, 47,0 mmol) seguido de la adición gota a gota de cloroformiato de fenilo (2,60 ml, 20,7 mmol) bajo una atmósfera de argón. Se formó un precipitado espeso que, cuando se agitó intensamente, se tornó una suspensión fina. Después de 4,5 h, la mezcla se concentró a un tercio de su volumen original y luego se extrajo con acetato de etilo (50 ml) y se lavó con agua (40 ml), $KHSO_4$ 0,5 M (40 ml), 5 % de $NaHCO_3$ (2x 40 ml) y salmuera (50 ml). La fase orgánica se secó sobre $MgSO_4$ y se evaporó para dar el carbamato de fenilo como un aceite incoloro que se cristalizó lentamente durante un período de días (6,63 g, cuantitativo).

E11-6: A una solución de E11-5 (1,00 g, 2,93 mmol) en DMSO (2,00 ml) que contenía acetonitrilo (1,00 ml) se agregó diisopropiletilamina (817 µl) seguida de la amina E11-2 (477 mg, 3,52 mmol). La reacción se agitó a temperatura ambiente durante 2 h y luego se calentó a 70°C durante 45 min. Luego, la solución se diluyó con acetato de etilo (30 ml), se lavó con 5% de K_2CO_3 ac. (4x 50 ml) y salmuera (50 ml). La fase orgánica se secó sobre $MgSO_4$, el solvente se evaporó y el residuo se purificó mediante cromatografía flash sobre gel de sílice de grado de TLC empleando hexano/acetato de etilo 10:1 a 5:1 (gradiente) como eluyente que dio la urea E11-6 como un sólido cristalino blanco (798 mg, 79%).

E11-7: A una solución de urea E11-6 (780 mg, 2,25 mmol) en etanol absoluto (10 ml) bajo una atmósfera de argón se agregó catalizador de Pd-C 10% (100 mg). El sistema se purgó tres veces con H_2 y luego se agitó vigorosamente bajo un balón de hidrógeno. Después de 3 h, el catalizador se filtró sobre Celite y el filtrado se evaporó. El residuo se disolvió entonces en metanol ca. (10 ml), se filtró a través de un filtro Millipore Millex de 0,45 uM y luego se evaporó para dar el ácido E11-7 como un sólido blanco (539 mg, 93%).

15b: El Boc-dipéptido 15a (1,23 g, 2,11 mmol) se disolvió en dioxano anhidro (2 ml) y se agregó una solución de HCl 4N en dioxano (10 ml, 40 mmol), dando una solución amarilla brillante que se dejó en reposo a temperatura ambiente. Después de 3 h, el solvente se evaporó dando un sólido amarillo gomoso que se trituró con diclorometano (10 ml ca.) y se evaporó a un polvo amarillo canario que se secó en alto vacío (1,23 g, cuantitativo).

E11-8: La urea E11-7 (239 mg, 0,932 mmol) y TBTU (3,06 mg, 0,979 mmol) se disolvieron/suspendieron en diclorometano anhidro (4 ml) y se agregó diisopropiletilamina (157 µl, 0,900 mmol). La reacción se agitó a temperatura ambiente bajo una atmósfera

de nitrógeno hasta que la solución se tornó casi homogénea (5 min ca.). Se agregó luego una solución del dipéptido **15b** (494 mg, 0,888 mmol) en diclorometano conteniendo diisopropiletilamina (314 µl, 1,8 mmol) y la solución resultante se dejó en agitación durante 3 h después que la reacción se basificó mediante la adición de diisopropiletilamina adicional (0,15 ml ca.). El solvente se evaporó dando un jarabe amarillo que se extrajo con acetato de etilo (2x 50 ml) y se lavó con $NaHCO_3$ saturado (2x 50 ml) y salmuera (30 ml). Los extractos combinados se secaron entonces sobre $MgSO_4$ y se evaporaron para dar el tripéptido **E11-8** como un sólido blanco fibroso (650 mg, 97%).

E11-9: El éster **E11-8** (645 mg, 0,894 mmol) se disolvió en tetrahidrofurano (16 ml) conteniendo metanol (8 ml) y luego se agregó solución acuosa 1,0N de hidróxido de sodio (900 ml, 0,900 mmol) gota a gota agitando vigorosamente a temperatura ambiente. Después de 5 h, la solución se evaporó (manteniendo la temperatura del baño a menos de 30°C) y luego se colocó en alto vacío hasta el día siguiente para dar la sal carboxilato como un sólido amarillo pálido (725 mg, cuantitativo) que se usó sin purificación adicional (aprox. 10% de diácido presente).

E11-10: A una suspensión agitada, helada de sal de sodio **E11-9** (0,894 mmol) en tetrahidrofurano (10 ml) bajo una atmósfera de argón se agregó trietilamina (240 µl, 1,72 mmol) seguida por la adición gota a gota de cloroformiato de isobutilo (174 µl, 1,34 mmol). La suspensión resultante se agitó a 0°C durante 3 h y luego se agregó una solución de diazometano en etiléter (0,7M, 10 ml, 7 mmol). La suspensión amarilla se agitó durante 30 min a 0°C y luego se dejó que se caliente a temperatura ambiente. Después de 1 h, se burbujeó nitrógeno a través de la suspensión durante 15 min. para eliminar el diazometano en exceso y el solvente se evaporó. El residuo se extrajo con acetato de etilo (20 ml) y se lavó con 5% de $NaHCO_3$ acuoso (20 ml) y salmuera (20 ml). La fase orgánica se secó sobre $MgSO_4$ y se evaporó para dar la diazocetona **E11-10** como un sólido amarillo (626 mg (96%).

E11-11: A una solución helada, agitada de diazocetona **E11-10** (620 mg, 0,850 mmol) en tetrahidrofurano (2 ml) se agregó gota a gota ácido bromhídrico acuoso 48% (144 µl, 0,850 mmol) y la reacción se agitó durante 30 min. luego, la solución se diluyó y se extrajo con acetato de etilo (30 ml) y se lavó con $NaHCO_3$ acuoso 5% (2x 20 ml) y salmuera (20 ml). La fase orgánica se secó sobre $MgSO_4$ y se evaporó para dar la bromocetona **E11-11** como un sólido amarillo (611 mg, 92%).

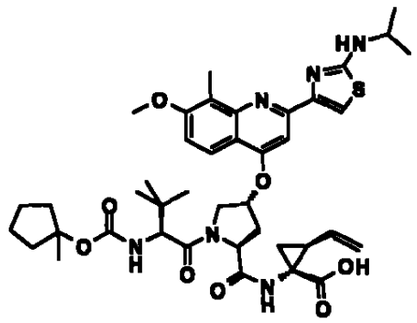
E11-12: A una solución de la bromocetona **E11-11** (75 mg, 0,10 mmol) en isopropanol (0,30 ml) se agregó diisopropiletilamina (87 µl, 0,50 mmol) y *N*-acetiltiourea (18 mg, 0,15

mmol). La mezcla agitada se calentó a 70°C durante 1 h y luego se extrajo con acetato de etilo (30 ml) y se lavó con $NaHCO_3$ acuoso 5% (20 ml) y salmuera (20 ml). La fase orgánica se secó sobre $MgSO_4$ y se evaporó para dar el aminotiazol bruto como un sólido amarillo que se usó sin purificación adicional.

Compuesto 2015: El éster **E11-12** (0,10 mmol) se disolvió en tetrahidrofurano (0,80 ml) y metanol (0,25 ml) y se agregó hidróxido de litio 1,0 N (800 µl, 0,80 mmol). Después de agitar a temperatura ambiente durante 2,5 horas, los solventes orgánicos se evaporaron y el residuo acuoso resultante se diluyó con DMSO (1 ml) y ácido acético (0,7 ml) y la solución se inyectó en una columna de HPLC Combi-Prep. Las fracciones puras se combinaron y liofilizaron para dar el inhibidor final **2015** como un sólido amarillo amorfo (sal trifluoroacetato, 16 mg, 20%): ^{1}H-RMN (400 MHz, DMSO-d_6): δ 0,87 y 0,96 (dos s, 9H), 1,19 y 1,28 (dos s, 3H), 1,24-1,90 (m, 9H), 2,03 (app q4, Japp = 8,8 Hz, 1H), 2,20 (s, 3H), 2,2-2,28 (m, 1H), 2,60 (s, 3H), 3,83-4,05 (m, 2H), 3,93 (s, 3H), 4,19-4,23 (m, 2H), 4,36-4,46 (m, 3H), 4,81 (app t, Japp = 7 Hz, 0,2H), 5,03-5,07 (dos conjuntos de dd superpuestos, 1H), 5,16-5,24 (dos grupos de dd superpuestos, 1H), 5,38 y 5,42 (dos br. s, 1H), 5,67-5,83 (m, 1H), 5,95-6,04 (m, 2H), 7,26 (d, J = 9,4 Hz, 0,8H), 7,40 (d, J = 9,4 Hz, 0,2H), 7,43-7,55 (br. m, 1H), 7,89 (d, J = 9,2 Hz, 0,2 H), 8,04 (d, J = 9,2 Hz, 0,8H), 8,08 (br. s, 1H), 8,54 (s, 0,8H), 8,87 (s, 0,2H), 12,37 y 12,42 (dos br. s, 1H).

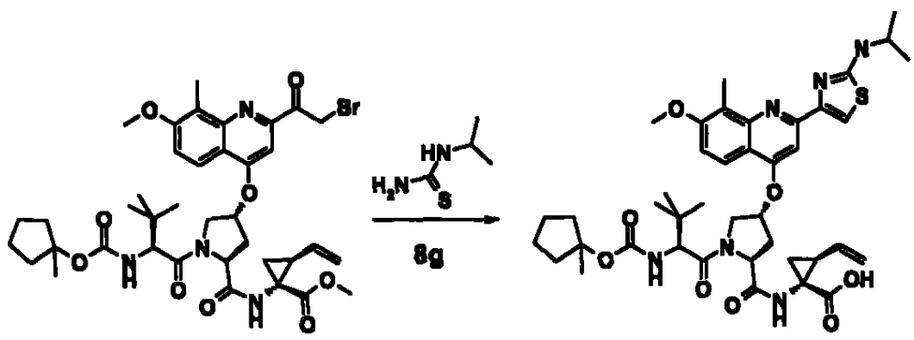
Ejemplo 12

Síntesis del compuesto 1038



Compuesto 1038

Empleando una secuencia de reacciones similar a la descripta en los últimos seis pasos del Ejemplo 11, pero empleando carbamato 4c (Ejemplo 15) en lugar de urea **11-7**, se preparó la siguiente carbamato bromocetona **E12-1**:



E12-1 **Compuesto 1038**

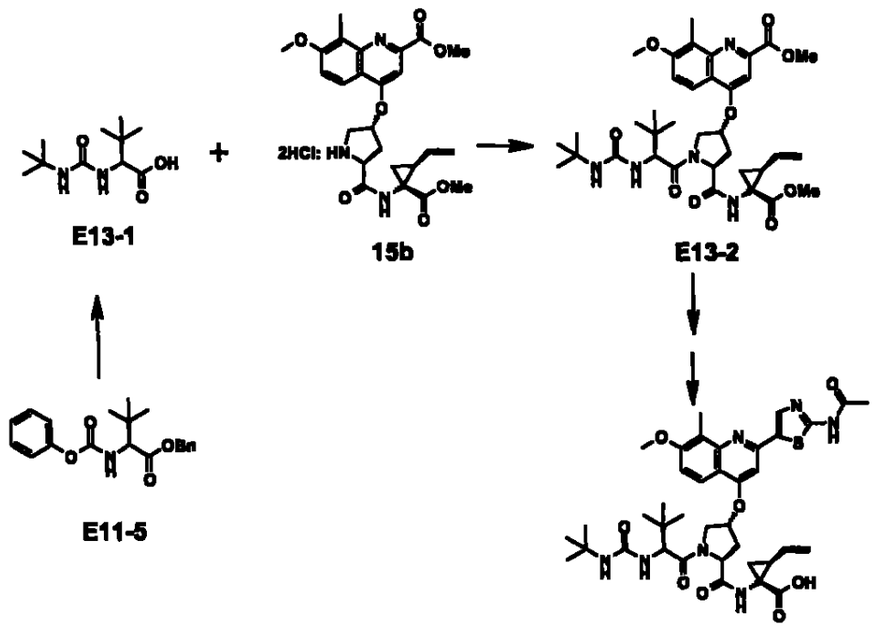
La conversión de la bromocetona en el compuesto final se llevó a cabo de la siguiente manera:

A una solución de la bromocetona **E12-1** (60 mg, 0,076 mmol) en isopropanol (3 ml) se agregó isopropiltiourea **8g** (11,7 mg, 0,99 mmol). La mezcla de reacción se calentó a 70°C durante 45 minutos. La HPLC reveló el consumo total del material de partida. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con THF (3 ml) y se agregó solución de hidróxido de sodio 1,0N (1 ml). Después de agitar a temperatura ambiente durante 12 horas, la mezcla de reacción se concentró hasta sequedad. El residuo se disolvió en DMSO (2 ml) y la solución se inyectó en una columna de HPLC Combi-prep. Las fracciones puras se agruparon y liofilizaron para dar 9 mg de **Compuesto 1038** como un sólido amarillo amorfo (sal trifluoroacetato) (15% de rendimiento).

^{1}H-RMN 400 MHz, DMSO-d_6): δ 12,35 (br s, 1H), 8,56 y 8,76 (dos s, 1H), 7,72-8,27 (m, 2H), 7,2$_{3-7}$,68 (m, 2H), 6,68-6,95 (d, J= 9Hz, 0,8H), 6,18-6,34 (d, J= 9Hz, 0,2H), 5,61-5,81 (m, 1H), 5,52 (s amplio , 1H), 5,13-5,27 (m, 1H), 4,96-5,13 (m, 1H), 4,3$_{1-4}$,50 (m, 3H), 3,74-4,17 (m, 8H), 2,53-2,60 (m, 3H), 2,20-2,36 (m, 1H), 1,95-2,09 (m, 1H), 1,70-1,91 (m, 2H), 1,95-2,09 (m, 1H), 1,37-1,61, (m, 6H), 1,18-1,32 (m, 9H), 0,87 y 0,96 (dos s, 9H).

Ejemplo 13

Síntesis del compuesto 2013



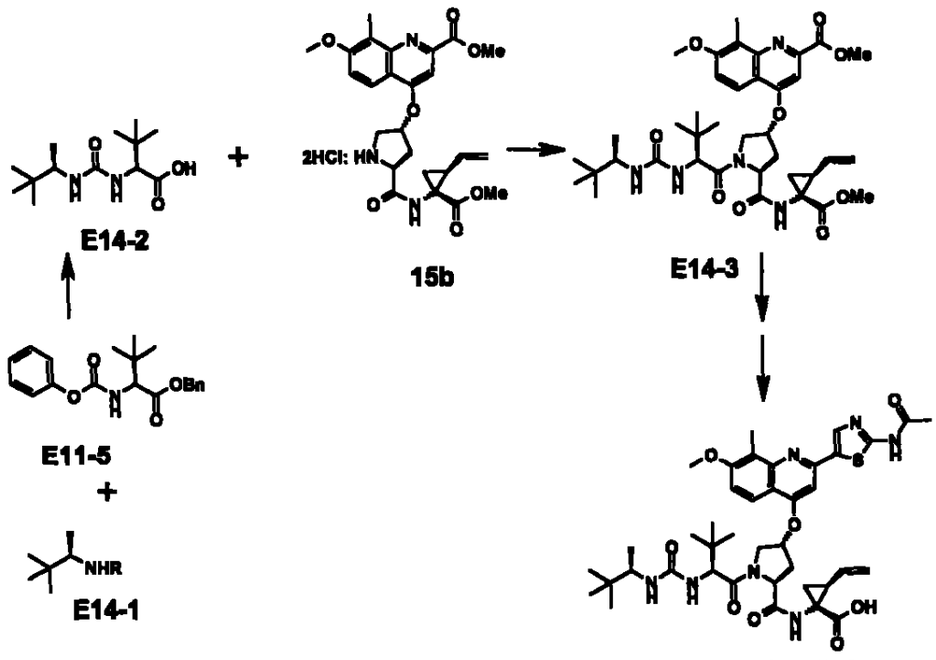
Urea-Ácido E13-1: El ácido urea-P3 se preparó a partir de ter-butilamina y **E11-5** mediante la misma secuencia de reacciones descripta en el Ejemplo 11.

Éster tripéptido E13-2: El ácido urea-P3 se acopló con el fragmento P1-P2 **15b** según se describió en el Ejemplo 11.

Compuesto 2013: El Inhibidor final se preparó a partir de **E13-2** mediante una secuencia de pasos idéntica a la descripta en el Ejemplo 11. El producto de la saponificación final se aisló como un polvo amarillo amorfo (sal trifluoroacetato, 21 mg, 28%). ^{1}H-RMN (400 MHz, DMSO-d_6): δ 0,91 y 0,96 (dos s, 9H), 1,15 y 1,21 (dos s, 9H), 1,26 (dd, J = 5,0, 9,4 Hz, 0,8H), 1,53 (dd, J = 5,0, 7,8 Hz, 0,8H), 1,58 (dd, J = 4,3, 9,2 Hz, 0,2H), 2,03 (app q4, Japp = 8,8 Hz, 1H), 2,20 (s, 3H), 2,2-2,28 (m, 1H), 2,58 (s, 3H), 3,80-4,04 (m, 2H), 3,93 y 3,96 (dos s, 3H), 4,18-4,20 (m, 2H), 4,35-4,45 (m, 3H), 4,83 (app t, Japp = 7 Hz, 0,2H), 5,03-5,07 (dos conjuntos de dd solapados, 1H), 5,17-5,24 (dos conjuntos de dd solapados, 1H), 5,36 y 5,42 (dos br. s, 1H), 5,66-5,80 (m, 1H), 5,86-6,04 (br. m, 2H), 7,25 (d, J = 9,2 Hz, 0,8H), 7,40 (d, J = 9,2 Hz, 0,2H), 7,4-7,50 (br. m, 1H), 7,88 (d, J = 9,0 Hz, 0,2 H), 8,03-8,15 (br. m, 1,8H), 8,54 (s, 0,8H), 8,89 (s, 0,2H), 12,38 y 12,42 (dos br. s, 1H).

Ejemplo 14

Síntesis del compuesto 2018



E14-2: El ácido urea-P3 **E14-2** se preparó a partir de **E11-5** y la amina **E14-1** mediante la misma secuencia de reacciones descripta en el Ejemplo 11.

E14-3: El ácido urea-P3 se acopló con el fragmento P1-P2 **15b** según se describió en el Ejemplo 11.

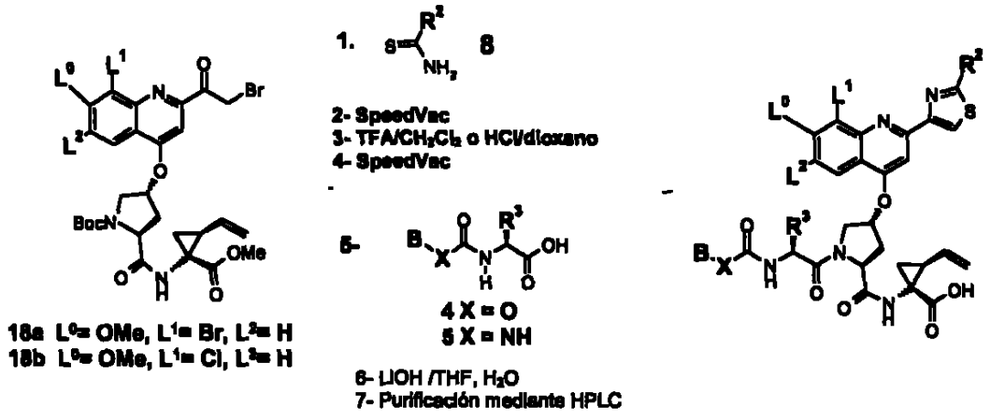
El inhibidor final se preparó a partir de **E14-3** mediante una secuencia de pasos idéntica a la descripta en el Ejemplo 11. El producto de la saponificación final se aisló como un polvo amarillo amorfo (sal trifluoroacetato, 10 mg, 21%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ 0,74-0,97 (m, 21H), 1,25 (dd, J=5, 9Hz, 1H), 1,47 (dd, J=8, 4Hz, 0,2H), 1,53 (dd, J=8, 5Hz, 0,8H), 2,02 (app q^4, J_{app}=8Hz, 0,8H), 2,19 (s, 3H), 2,2-2,27 (m, 1H), 2,59 (s, 3H), 3,31-3,43 (m, 1H), 3,93 y 3,95 (dos s, 3H), 3,98-4,02* (m), 4,22-4,26* (m), 4,35-4,39* (m), 4,82 (app t, J_{app}=7Hz, 0,2H), 5,01-5,06 (dos conjuntos de dd solapados, 1H), 5,16-5,23 (dos conjuntos de dd solapados, 1H), 5,35 y 5,41 (dos br. s, 1H), 5,67-5,79 (m, 1H), 5,87 (d, J= 9,4Hz, 0,8H), 5,91 (d, J= 9,4Hz, 0,2H), 6,07 (d, J= 8,6 Hz, 0,8H), 6,14 (d, J= 9,2Hz, 0,2H), 7,24-7,5 (m, 2H), 7,89 (d, J= 9,2Hz, 0,2H), 8,04-8,12 (m, 1,8H), 8,54 (s, 0,8H), 8,87 (s, 0,2H), 12,37 y 12,41 (dos s, 1H). * oscurecidos por la señal de HOD.

Ejemplo 15

Biblioteca de Permutación:

Ambas bromocetonas **18a** y **18b** se emplearon en una biblioteca de permutación para la síntesis paralela del compuestos según se muestra en el siguiente esquema:



Paso 1: Formación del anillo del aminotiazol

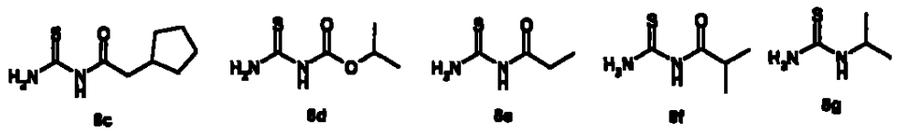
Una serie de viales de 8 ml se colocaron en un bloque de reacción de un sintetizador ACT496 (de Advanced Chemtech). En cada vial se agregó el tio-derivado (**8**) de interés (0,0688 mmol), la bromocetona (0,0625 mmol) e isopropanol (500 μl). Los viales cerrados se calentaron a 70°C durante 1 h. El solvente se evaporó entonces empleando una centrífuga de vacío (SpeedVac) y se co-evaporó con 1,2-dicloroetano. Los productos brutos se secaron en alto vacío hasta el día siguiente.

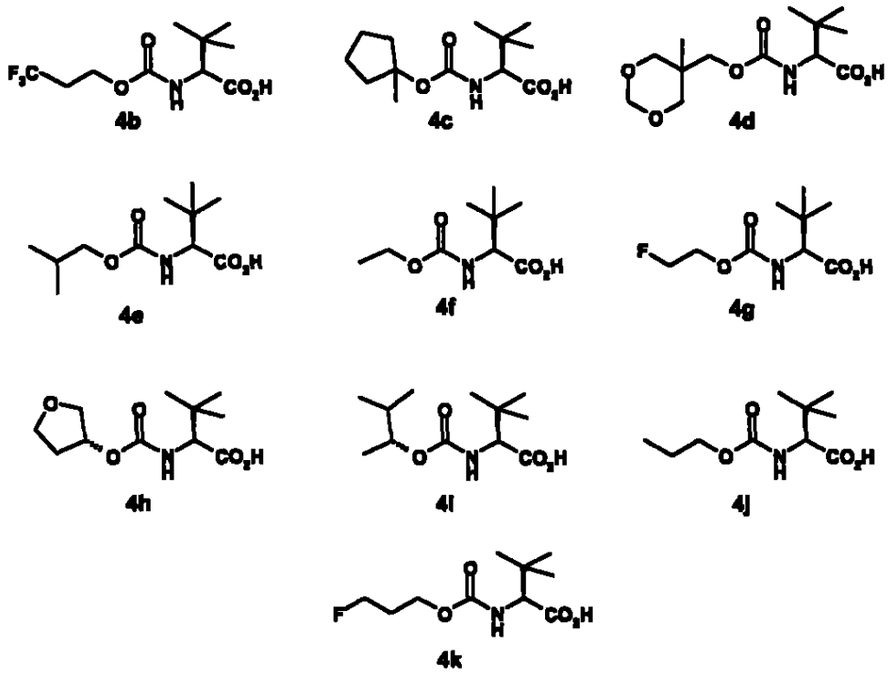
Paso 2: Eliminación del grupo protector Boc

Todos los viales se trataron con TFA 30% en DMC (500 μl) durante 1 h. Todos los viales se transfirieron a una centrífuga de vacío para eliminar el material volátil.

Paso 3: Acoplamiento

En cada vial se agregó el carbamato correspondiente (**21c** a **21g**) y ácido carbámico (**4b** a **4k**) (0,0875 mmol), HATU (0,0875 mmol, 33,27 mg) y DIPEA (0,313 mmol, 55 μl) en 500 μl de DMSO y se permitió que la mezcla de reacción procediera hasta el día siguiente.





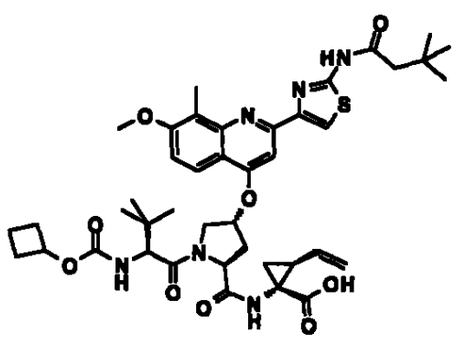
Paso 4: Saponificación y Purificación

Todas las reacciones se diluyeron con 400 µl de DMSO y 200 µl THF. Se agregó una solución de 500 µl de LiOH 2N ac. (1 mmol) a cada vial y se dejó que continúe hasta el día siguiente después de tal período, la mezcla se neutralizó mediante la adición de 400 µl de AcOH. Todos los compuestos se purificaron mediante HPLC de fase reversa semi-preparativa (columna Symmetry de 5 cm x 19 cm, gradiente de CH_3CN/H_2O 0,06% de TFA).

Ejemplo 16

Los siguientes compuestos se prepararon usando secuencias de reacción y metodologías descriptas en los ejemplos anteriores:

Compuestos de la Tabla 1

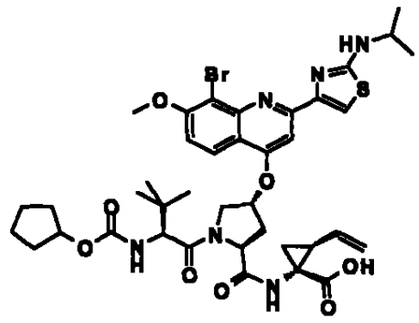


Compuesto 1006

Compuesto 1006:

^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 12,31 (br s, 1H), 8,56 (s, 1H), 8,14 (br s, 1H), 8,06 (d, J = 9,0 Hz, 1H), 7,47 (br s, 1H), 7,34 (d, J = 9,0 Hz, 1H), 7,11 (d, J = 8,4 Hz, 1H), 5,79-5,66 (m, 1H), 5,51-5,41 (m, 1H), 5,24-5,15 (m, 1H), 5,11-5,03 (m, 1H), 4,53-4,40 (m, 2H), 4,40-4,32 (m, 1H), 4,07 (d, J = 8,6 Hz, 1H), 4,04-3,92 (m, 1H), 3,96 (s, 3H), 2,61 (s, 3H), 2,58-2,50 (m, 1H), 2,40 (br s, 2H), 2,31-2,17 (m, 1H), 2,12-1,95 (m, 3H), 1,91-1,76 (m, 2H), 1,71-1,39 (m, 3H), 1,31-1,23 (m, 1H), 1,04 (m, 9H), 0,97 (s, 9H).

M.S. (electroaspersión) : 817,4 $(M-H)^-$ 819,5 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 99 %

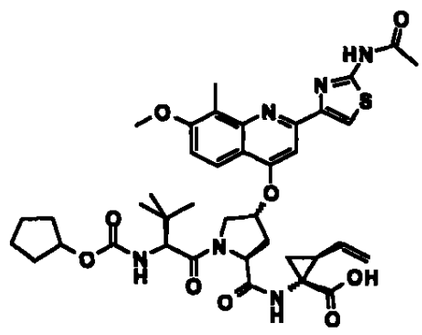


Compuesto 1030

Compuesto 1030:

^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 8,56 (s, 1H), 8,14 (d, J = 9,0 Hz, 1H), 8,00-7,78 (m, 1H), 7,73-7,56 (m, 1H), 7,52 (s, 1H), 7,37 (d, J = 9,2 Hz, 1H), 6,97 (d, J = 8,6 Hz, 1H), 5,78-5,65 (m, 1H), 5,52-5,45 (m, 1H), 5,23-5,15 (m, 1H), 5,13-5,03 (m, 1H), 4,58-4,50 (m, 1H), 4,50-4,42 (m, 1H), 4,39-4,31 (m, 1H), 4,10-4,03 (m, 1H), 4,01 (s, 3H), 3,99-3,70 (m, bajo H2O, 2H), 2,34-2,23 (m, 1H), 2,07-1,98 (m, 1H), 1,70-1,37 (m, 9H), 1,34-1,23 (m, 2H), 1,26 (br d, J = 6,4 Hz, 6H), 0,96 (s, 9H).

M.S. (electroaspersión): 839 $(M-H)^-$ 841,3 $(M-H+2)^-$ 841,3 $(M+H)^+$ 843,3 $(MH+2)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 98%

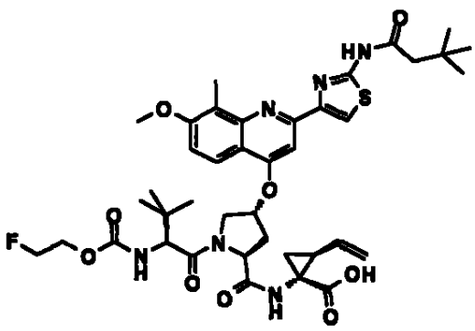


Compuesto 1015 .

Compuesto 1015:

^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 12,32 (br s, 1H), 8,57 (s, 1H), 8,15-8,03 (m, 1H), 8,04 (d, J = 9,2 Hz, 1H), 7,47-7,37 (m, 1H), 7,29 (d, J = 8,8 Hz, 1H), 7,03 (d, J = 8,6 Hz, 1H), 5,78-5,65 (m, 1H), 5,45-5,38 (m, 1H), 5,23-5,14 (m, 1H), 5,09-5,02 (m, 1H), 4,72-4,62 (m, 1H), 4,46-4,32 (m, 2H), 4,16-4,08 (m, 1H), 4,03-3,90 (m, 1H), 3,94 (s, 3H), 2,60 (s, 3H), 2,30-2,19 (m, 1H), 2,20 (s, 3H), 2,06-1,97 (m, 1H), 1,81-1,21 (m, 11H), 0,97 (s, 9H).

M.S. (electroaspersión) : 775,4 $(M-H)^-$ 777,5 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; CH_3CN:H_2O): 99 %

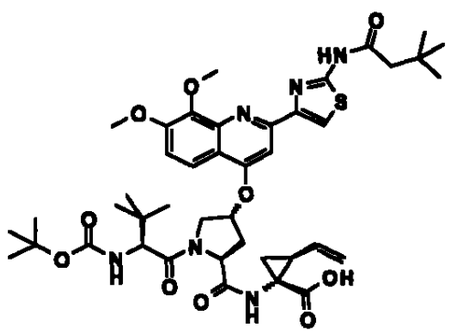


Compuesto 1024

Compuesto 1024:

^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 12,31 (s, 1H), 8,55 (s, 1H), 8,20-8,05 (m, 1H), 8,03 (d, J = 9,2 Hz, 1H), 7,54-7,40 (m, 1H), 7,38 (d, J = 8,6 Hz, 1H), 7,33 (d, J = 9,4 Hz, 1H), 5,79-5,66 (m, 1H), 5,49-5,41 (m, 1H), 5,23-5,15 (m, 1H), 5,09-5,02 (m, 1H), 4,77-3,85 (m, 8H), 3,95 (s, 3H), 2,60 (s, 3H), 2,58-2,47 (m, 1H), 2,43-2,36 (m, 2H), 2,31-2,20 (m, 1H), 2,07-1,98 (m, 1H), 1,57-1,51 (m, 1H), 1,31-1,23 (m, 1H), 1,04 (s, 9H), 1,00 (s, 9H).

M.S. (electroaspersión) : 809,4 $(M-H)^-$ 811,4 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; CH_3CN:H_2O): 98 %.

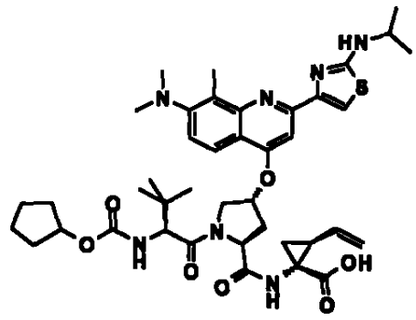


Compuesto 1001

Compuesto 1001:

^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 7:3, descripción del rotámero principal; δ 8,01 (br s, 1H), 7,92 (s, 1H), 7,90-7,77 (m, 2H), 7,70 (br s, 1H), 7,31 (d, J = 9,4 Hz, 1H), 6,72 (d, J = 8,8 Hz, 1H), 6,28-6,10 (m, 1H), 5,53-5,33 (m, 1H), 5,03-5,92 (m, 1H), 4,85-4,71 (m, 1H), 4,49-4,40 (m, 1H), 4,19-4,02 (m, 3H), 4,03 (s, 3H), 3,93 (s, 3H), 2,82-2,45 (m, 3H), 2,36-2,23 (m, 1H), 1,90-1,79 (m, 1H), 1,34 (m, 9H), 1,37-1,14 (m, 2H), 1,03 (s, 9H), 0,98 (s, 9H).

M.S. (electroaspersión): 835,4 $(M-H)^-$ 837,3 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; CH_3CN:H_2O): 99%

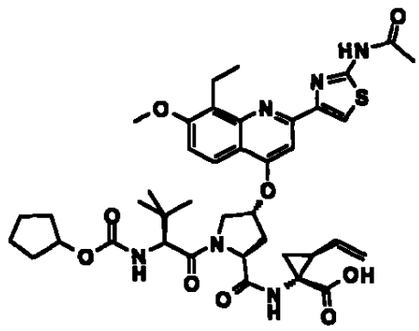


Compuesto 1011

Compuesto 1011:

^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 8,53 (s, 1H), 7,92 (d, J = 8,8 Hz, 1H), 7,69 (d, J = 7,4 Hz, 1H), 7,46 (s, 1H), 7,39 (s, 1H), 7,25 (d, J = 9,0 Hz, 1H), 6,99 (d, J = 8,8 Hz, 1H), 5,79-5,64 (m, 1H), 5,44-5,33 (m, 1H), 5,23-5,13 (m, 1H), 5,10-5,00 (m, 1H), 4,8$_{1-4}$,70 (m, 1H), 4,45-4,27 (m, 2H), 4,19-4,11 (m, 1H), 4,04-3,91 (m, 1H), 3,87-3,72 (m, 1H), 2,75 (s, 6H), 2,66 (s, 3H), 2,56-2,42 (m, 1H), 2,29-2,17 (m, 1H), 2,07-1,97 (m, 1H), 1,80-1,21 (m, 10H), 1,25 (br d, J = 6,5 Hz, 6H), 0,97 (s, 9H).

M.S. (electroaspersión): 788,4 $(M-H)^-$ 790,5 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; CH_3CN:H_2O): 95%

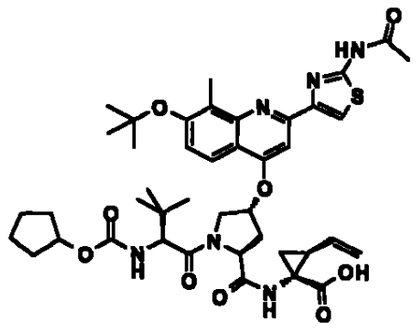


Compuesto 1023

Compuesto 1023:

^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 12,36 (s, 1H), 8,55 (s, 1H), 8,09-7,97 (m, 2H), 7,42 (br s, 1H), 7,29 (d, J = 9,2 Hz, 1H), 6,99 (d, J = 8,6 Hz, 1H), 5,79-5,66 (m, 1H), 5,45-5,38 (m, 1H), 5,23-5,15 (m, 1H), 5,09-5,02 (m, 1H), 4,75-4,66 (m, 1H), 4,47-4,31 (m, 2H), 4,16-4,09 (m, 1H), 4,03-3,91 (m, 1H), 3,94 (s, 3H), 3,29-3,18 (m, 2H), 2,60-2,43 (m, 1H), 2,30-2,18 (m, 1H), 2,20 (s, 3H), 2,07-1,97 (m, 1H), 1,81-1,33 (m, 9H), 1,31-1,23 (m, 1H), 1,18 (t, J = 7,3 Hz, 3H), 0,97 (s, 9H).

M.S. (electroaspersión): 789,3 $(M-H)^-$ 791,4 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 98%

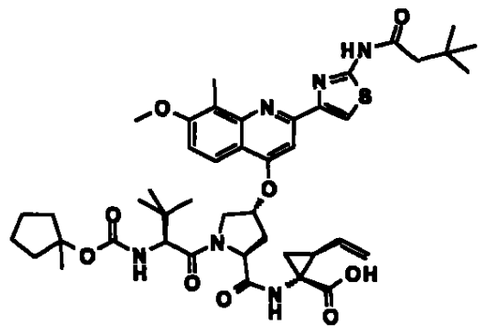


Compuesto 1033

Compuesto 1033:

^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 12,36 (s, 1H), 8,53 (s, 1H), 8,05 (s, 1H), 7,98 (d, J = 9,0 Hz, 1H), 7,46 (s, 1H), 7,20 (d, J = 9,0 Hz, 1H), 7,04 (d, J = 8,4 Hz, 1H), 5,80-5,65 (m, 1H), 5,44-5,37 (m, 1H), 5,24-5,14 (m, 1H), 5,10-5,01 (m, 1H), 4,85-4,76 (m, 1H), 4,45-4,34 (m, 2H), 4,21-4,10 (m, 1H), 4,04-3,89 (m, 1H), 2,62 (s, 3H), 2,58-2,47 (m, 1H), 2,28-2,18 (m, 1H), 2,20 (s, 3H), 2,06-1,96 (m, 1H), 1,81-1,38 (m, 9H), 1,39 (s, 9H), 1,29-1,22 (m, 1H), 0,99 (s, 9H).

M.S. (electroaspersión): 817,4 $(M-H)^-$ 819,4 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 98%

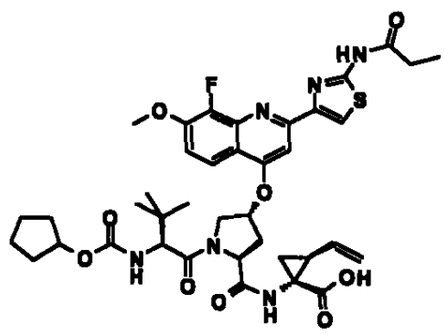


Compuesto 1037

Compuesto 1037:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 12,29 (s, 1H), 8,54 (s, 1H), 8,19-8,01 (m, 1H), 8,04 (d, J = 9,0 Hz, 1H), 7,44 (s, 1H), 7,25 (d, J = 9,2 Hz, 1H), 6,79 (d, J = 8,4 Hz, 1H), 5,78-5,65 (m, 1H), 5,47-5,37 (m, 1H), 5,22-5,13 (m, 1H), 5,08-5,02 (m, 1H), 4,45-4,33 (m, 2H), 4,13-4,06 (m, 1H), 3,98-3,90 (m, 1H), 3,92 (s, 3H), 2,59 (s, 3H), 2,56-2,46 (m, 1H), 2,41-2,36 (m, 2H), 2,28-2,18 (m, 1H), 2,05-1,96 (m, 1H), 1,93-1,43 (m, 9H), 1,33 (br s, 3H), 1,29-1,22 (m, 1H), 1,03 (s, 9H), 0,97 (s, 9H).

M.S. (electroaspersión): 845,5 $(M-H)^-$ 847,5 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 96%



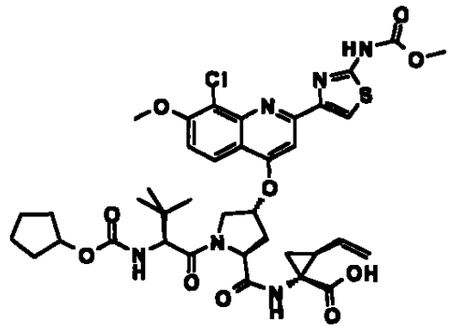
Compuesto 1051

Compuesto 1051:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 12,35 (s, 1H), 8,54 (s, 1H), 8,03 (s, 1H), 7,92 (d, J = 9,2 Hz, 1H), 7,47 (s, 1H), 7,38 (t, J = 8,3 Hz, 1H), 6,98 (d, J = 8,7 Hz, 1H), 5,78-5,65 (m, 1H), 5,47-5,38 (m, 1H), 5,23-5,13 (m, 1H), 5,09-5,00 (m, 1H), 4,69-4,60 (m, 1H), 4,48-4,30 (m, 2H), 4,14-3,90 (m, 2H), 3,98 (s, 3H), 2,60-2,39 (m, 3H), 2,30-2,20 (m, 1H), 2,06-1,97 (m, 1H), 1,80-1,37 (m, 8H), 1,37-1,20 (m, 2H), 1,12 (t, J = 7,5 Hz, 3H), 0,96 (s, 9H).

294
295

M.S. (electroaspersión): 793,3 $(M-H)^-$ 795,3 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 98%

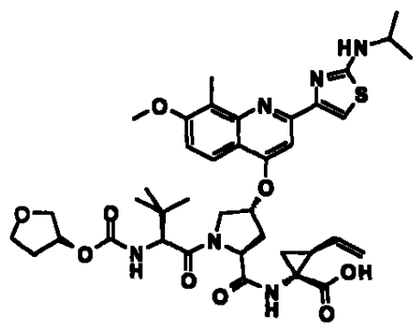


Compuesto 1053

Compuesto 1053:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal: δ 12,06 (br s, 1H), 8,55 (s, 1H), 8,12 (d, J = 9,2 Hz, 1H), 8,05 (s, 1H), 7,46 (m, 1H), 7,39 (d, J = 9,3 Hz, 1H), 6,98 (d, J = 8,6 Hz, 1H), 5,78-5,66 (m, 1H), 5,44-5,38 (m, 1H), 5,23-5,15 (m, 1H), 5,09-5,02 (m, 1H), 4,65-4,52 (m, 1H), 4,49-4,32 (m, 2H), 4,12-4,05 (m, 1H), 4,01 (s, 3H), 3,99-3,91 (m, 1H), 3,78 (s, 3H), 2,60-2,45 (m, 1H), 2,31-2,20 (m, 1H), 2,07-1,97 (m, 1H), 1,81-1,37 (m, 8H), 1,37-1,22 (m, 2H), 0,96 (s, 9H).

M.S. (electroaspersión): 811,1 $(M-H)^-$ 813,2 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 96%



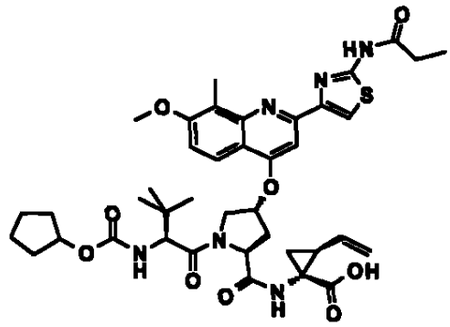
Compuesto 1027

Compuesto 1027:

^1H RMN (400MHz, DMSO-d_6): δ 8,58 (s, 1H), 8,06 (d, J= 9Hz, 1H), 7,91, 7,89 (2s, 1H), 7,57 (brs, 1H), 7,40,7,38 (2s, 1H), 7,25 (d, J=9Hz, 1H), 5,57-5,68 (m, 1H), 5,55 (brs, 1H), 5,20 (d, J=16Hz, 1H), 5,06 (d, J= 11Hz, 1H)), 4,69 (brs, 1H), 4,47 (t, J= 9Hz, 1H), 4,30-4,35 (m, 1H), 4,08 (d, J= 9Hz, 2H), 4,05-3,96 (m, 2H), 3,97 (s,3H), 3,66-3,40 (m, 8H), 2,56 (s, 3H), 2,35-2,25 (m, 1H), 2,08-1,98 (m, 1H), 1,60-1,50 (m, 2H), 1,28,1,26 (2s, 6H), 0,97 (s, 9H).

EIMS: (M+H) = 779,3, (M-H) = 777,3

Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 99%.

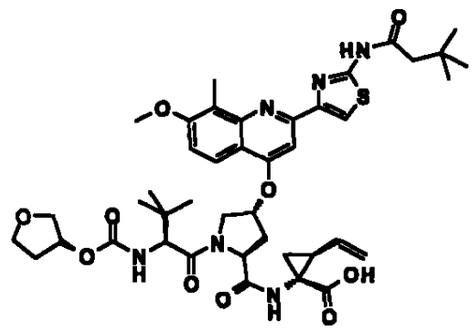


Compuesto 1041

Compuesto 1041:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 12,33 (br s, 1H), 8,55 (s, 1H), 8,15-8,02 (m, 1H), 8,04 (d, J = 9,0 Hz, 1H), 7,49-7,38 (m, 1H), 7,29 (d, J = 9,2 Hz, 1H), 6,99 (d, J = 8,8 Hz, 1H), 5,78-5,66 (m, 1H), 5,46-5,39 (m, 1H), 5,23-5,14 (m, 1H), 5,09-5,02 (m, 1H), 4,7$_{1-4}$,62 (m, 1H), 4,47-4,32 (m, 2H), 4,15-4,09 (m, 1H), 4,03-3,92 (m, 1H), 3,94 (s, 3H), 2,60 (s, 3H), 2,58-2,40 (m, 2H), 2,30-2,20 (m, 1H), 2,07-1,97 (m, 1H), 1,80-1,21 (m, 11H), 1,13 (t, J = 7,5 Hz, 3H), 0,97 (s, 9H).

M.S. (electroaspersión): 789,4 $(M-H)^-$ 791,4 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 98%.

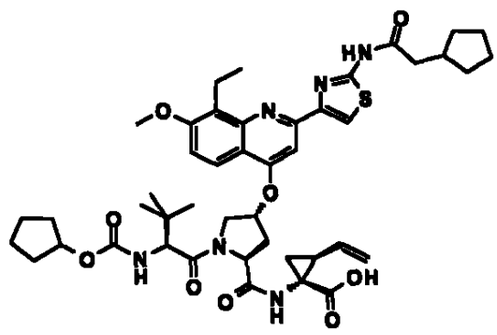


Compuesto 1026

Compuesto 1026:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 12,30 (s, 1H), 8,56 (s, 1H), 8,09 (br s, 1H), 8,02 (d, J = 9,0 Hz, 1H), 7,44 (br s, 1H), 7,32 (d, J = 9,2 Hz, 1H), 7,24 (d, J = 8,8 Hz, 1H), 5,78-5,66 (m, 1H), 5,47-5,39 (m, 1H), 5,23-5,15 (m, 1H), 5,10-5,03 (m, 1H), 4,80-4,72 (m, 1H), 4,49-4,41 (m, 1H), 4,37-4,29 (m, 1H), 4,15-4,08 (m, 1H), 4,05-3,95 (m, 1H), 3,95 (s, 3H), 3,80-3,51 (m, bajo H2O, 4H), 2,60 (s, 3H), 2,57-2,48 (m, 1H), 2,41-2,37 (m, 2H), 2,31-2,21 (m, 1H), 2,07-

1,98 (m, 1H), 1,95-1,83 (m, 1H), 1,62-1,46 (m, 2H), 1,31-1,22 (m, 1H), 1,04 (s, 9H), 0,97 (s, 9H). M.S. (electroaspersión): 833,3 $(M-H)^-$ 835,4 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 99%

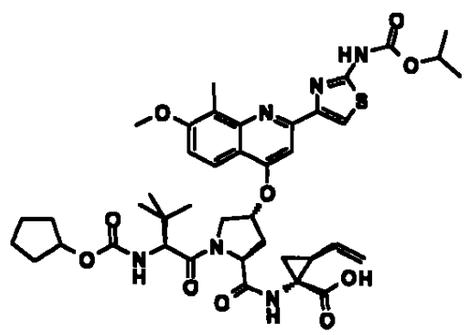


Compuesto 1022

Compuesto 1022:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 12,32 (s, 1H), 8,55 (s, 1H), 8,08-7,97 (m, 2H), 7,42 (br s, 1H), 7,29 (d, J = 9,2 Hz, 1H), 6,99 (d, J = 8,8 Hz, 1H), 5,79-5,66 (m, 1H), 5,44-5,37 (m, 1H), 5,24-5,15 (m, 1H), 5,09-5,02 (m, 1H), 4,75-4,67 (m, 1H), 4,43-4,32 (m, 2H), 4,16-3,95 (m, 2H), 3,94 (s, 3H), 3,29-3,18 (m, 2H), 2,59-2,48 (m, 1H), 2,34-2,20 (m, 3H), 2,06-1,98 (m, 1H), 1,81-1,16 (m, 19H), 1,18 (t, J = 7,2 Hz, 3H), 0,97 (s, 9H).

M.S. (electroaspersión): 857,4 $(M-H)^-$ 859,5 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 98%



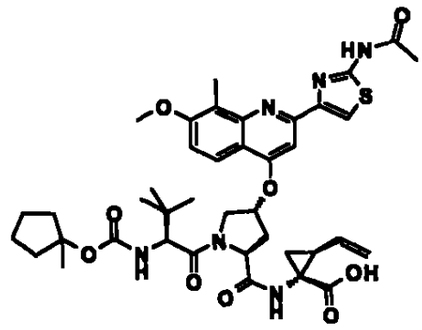
Compuesto 1046

Compuesto 1046:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 11,91 (br s, 1H), 8,56 (s, 1H), 8,08 (br s, 1H), 8,04 (d, J = 9,2 Hz, 1H), 7,43 (s, 1H), 7,30 (d, J = 9,0 Hz, 1H), 6,99 (d, J = 8,8 Hz, 1H), 5,78-5,66 (m, 1H), 5,46-5,38 (m, 1H), 5,23-5,15 (m, 1H), 5,09-5,03 (m, 1H), 5,03-4,93 (m, 1H), 4,7$_{1-4}$,62 (m, 1H), 4,47-4,32 (m, 2H), 4,15-4,08 (m, 1H), 4,05-3,95 (m, 1H), 3,94 (s, 3H), 2,59 (s, 3H),

2,58-2,47 (m, 1H), 2,31-2,20 (m, 1H), 2,07-1,97 (m, 1H), 1,81-1,22 (m, 10H), 1,29 (d, J = 6,3 Hz, 6H), 0,97 (s, 9H).

M.S. (electroaspersión): 819,4 $(M-H)^-$ 821,4 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 99%

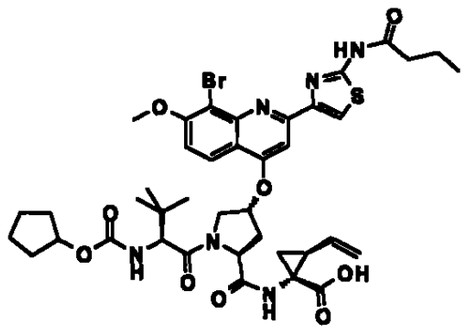


Compuesto 1036

Compuesto 1036:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 12,35 (s, 1H), 8,53 (s, 1H), 8,12-7,98 (m, 2H), 7,41 (s, 1H), 7,24 (d, J = 9,2 Hz, 1H), 6,79 (d, J = 8,4 Hz, 1H), 5,78-5,64 (m, 1H), 5,44-5,34 (m, 1H), 5,22-5,13 (m, 1H), 5,08-5,01 (m, 1H), 4,46-4,33 (m, 2H), 4,15-4,06 (m, 1H), 4,04-3,95 (m, 1H), 3,92 (s, 3H), 2,59 (s, 3H), 2,57-2,47 (m, 1H), 2,28-2,17 (m, 1H), 2,19 (s, 3H), 2,06-1,96 (m, 1H), 1,94-1,77 (m, 2H), 1,72-1,43 (m, 7H), 1,34 (s, 3H), 1,29-1,21 (m, 1H), 0,97 (s, 9H).

M.S. (electroaspersión): 789,4 $(M-H)^-$ 791,4 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 95%



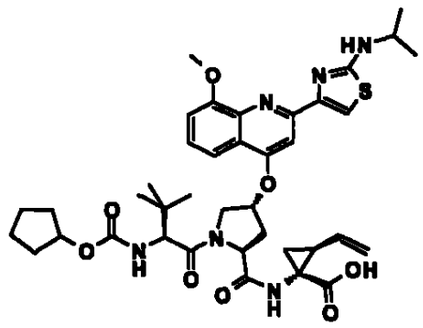
Compuesto 1056

Compuesto 1056:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 12,35 (s, 1H), 8,55 (s, 1H), 8,17 (d, J = 9,2 Hz, 1H), 8,05 (s, 1H), 7,47 (s, 1H), 7,35 (d, J = 9,4 Hz, 1H), 6,98 (d, J = 8,6 Hz, 1H), 5,78-5,66 (m, 1H), 5,46-5,40 (m, 1H), 5,23-5,15 (m, 1H), 5,09-5,03 (m, 1H), 4,63-4,56 (m, 1H), 4,49-4,34 (m, 2H), 4,13-3,90 (m, bajo H2O, 2H), 4,01 (s, 3H), 2,60-2,51 (m, 1H), 2,49-2,43 (m, 2H), 2,32-

2,21 (m, 1H), 2,07-1,98 (m, 1H), 1,81-1,37 (m, 9H), 1,36-1,16 (m, 3H), 0,96 (s, 9H), 0,93 (t, J = 7,4 Hz, 3H).

M.S. (electroaspersión): 869,1 $(M-H)^-$ 871,1 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 98%



Compuesto 1181

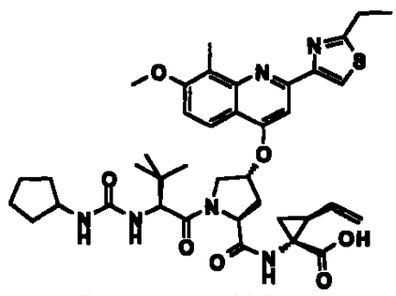
Compuesto 1181:

^1H RMN (400 MHz, DMSO-d_6): δ 8,57 (s, 1H), 8,2-7,96 (m, 1H), 7,88-7,70 (m, 2H), 7,62-7,35 (m, 2H), 7,02 (d, J = 7,2 Hz, 1H), 5,78-5,65 (m, 1H), 5,65-5,55 (m, 1H), 5,19 (d, *J* = 17,2 Hz, 1H), 5,065 (d, *J* = 11,9 Hz, 1H), 4,63-4,52 (m, 1H), 4,50-4,40 (m, 1H), 4,13-4,08 (m, 2H), 4,06 (s, 3H), 3,98 (bd, J = 10 Hz, 1H), 3,92-3,80 (m, 1H), 2,62-2,53 (m, 1H), 2,38-2,27 (m, 1H), 2,02 (dd, *J* = 8,6, 8,6 Hz, 1H), 1,69-1,52 (m, 6H), 1,51-1,41 (m, 3H), 1,40-1,31 (m, 1H), 1,27 (d, J = 6,5 Hz, 6H), 0,97 (s, 9H).

MS (electroaspersión): $(M+H)^+$; 763,4 y $(M-H)^-$ 761,3.

Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 99%.

Compuestos de la Tabla 2



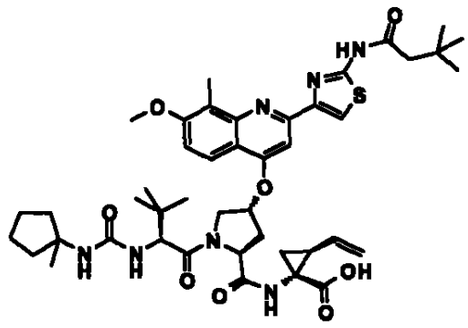
Compuesto 2010

Compuesto 2010:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 8:2, descripción del rotámero principal; δ 8,56 (s, 1H), 8,41 (br s, 1H), 8,04 (d, J = 9,2 Hz, 1H), 7,55 (s, 1H), 7,29 (d, J = 9,2 Hz, 1H), 6,09-5,99 (m, 1H), 5,97-5,88 (m, 1H), 5,78-5,65 (m, 1H), 5,54-5,48 (m, 1H), 5,23-5,15 (m, 1H), 5,09-5,02 (m, 1H), 4,47-4,33 (m, 2H), 4,27-4,20 (m, 1H), 4,19-3,85 (m,

bajo H2O, 2H), 3,94 (s, 3H), 3,13 (q, J = 7,5 Hz, 2H), 2,60 (s, 3H), 2,55-2,42 (m, 1H), 2,34-2,23 (m, 1H), 2,09-2,00 (m, 1H), 1,80-1,37 (m, 7H), 1,40 (t, J = 7,5 Hz, 3H), 1,31-1,05 (m, 3H), 0,96 (s, 9H).

M.S. (electroaspersión): 745,4 $(M-H)^-$ 747,4 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 96%

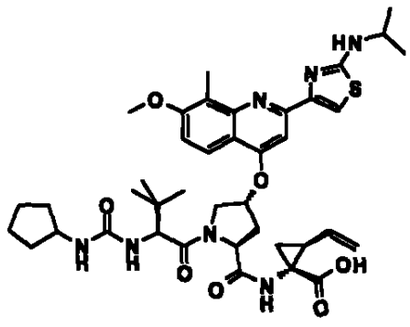


Compuesto 2012

Compuesto 2012:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 8:2, descripción del rotámero principal; δ 12,29 (s, 1H), 8,54 (s, 1H), 8,08 (br s, 1H), 8,04 (d, J = 9,0 Hz, 1H), 7,44 (br s, 1H), 7,25 (d, J = 9,2 Hz, 1H), 6,08-5,90 (m, 2H), 5,80-5,65 (m, 1H), 5,45-5,37 (m, 1H), 5,22-5,13 (m, 1H), 5,09-5,02 (m, 1H), 4,48-4,34 (m, 2H), 4,26-4,19 (m, 1H), 4,04-3,90 (m, 1H), 3,93 (s, 3H), 2,60 (s, 3H), 2,68-2,57 (m, 1H), 2,42-2,35 (m, 2H), 2,28-2,18 (m, 1H), 2,08-1,98 (m, 1H), 1,81-1,21 (m, 10H), 1,19 (s, 3H), 1,04 (s, 9H), 0,96 (s, 9H).

M.S. (electroaspersión): 844,5 $(M-H)^-$ 846,5 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 99%



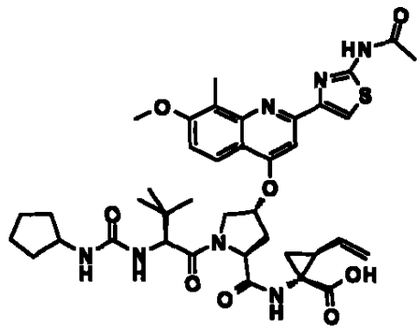
Compuesto 2002

Compuesto 2002:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 8:2, descripción del rotámero principal; δ 8,57 (s, 1H), 8,28-7,77 (m, 3H), 7,66-7,30 (m, 2H), 6,09-5,98 (m, 1H), 5,96-5,86 (m, 1H), 5,78-5,66 (m, 1H), 5,61-5,48 (m, 1H), 5,26-5,15 (m, 1H), 5,11-5,03 (m, 1H), 4,53-4,39 (m, 2H), 4,25-4,15 (m, 1H), 4,05-3,93 (m, 1H), 3,97 (s, 3H), 3,92-3,50 (m, bajo

H2O, 2H), 2,55 (s, 3H), 2,59-2,42 (m, 1H), 2,36-2,26 (m, 1H), 2,18-1,99 (m, 1H), 1,80-1,36 (m, 7H), 1,27 (d, J = 6,3 Hz, 6H), 1,31-1,05 (m, 3H), 0,95 (s, 9H).

M.S. (electroaspersión): 774,4 $(M-H)^-$ 776,5 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 94%

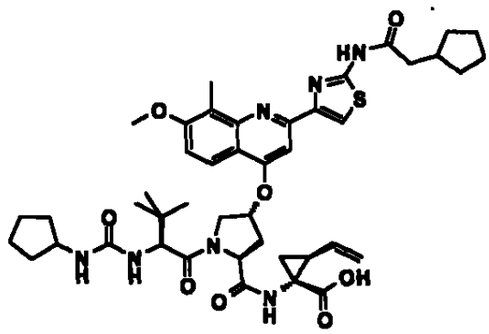


Compuesto 2007

Compuesto 2007:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 8:2, descripción del rotámero principal; δ 12,38 (s, 1H), 8,55 (s, 1H), 8,09 (br s, 1H), 8,06 (d, J = 9,2 Hz, 1H), 7,44 (s, 1H), 7,28 (d, J = 9,2 Hz, 1H), 6,12-6,01 (m, 1H), 5,98-5,89 (m, 1H), 5,78-5,66 (m, 1H), 5,46-5,38 (m, 1H), 5,23-5,15 (m, 1H), 5,10-5,01 (m, 1H), 4,47-4,36 (m, 2H), 4,28-4,20 (m, 1H), 4,04-3,92 (m, 1H), 3,94 (s, 3H), 3,90-3,50 (m, bajo H2O, 1H), 2,60 (s, 3H), 2,55-2,47 (m, 1H), 2,31-2,22 (m, 1H), 2,20 (s, 3H), 2,08-1,99 (m, 1H), 1,81-1,38 (m, 7H), 1,31-1,09 (m, 3H), 0,96 (s, 9H).

M.S. (electroaspersión): 774,4 $(M-H)^-$ 776,4 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 94%



Compuesto 2008

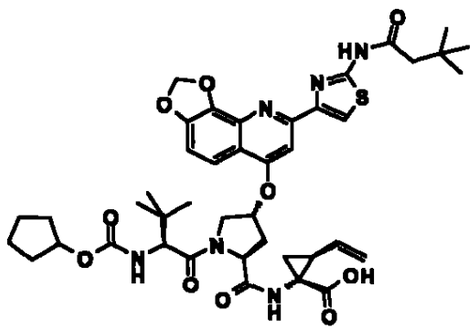
Compuesto 2008:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 8:2, descripción del rotámero principal; δ 12,34 (br s, 1H), 8,55 (s, 1H), 8,17-8,05 (m, 1H), 8,07 (d, J = 9,2 Hz, 1H), 7,50-7,42 (m, 1H), 7,28 (d, J = 9,2 Hz, 1H), 6,11-6,01 (m, 1H), 5,98-5,88 (m, 1H), 5,78-5,66 (m, 1H), 5,46-5,38 (m, 1H), 5,24-5,14 (m, 1H), 5,10-5,01 (m, 1H), 4,48-4,36 (m, 2H), 4,28-

4,20 (m, 1H), 4,07-3,95 (m, 1H), 3,94 (s, 3H), 3,80-3,65 (m, bajo H2O, 1H), 2,60 (s, 3H), 2,60-2,50 (m, 1H), 2,31-2,20 (m, 2H), 2,08-1,98 (m, 1H), 1,82-1,37 (m, 15H), 1,31-1,07 (m, 5H), 0,96 (s, 9H).

M.S. (electroaspersión): 842,5 $(M-H)^-$ 844,5 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 97%

Compuestos de la Tabla 3

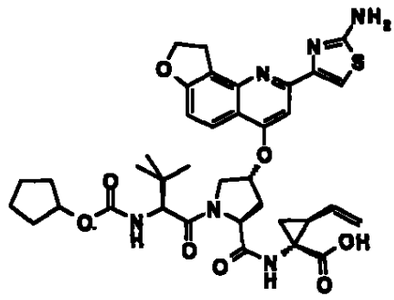


Compuesto 3002

Compuesto 3002:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 12,33 (s, 1H), 8,55 (s, 1H), 7,98 (s, 1H), 7,75 (d, J = 8,6 Hz, 1H), 7,40 (s, 1H), 7,19 (d, J = 8,8 Hz, 1H), 6,99 (d, J = 8,6 Hz, 1H), 6,26 (s, 2H), 5,79-5,66 (m, 1H), 5,46-5,38 (m, 1H), 5,23-5,14 (m, 1H), 5,10-5,01 (m, 1H), 4,76-4,67 (m, 1H), 4,47-4,30 (m, 2H), 4,11 (d, J = 8,8 Hz, 1H), 4,00-3,91 (m, 1H), 2,41-2,36 (m, 2H), 2,29-2,19 (m, 1H), 2,08-1,97 (m, 1H), 1,82-1,22 (m, 11H), 1,03 (s, 9H), 0,96 (s, 9H).

M.S. (electroaspersión): 831,5 $(M-H)^-$ 833,6 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 99%



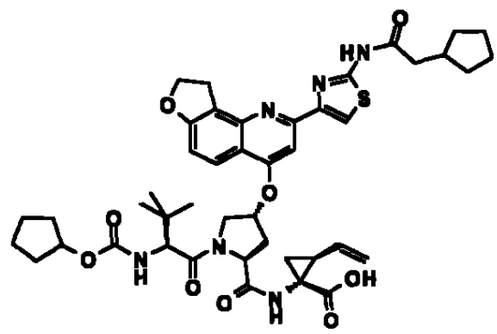
Compuesto 3007

Compuesto 3007:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 8,56 (s, 1H), 8,04 (d, J = 8,8 Hz, 1H), 7,94-7,64 (m, 3H), 7,49-7,37 (m, 1H), 7,09 (d, J = 8,4 Hz, 1H), 7,00 (d, J = 8,6 Hz, 1H), 5,80-5,66 (m, 1H), 5,58-5,46

(m, 1H), 5,24-5,14 (m, 1H), 5,11-5,01 (m, 1H), 4,85-4,70 (m, 2H), 4,69-4,58 (m, 1H), 4,49-4,81 (m, 2H), 4,09 (d, J = 8,6 Hz, 1H), 4,00-3,88 (m, 1H), 3,75-3,30 (m, bajo H2O, 2H), 2,35-2,22 (m, 1H), 2,07-1,97 (m, 1H), 1,81-1,20 (m, 11H), 0,97 (s, 9H).

M.S. (electroaspersión): 731,3 $(M-H)^-$ 733,3 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 94%

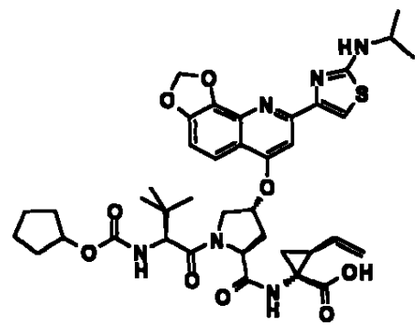


Compuesto 3010

Compuesto 3010:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, <u>descripción del rotámero principal</u>; δ 12,37 (s, 1H), 8,56 (s, 1H), 8,1$_{5-7}$,96 (m, 2H), 7,43 (s, 1H), 7,05 (d, J = 8,8 Hz, 1H), 7,00 (d, J = 8,6 Hz, 1H), 5,80-5,64 (m, 1H), 5,50-5,37 (m, 1H), 5,24-5,11 (m, 1H), 5,10-4,98 (m, 1H), 4,83-4,63 (m, 3H), 4,47-4,30 (m, 2H), 4,19-4,05 (m, 1H), 4,04-3,86 (m, 1H), 3,75-3,30 (m, bajo H2O, 2H), 2,34-2,19 (m, 3H), 2,07-1,97 (m, 1H), 1,82-1,13 (m, 20H), 0,97 (s, 9H).

M.S. (electroaspersión): 841,3 $(M-H)^-$ 843,4 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 99%



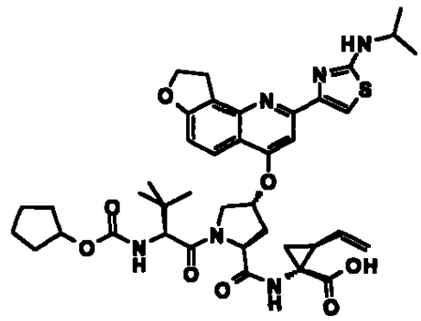
Compuesto 3001

Compuesto 3001:

^1H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, <u>descripción del rotámero principal</u>; δ 8,55 (s, 1H), 7,95-7,76 (m, 1H), 7,72 (d, J = 8,8 Hz, 1H), 7,49 (s, 1H), 7,41 (s, 1H), 7,18 (d, J = 8,6 Hz, 1H), 6,98 (d, J = 8,6 Hz, 1H), 6,25 (s, 2H), 5,80-5,65 (m,

1H), 5,52-5,46 (m, 1H), 5,24-5,14 (m, 1H), 5,10-5,01 (m, 1H), 4,75-4,66 (m, 1H), 4,48-4,39 (m, 1H), 4,37-4,27 (m, 1H), 4,17-4,07 (m, 1H), 4,01-3,92 (m, 1H), 3,90-3,75 (m, 1H), 2,62-2,44 (m, 1H), 2,31-2,20 (m, 1H), 2,09-1,97 (m, 1H), 1,81-1,20 (m, 10H), 1,25 (br d, J = 6,4 Hz, 6H), 0,96 (s, 9H).

M.S. (electroaspersión): 775,5 $(M-H)^-$ 777,6 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 99%



Compuesto 3004

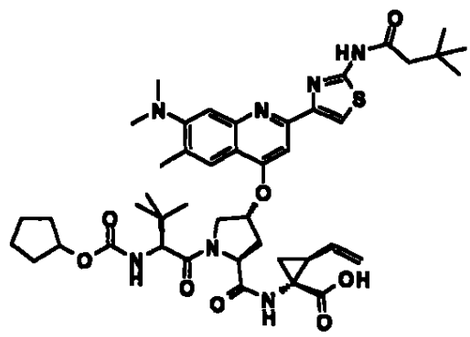
Compuesto 3004:

Mezcla de rotámeros (aprox. 85:15), ^1H RMN del rotámero principal dado (400 MHz, DMSO-d_6): δ 8,57 (s, 1H); 8,10 – 8,13 (m, 1H); 8,08 (d, J = 8,8 Hz, 1H) 7,86 – 7,88 (m, 2H); 7,53 (s, 1H); 7,14 (d, J = 8,5 Hz, 1H); 7,00 (d, J = 8,5, 1H); 5,68 – 5,78 (m, 1H); 5,57 (s, 1H); 5,19 (d, J = 17,0 Hz, 1H); 5,07 (d, J = 11,9 Hz, 1H); 4,78 – 4,82 (m , 2H); 4,58 – 4,63 (m, 1H); 4,35 – 4,47 (m, 2H); 3,87 – 4,08 (m, 8H); 3,58 – 3,62 (m, 2H); 2,53 – 2,56 (m, 1H); 2,27 – 2,33 (m, 1H); 1,99 – 2,04 (m, 1H); 1,43 – 1,65 (m, 4H); 1,28 – 1,30 (m, 1H); 1,26 (d, J = 6,2 Hz, 6H); 0,96 (s, 9H).

M.S. (electroaspersión): 775,4 $(M+H)^+$, 773,4 $(M-H)^-$.

Homogeneidad (0,06% de TFA; $CH_3CN:H_2O$): 98,8%

Compuestos de la Tabla 4

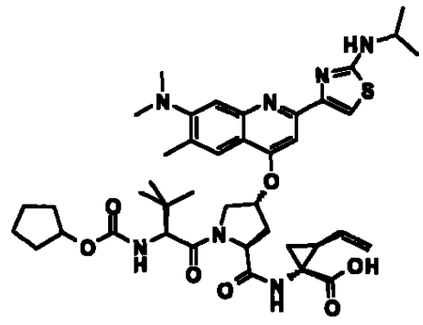


Compuesto 4005

Compuesto 4005:

^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 12,36 (br s, 1H), 8,57 (s, 1H), 8,60-8,20 (m, 1H), 7,90 (s, 1H), 7,68-7,45 (m, 2H), 6,99 (d, J = 8,3 Hz, 1H), 5,78-5,66 (m, 1H), 5,66-5,83 (m, 1H), 5,60-5,50 (m, 1H), 5,23-5,14 (m, 1H), 5,10-5,01 (m, 1H), 4,62-4,36 (m, 3H), 4,11-3,92 (m, 1H), 2,88 (s, 6H), 2,62-2,51 (m, 1H), 2,47 (s, 3H), 2,44-2,38 (m, 2H), 2,36-2,19 (m, 1H), 2,08-1,96 (m, 1H), 1,81-1,20 (m, 10H), 1,03 (s, 9H), 0,96 (s, 9H).

M.S. (electroaspersión): 844,4 $(M-H)^-$ 846,5 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; CH_3CN:H_2O): 99%

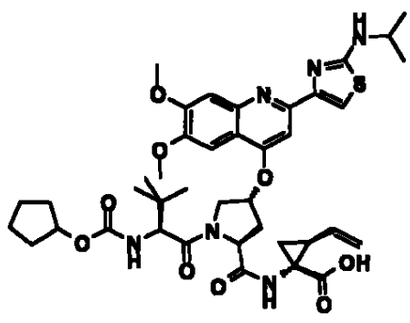


Compuesto 4007

Compuesto 4007:

^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 8,59 (s, 1H), 8,27-8,12 (m, 1H), 8,06-7,97 (m, 1H), 7,89 (s, 1H), 7,73 (s, 1H), 7,64 (s, 1H), 6,99 (d, J = 8,5 Hz, 1H), 5,79-5,64 (m, 2H), 5,24-5,14 (m, 1H), 5,10-5,01 (m, 1H), 4,54-4,38 (m, 2H), 4,23-4,08 (m, 1H), 4,02 (d, J = 8,4 Hz, 1H), 4,00-3,91 (m, 1H), 3,70-3,30 (m, bajo H2O, 1H), 2,90 (s, 6H), 2,64-2,52 (m, 1H), 2,46 (s, 3H), 2,38-2,26 (m, 1H), 2,07-1,96 (m, 1H), 1,81-1,20 (m, 10H), 1,24 (br d, J = 6,5 Hz, 6H), 0,95 (s, 9H).

M.S. (electroaspersión): 788,4 $(M-H)^-$ 790,5 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; CH_3CN:H_2O): 98%

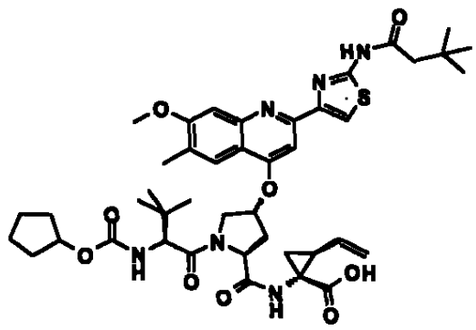


Compuesto 4014

Compuesto 4014:

^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 8,61 (s, 1H), 8,33-7,60 (m, 4H), 7,33 (s, 1H), 6,95 (d, J = 8,4 Hz, 1H), 5,79-5,67 (m, 2H), 5,24-5,16 (m, 1H), 5,10-5,03 (m, 1H), 4,57-4,32 (m, 2H), 4,20-3,88 (m, 3H), 3,99 (s, 3H), 3,93 (s, 3H), 3,65-3,30 (m, bajo H2O, 1H), 2,65-2,55 (m, 1H), 2,40-2,28 (m, 1H), 2,08-1,98 (m, 1H), 1,81-1,21 (m, 10H), 1,25 (br d, J = 6,5 Hz, 6H), 0,95 (s, 9H).

M.S. (electroaspersión): 791,3 $(M-H)^-$ 793,4 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; CH_3CN:H_2O): 86%

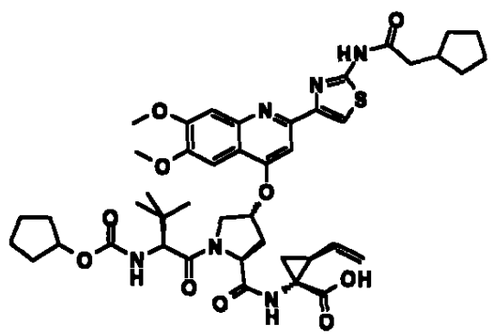


Compuesto 4001

Compuesto 4001:

^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 12,40 (s, 1H), 8,58 (s, 1H), 8,50-8,20 (m, 1H), 7,95 (br s, 1H), 7,72-7,44 (m, 2H), 7,00 (d, J = 8,2 Hz, 1H), 5,80-5,67 (m, 1H), 5,67-5,51 (m, 1H), 5,24-5,14 (m, 1H), 5,12-5,02 (m, 1H), 4,63-4,45 (m, 2H), 4,45-4,36 (m, 1H), 4,14-3,93 (m, 2H), 3,99 (s, 3H), 2,64-2,46 (m, 1H), 2,45-2,39 (m, 2H), 2,35 (s, 3H), 2,39-2,28 (m, 1H), 2,08-1,98 (m, 1H), 1,82-1,23 (m, 10H), 1,04 (s, 9H), 0,97 (s, 9H).

M.S. (electroaspersión): 831,4 $(M-H)^-$ 833,5 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; CH_3CN:H_2O): 99%



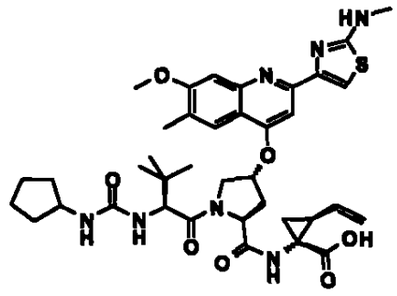
Compuesto 4013

Compuesto 4013:

^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal: δ. 12,36 (s, 1H), 8,59 (s, 1H), 8,36-7,96 (m, 1H), 7,70-7,42 (m, 2H), 7,32 (s, 1H), 6,94 (d, J = 8,2 Hz, 1H), 5,79-5,66 (m, 1H), 5,63-5,50 (m, 1H), 5,23-5,15 (m, 1H), 5,10-5,02 (m, 1H), 4,58-4,45 (m, 2H), 4,38-4,28 (m, 1H), 4,12-3,90 (m, 2H), 3,97 (s, 3H), 3,91 (s, 3H), 2,62-2,52 (m, 1H), 2,37-2,21 (m, 3H), 2,08-1,98 (m, 1H), 1,77-1,14 (m, 19H), 0,97 (s, 9H).

M.S. (electroaspersión): 859,4 $(M-H)^-$ 861,4 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; CH_3CN:H_2O): 92%

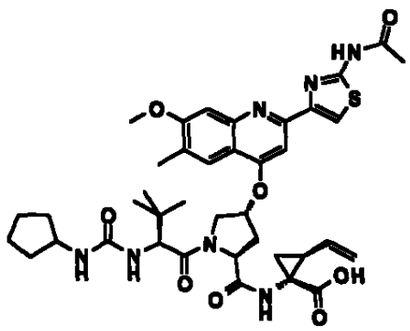
Compuestos de la Tabla 5



Compuesto 5001

Compuesto 5001:

^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal: δ 8,60 (s, 1H), 8,34-8,19 (m, 1H), 8,04-7,98 (m, 1H), 7,97 (s, 1H), 7,91-7,81 (m, 1H), 7,73 (s, 1H), 5,99-5,91 (m, 1H), 5,90-5,83 (m, 1H), 5,78-5,66 (m, 2H), 5,25-5,15 (m, 1H), 5,11-5,04 (m, 1H), 4,58-4,46 (m, 2H), 4,15-4,07 (m, 1H), 4,00 (s, 3H), 4,03-3,94 (m, 1H), 3,60-3,15 (m, bajo H2O, 1H), 3,05 (d, J = 4,3 Hz, 3H), 2,63-2,55 (m, 1H), 2,42-2,30 (m, 1H), 2,35 (m, 3H), 2,08-1,99 (m, 1H), 1,80-1,22 (m, 9H), 1,13-1,03 (m, 1H), 0,94 (s, 9H). M.S. (electroaspersión): 746,3 $(M-H)^-$ 748,4 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; CH_3CN:H_2O): 99%



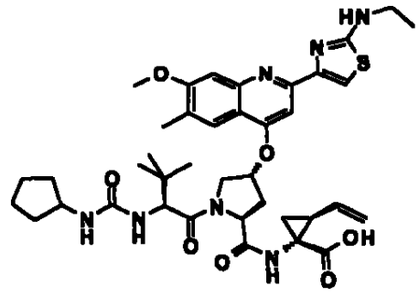
Compuesto 5002

306
308

Compuesto 5002:

^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 8:2, descripción del rotámero principal; δ 12,44 (s, 1H), 8,59 (s, 1H), 8,52-8,25 (m, 1H), 7,97 (s, 1H), 7,70-7,46 (m, 2H), 6,03-5,96 (m, 1H), 5,90 (d, J = 9,2 Hz, 1H), 5,79-5,66 (m, 1H), 5,64-5,54 (m, 1H), 5,24-5,16 (m, 1H), 5,11-5,04 (m, 1H), 4,55-4,43 (m, 2H), 4,19-4,12 (m, 1H), 4,05-3,94 (m, 1H), 3,99 (s, 3H), 3,80-3,30 (m, bajo H2O, 1H), 2,68-2,54 (m, 1H), 2,39-2,28 (m, 1H), 2,35 (s, 3H), 2,23 (s, 3H), 2,08-1,99 (m, 1H), 1,80-1,21 (m, 8H), 1,17-1,07 (m, 1H), 1,06-0,95 (m, 1H), 0,95 (s, 9H).

M.S. (electroaspersión): 774,4 $(M-H)^-$ 776,4 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; CH_3CN:H_2O): 99%



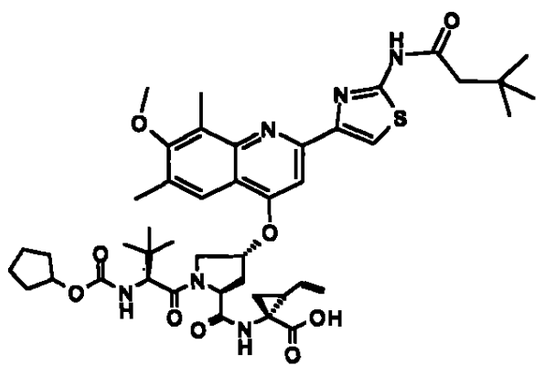
Compuesto 5004

Compuesto 5004:

^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; δ 8,60 (s, 1H), 8,31-8,16 (m, 1H), 8,11-8,02 (m, 1H), 7,97 (s, 1H), 7,89-7,78 (m, 1H), 7,75-7,67 (m, 1H), 6,00-5,92 (m, 1H), 5,90-5,83 (m, 1H), 5,80-5,65 (m, 2H), 5,26-5,16 (m, 1H), 5,11-5,04 (m, 1H), 4,58-4,46 (m, 2H), 4,11 (d, J = 9,2 Hz, 1H), 4,05-3,94 (m, 1H), 4,00 (s, 3H), 3,65-3,15 (m, bajo H2O, 3H), 2,69-2,54 (m, 1H), 2,42-2,30 (m, 1H), 2,35 (s, 3H), 2,08-1,99 (m, 1H), 1,80-1,21 (m, 8H), 1,24 (t, J = 7,0 Hz, 3H), 1,14-1,02 (m, 1H), 1,00-0,87 (m, 1H), 0,94 (s, 9H).

M.S. (electroaspersión): 760,4 $(M-H)^-$ 762,4 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; CH_3CN:H_2O): 96%.

Compuestos de la Tabla 6



Compuesto 6016

Compuesto 6016:

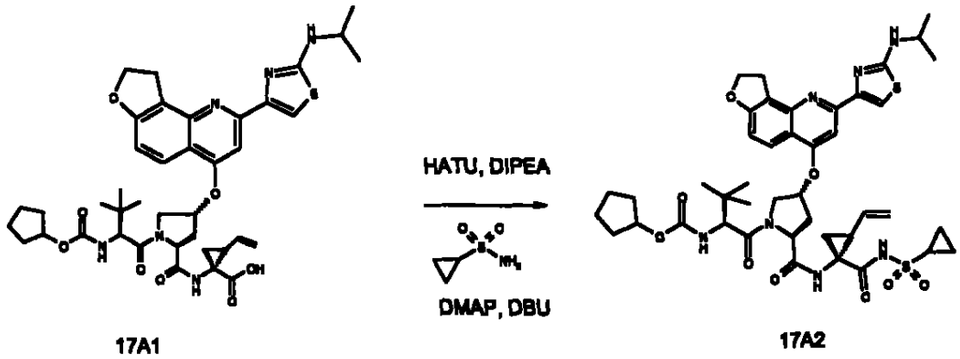
^{1}H RMN (400 MHz, DMSO-d_6): mezcla de rotámeros aprox. 85:15, descripción del rotámero principal; &12,28 (s, 2H); 8,56 (s, 1H); 8,04 (s, 1H) 7,79 (s, 1H); 7,46 (s, 1H); 6,96 – 7,00 (m, 1H); 5,68 – 5,75 (m, 1H); 5,40 (s, br, 1H); 5,19 (d, J = 17,0 Hz, 1H); 5,06 (d, J = 10,1 Hz, 1H); 4,71 – 4,76 (m , 2H); 4,43 (t, J = 8,3, 1H); 4,32 – 4,34 (m, 1H); 4,13 (d, J = 8,3 Hz, 1H); 3,96 – 4,03 (m, 1H); 3,77 (s, 3H); 2,67 (s, 3H); 2,40 (d, J = 4,1 Hz, 3H); 2,24 – 2,36 (m, 3H); 2,03 (q, J = 8,6 Hz, 1H); 1,17 - 1,75 (m, 10H); 1,04 (s, 9H); 0,98 (s, 9H).

M.S. (electroaspersión): 845,4 $(M-H)^-$ 847,5 $(M+H)^+$. Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; CH_3CN:H_2O): 96,7%

Síntesis de compuestos de fórmula I donde R^C es $NHSO_2R^8$:

Ejemplo 17A

Síntesis del compuesto 7001:



17A1 17A2

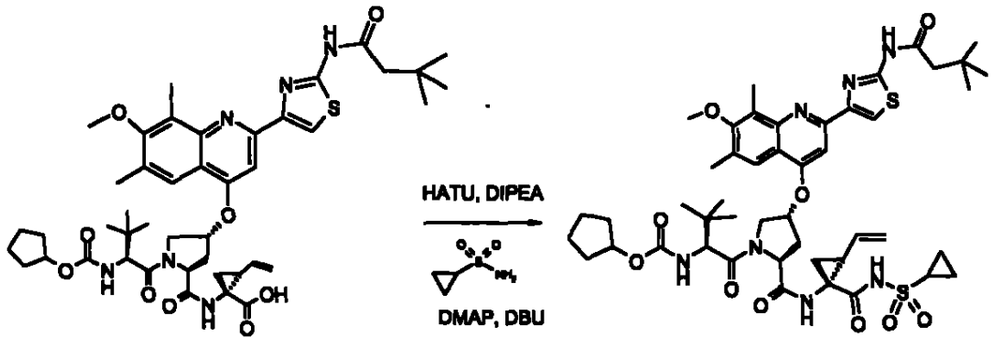
Se agregó HATU (20 mg, 0,05 mmol) a una solución de compuesto **17A1** (Compuesto 3004, Tabla 3; 20 mg, 0,03 mmol) y DIPEA (0,03 ml, 0,16 mmol) en DMF (1,5 ml) a TA. La solución se agitó durante 1h seguido de la adición de DMAP (16 mg, 0,13 mmol) y ciclopropansulfonamida (7,0 mg, 0,06 mmol). Una vez completa la adición,

se dejó agitar la mezcla durante 15 min y se agregó DBU (0,02 ml, 0,14 mmol) gota a gota. La solución resultante se agitó durante 16 h a 23°C, luego se diluyó con DMSO a 2,5 ml de volumen total y se purificó mediante HPLC preparativa (H_2O/CH_3CN + 0,06% de TFA). Las fracciones que contenían el producto puro se combinaron y los solventes se eliminaron mediante liofilización para dar **17A2** como un sólido amarillo (Compuesto 7001, tabla 7, 5,4 mg, 23%).

Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 98,9% (220 nm). MS: 878,8 $(M+H)^+$, 876,4 $(M-H)^-$. ^1H RMN (400 MHz, DMSO-d_6): δ 10,47 (s, 1H); 8,82 (s, 1H); 8,06 (s, br, 1H); 7,52 (s, br, 1H); 7,15 (m, 1H); 7,03 (d, J = 8,0 Hz, 1H); 5,58 (m, 2H); 5,20 (d, J = 17,0 Hz, 1H); 5,09 (d, J = 11,5, 1H); 4,79 (m, 2H); 4,64 (m, 1H); 4,36 – 4,52 (m, 2H); 4,06 (d, J = 8,0 Hz, 1H); 4,00 – 4,03 (m, 1H); 2,88 – 2,96 (m, 1H); 2,54 – 2,57 (m, 1H); 2,10 – 2,20 (m, 2H); 1,32 – 1,71 (m, 11H); 1,24 (dd, J = 6,3, 1,2 Hz, 6H); 1,00 – 1,08 (m, 8 H); 0,97 (s, 9H).

Ejemplo 17B

Síntesis del compuesto 7002:



17B1 17B2

Empleando el procedimiento del Ejemplo 17A pero comenzando con el compuesto 17B1 (Compuesto 6016, Tabla 6), se preparó el compuesto **17B2** (Compuesto 7002, Tabla 7) como un sólido amarillo claro (5,4 mg, 16% de rendimiento).

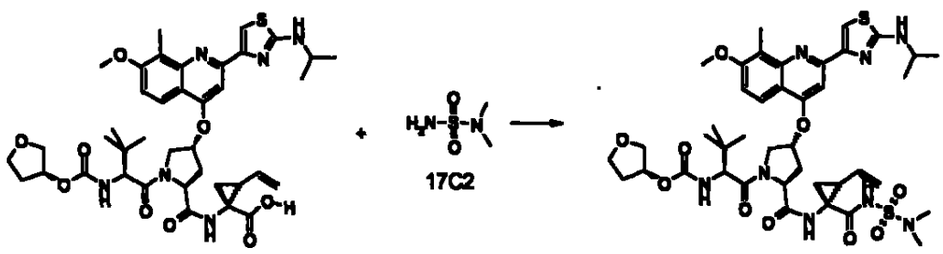
Homogeneidad de HPLC de Fase Reversa (0,06% de TFA; $CH_3CN:H_2O$): 93,1% (220 nm).

MS: 950,4 $(M+H)^+$, 948,4 $(M-H)^-$. ^1H RMN (400 MHz, DMSO-d_6): δ 12,26 (s, 1H); 10,48 (s, 1H); 8,83 (s, 1H); 8,02 (s, 1H); 7,79 (s, 1H); 7,45 (s, 1H); 6,94 – 7,00 (m, 1H); 5,56 – 5,65 (m, 1H); 5,40 (s, 1H); 5,19 (d, J = 16,9, 1H); 5,07 (d, J = 11,4, 1H); 4,77 (s, 1H); 4,33 – 4,42 (m, 2H); 4,11 (d, J = 8,0 Hz, 1H); 3,97 (d, J = 9,6, 1H); 3,76 (s, 3H); 3,76 (s, 3H); 2,88 – 2,96 (m, 1H); 2,66 (s, 3H); 2,53 – 2,60 (m, 1H); 2,31 – 2,33 (m, 1H); 2,11 – 2,19

(m, 2H); 1,33 – 1,70 (m, 12H); 1,22 (s, br, 1H); 1,05 – 1,08 (m, 2H); 1,02 (s, 9H); 0,98 (s, 9H).

Ejemplo 17C

Síntesis del compuesto 7003:



17C1 17C2 17C3

Se disolvieron compuesto **17C1** (Compuesto 1027, Tabla 1; 35 mg, 0,045 mmol), N,N-dimetilsulfamida **17C2** (22,3 mg, 0,180 mmol) DIPEA (39,3 µl, 0,225 mmol) y DMAP (22 mg, 0,180 mmol) en DMF (2,5 ml) y a la mezcla se agregó DBU (28,5 µl, 0,203 mmol). La mezcla de reacción se agitó durante 5 min, luego se agregó HATU (18,8 mg, 0,05 mmol). Se continuó la agitación durante 12h y el residuo se filtró a través del filtro Millex y se purificó mediante HPLC preparativa (Combiscreen ODS-AQ, 20 x 50mm). Las fracciones puras se combinaron y se liofilizaron para dar 14 mg (rendimiento, 35%) del compuesto **17C3** (Compuesto 7003, Tabla 7) como un sólido amarillo.

^{1}HRMN (400MHz, DMSO-d_6): δ 10,23 (s, 1H), 8,74 (s, 1H), 8,07 (d, J=8Hz, 1H), 7,59 (s, 1H), 7,45-7,30 (m, 1H), 7,27 (d, J=8Hz, 1H), 5,53-5,49 (m, 2H), 5,20 (d, J= 17Hz, 1H), 5,10 (d, J=12Hz, 1H), 4,70 (bs, 1H), 4,50-4,30 (m, 3H), 4,15-4,05 (m, 2H), 3,97 (s, 3H), 2,76 (s, 6H), 2,55 (s,3H), 2,38-2,32 (m,1H), 2,23-2,08 (m, 2H), 1,97-1,81 (m, 1H), 1,75-1,45 (m,4H), 1,32-1,14 (m,9H), 1,04-0,86 (m, 11H).

EIMS: (M+H) = 885,4, (M-H) = 883,4

Ejemplo 18

Ensayo de proteasa NS3-NS4A

El ensayo enzimático empleado para evaluar el presente compuesto se describe en WO 00/09543 y WO 00/59929.

Ejemplo 19

Ensayo de Replicación de ARN del VHC Basado en Células

Cultivo Celular

Se establecieron células Huh7 que mantienen de manera estable un replicón de VHC subgenómico según se describió anteriormente (Lohman et al., 1999, Science **285**: 110-113) y se denominaron línea celular S22.3. Las células de S22,3 se mantienen en

pocillos (COSTAR # 3997) y el volumen se completó para 100 µl con TE. En general, se empleó la columna 1 de la placa de 96 pocillos para la curva estándar y los otros pocillos se emplearon para cuantificar las muestras de ARN. 10 µl de cada muestra de ARN a cuantificar se transfirieron al pocillo correspondiente de la placa de 96 pocillos y se agregaron 90 µl de TE. Se agregó un volumen (100 µl) de reactivo RiboGreen diluido a cada pocillo de la placa de 96 pocillos y se incubó durante 2 a 5 minutos a temperatura ambiente, se protegió de la luz (una muestra de ARN de 10 µl en un volumen final de 200 µl genera una dilución de 20X). La intensidad de fluorescencia de cada pocillo se midió en el sistema STORM® (Molecular Dynamics®). Se creó una curva estándar en base a las cantidades conocidas del ARN ribosomal e intensidades fluorescentes resultantes. La concentración de ARN en las muestras experimentales se determinó a partir de la curva estándar y se corrigió para la dilución de 20X.

Reactivos y Materiales:

Producto	Compañía	Catálogo #	Almace-namiento
DEPC	Sigma	D5758	4°C
EDTA	Sigma	E5134	T.A.
Trizma-Base	Sigma	T8524	T.A.
Trizma-HCl	Sigma	T7149	T.A.
Tiras de Tubos de Recolección	Qiagen	19562	T.A.
Kit de Cuantificación de ARN Ribogreen	Sonda Molecular	R11490	-20°C
Kit Rneasy 96	Qiagen	74183	T.A.
Bloques de Pocillos cuadrados	Qiagen	19573	T.A.

R.T.-PCR en Tiempo Real

La R.T.-PCR en Tiempo Real se llevó a cabo en el Sistema de Detección de Secuencia ABI Prism 7700 empleando el kit de R.T.-PCR de TaqMan EZ (Perkin-Elmer Applied Biosystems®). La R.T.-PCR se optimizó para la cuantificación del 5' IRES del ARN del VHC empleando la tecnología de Taqman (Roche Molecular Diagnostics Systems) similar a la técnica descripta anteriormente (Martell et al., 1999, J. Clin. Microbiol. 37: 327-332). El sistema aprovecha la actividad nucleolítica de 5'-3' de la ADN polimerasa de AmpliTaq. En resumen, el método emplea una sonda de hibridación fluorogénica de doble rótulo (sonda PUTR) que se alinea específicamente al molde entre los cebadores de PCR (cebadores 8125 y 7028). El extremo 5' de la sonda contiene un indicador fluorescente (6-carboxifluoresceína [FAM]) y el extremo 3' contiene un

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373

desactivador fluorescente (6-carboxitetrametilrodamina [TAMRA]). El espectro de emisión del indicador FAM se suprimió mediante el desactivador en la sonda intacta de hibridación. La degradación de nucleasa de la sonda de hibridación libera al indicador, dando un incremento en la emisión de fluorescencia. El detector de secuencias ABI Prism 7700 mide el incremento en la emisión de fluorescencia continuamente durante la ampliación de PCR de manera que el producto ampliado sea directamente proporcional a la señal. El gráfico de amplificación se analizó de manera temprana en la reacción en un punto que representa la fase logarítmica de la acumulación del producto. Un punto que representa un umbral de detección definido del incremento en la señal fluorescente asociada con el crecimiento exponencial del producto de PCR para el detector de secuencia se definió como el umbral del ciclo (C_T). Los valores de C_T son inversamente proporcionales a la cantidad de ARN de entrada del VHC; de manera que en condiciones de PCR idénticas, cuanto mayor sea la concentración de partida del ARN del VHC, menor será el C_T. Se creó automáticamente una curva estándar mediante el sistema de detección ABI Prism 7700 graficando el C_T contra cada dilución estándar de la concentración del ARN del VHC conocida.

Las muestras de referencia para la curva estándar se incluyen en cada placa de R.T.-PCR. El ARN del replicón de VHC se sintetizó (mediante transcripción de T7) *in vitro*, se purificó y se cuantificó mediante DO_{260}. Considerando que 1 μg de este ARN = 2,15 X 10^{11} copias de ARN, se llevan a cabo diluciones para tener 10^8, 10^7, 10^6, 10^5, 10^4, 10^3 o 10^2 copias de ARN genómico/5 μL. También se incorporó ARN Total celular Huh-7 con cada dilución (50 ng/5 μl). Se combinaron 5 μl de cada estándar de referencia (Replicón del VHC + ARN Huh-7) con 45 μl de mezcla de reactivo y se empleó en la reacción de R.T.-PCR en Tiempo Real.

La reacción de R.T.-PCR en Tiempo Real se preparó para las muestras experimentales que se purificaron en placas de 96 pocillos RNeasy 96 combinando 5 μl de cada muestra de ARN total celular con 45 μl de mezcla de reactivo.

Reactivos y Materiales:

Producto	Compañía	**Catálogo #**	**Almacena-miento**
Kit de TaqMan EZ de R.T.-PCR	PE Applied Biosystems	N808-0236	-20°C
Tapas Ópticas MicroAmp	PE Applied Biosystems	N801-0935	T.A.
Placa Óptica de Reacción de 96 pocillos MicroAmp	PE Applied Biosystems	N801-0560	T.A.

314
314

Preparación de Mezcla del Reactivo:

Componente	Volumen para una muestra (µl)	Volumen para una Placa (µl) (91 muestras + volumen de carga)	Conc. final
Agua libre de Rnasa	16,5	1617	
buffer TaqMan EZ 5X	10	980	1X
$Mn(OAc)_2$ (25 mM)	6	588	3 mM
dATP (10 mM)	1,5	147	300 µM
dCTP (10 mM)	1,5	147	300 µM
dGTP (10 mM)	1,5	147	300 µM
dUTP (20 mM)	1,5	147	600 µM
Cebador delantero (10 µM)	1	98	200 nM
Cebador inverso (10 µM)	1	98	200 nM
Sonda PUTR (5 µM)	2	196	200 nM
ADN Polimerrasa de rTth (2,5 U/µl)	2	196	0,1 U/µl
AmpErase UNG (1U/µl)	0,5	49	0,01 U/µl
Volumen Total	45	4410	

Secuencia del Cebador Delantero (SEC ID. 1): 5' - ACG CAG AAA GCG TCT AGC CAT GGC GTT AGT - 3'

Secuencia del Cebador Inverso (SEC ID NO. 2): 5' - TCC CGG GGC ACT CGC AAG CAC CCT ATC AGG - 3'

Nota: Aquellos cebadores amplifican una región de 256 nucleótidos presente en la región no traducida de 5' del VHC.

Secuencia de la Sonda PUTR (SEC ID NO. 3): [6FAM] - TGG TCT GCG GAA CCG GTG AGT ACA CC - [TAMRA]

Sin Controles de Molde (NTC): En cada placa, se emplearon 4 pocillos como "NTC". Para estos controles, se agregaron 5 µl de agua al pocillo en lugar del ARN.

Condiciones Térmicas de Ciclo:

50°C 2 min

60°C 30 min

95°C 5 min
95°C 15 seg
60°C 1 min } para 2 ciclos
90°C 15 seg
60°C 1 min } para 40 ciclos

A continuación de la terminación de la reacción de R.T.-PCR, el análisis de datos requiere determinar la señal de fluorescencia umbral para la placa de PCR y se construyó una curva estándar graficando el valor de C_T contra el número de copias de ARN empleado en cada reacción de referencia. Los valores de C_T que se obtuvieron para las muestras de ensayo se emplearon para interpolar un número de copias de ARN basado en la curva estándar.

Finalmente, el número de copias de ARN se normalizó (en base a la cuantificación de ARN de RiboGreen del ARN total que se extrajo del pocillo de cultivo celular) y se expresó como equivalentes del genoma/µg de ARN total [g.e./µg].

El número de copias de ARN [g.e./µg] de cada pocillo de la placa de cultivo celular fue una medida de la cantidad de ARN del VHC en replicación en presencia de diversas concentraciones del inhibidor. El % de inhibición se calculó con la siguiente ecuación: *100 - [(g.e./µg inh)/(g.e./µg ctl)x 100].*

Se aplicó una curva no lineal ajustada al modelo Hill a los datos de inhibición-concentración y se calculó la concentración efectiva de 50% (EC_{50}) empleando el software SAS (Statistical Software System; SAS Institute, Inc. Cary, N.C.).

Cuando se evalúan los compuestos de la presente invención en los ensayos enzimáticos y basados en células anteriores, se descubre que los compuestos son sumamente activos.

Ejemplo 20

Ensayos de especificidad

Los ensayos de especificidad empleados para evaluar la selectividad de este compuesto se describe en WO 00/09543.

Cuando se evaluaron los compuestos en los ensayos de especificidad, se descubrió que los compuestos de fórmula 1 son selectivos en el sentido que no muestran inhibición significativa (sin actividad mensurable en concentraciones de hasta 30 µM) en los ensayos de Elastasa de Leucocitos Humanos y Catepsina B.

Ejemplo 21

Propiedades farmacocinéticas

La presente invención comprende compuestos que muestran propiedades farmacocinéticas tales como niveles plasmáticos detectables en rata 1 hora y 2 horas después de la dosis oral de 5 mg/kg.

De manera más explícita, el siguiente ensayo, una exploración de absorción oral *in vivo*, se emplea para determinar niveles plasmáticos de compuestos de prueba en rata con posterioridad a la administración oral:

Materiales y Métodos:

1. **Método empleado para agrupar compuestos ("selección de casetes"):**

La selección de compuestos a agrupar en un "casete" se basó en su similitud estructural y propiedades fisicoquímicas. Se estableció un método de extracción de fase sólida que se puede aplicar a todos los compuestos seleccionados. En base al análisis inicial donde cada compuesto se insertó en plasma de rata y se corrió a través de HPLC o HPLC/MS a una concentración de 0,5 µM, se emplearon el tiempo de retención, masa iónica y la posible separación entre compuestos mediante HPLC y/o HPLC/MS como base para agrupar 3-4 compuestos en un "casete".

2. **Vehículo oral y preparación del compuesto:**

Cada "casete" contiene 3-4 compuestos a razón de 5 o 4 mg/kg para cada compuesto. Los casetes se prepararon como una suspensión oral en de metilcelulosa acuosa 0,5% y monooleato de de polioxietilen (20) sorbitán 0,3% (Tween-80). El volumen de dosis fue de 10 ml/kg mediante sonda oral.

3. **Dosificación y muestreo del plasma:**

Se hizo ayunar ratas macho Sprague Dawley hasta el día siguiente en jaulas individuales, con acceso a dextrosa acuosa 10%. Con cada "casete" se administró dosis a dos ratas. Las muestras de plasma (~1 ml) se recolectaron 1 y 2 h posteriores a proporcionar la dosis de las dos ratas y se combinaron para extracción y análisis.

4. **Extracción y análisis de compuestos:**

De cada casete se extrajeron muestras de plasma de las horas 1 y 2, plasma en blanco, plasma en blanco con todos los compuestos inoculados a razón de 0,5 µM de cada uno, a través del método de extracción de fase sólida. Las muestras se analizaron mediante HPLC y HPLC/MS con fines comparativos. Las concentraciones plasmáticas se estiman en base a la única concentración de estándar de 0,5 µM.

Resultados

Cuando se analizan en la exploración anterior, algunos compuestos de la presente invención se encuentran en el plasma en los intervalos de 1 y 2 horas a

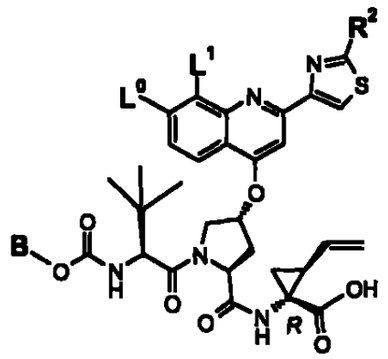
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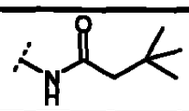
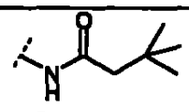
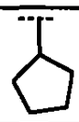
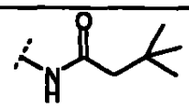
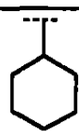
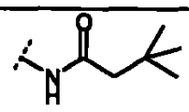
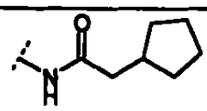
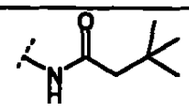
continuación de la administración oral, con niveles plasmáticos en sangre de hasta 1,5 µM.

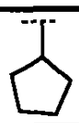
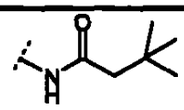
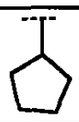
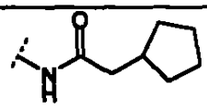
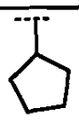
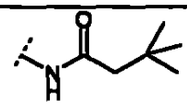
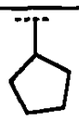
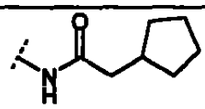
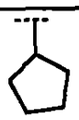
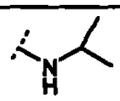
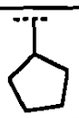
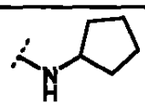
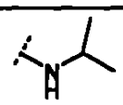
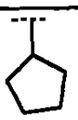
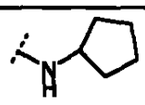
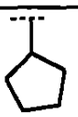
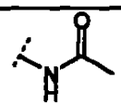
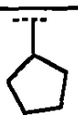
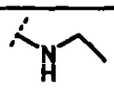
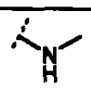
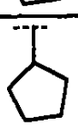
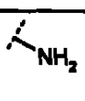
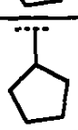
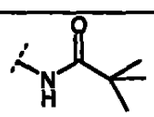
Tablas de Compuestos

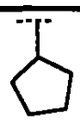
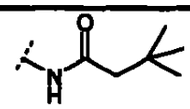
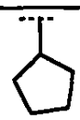
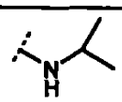
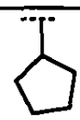
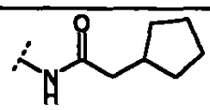
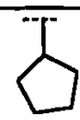
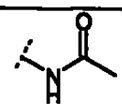
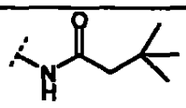
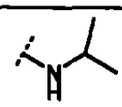
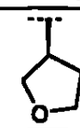
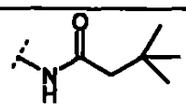
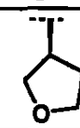
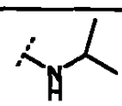
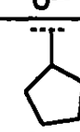
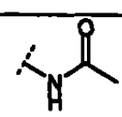
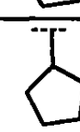
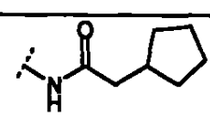
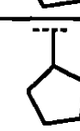
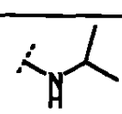
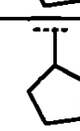
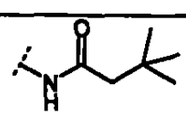
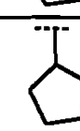
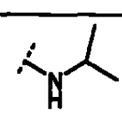
Los siguientes ejemplos de compuestos de acuerdo con la presente invención se enumeran en las Tablas 1 a 7, donde Me define metilo, Et define etilo y tBu define *ter*-butilo. Los compuestos de acuerdo con la presente invención comúnmente muestran valores de IC_{50} inferiores a alrededor de 200 nM y valores de EC_{50} inferiores a alrededor de 300 nM.

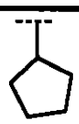
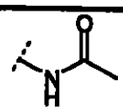
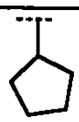
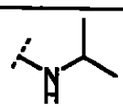
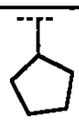
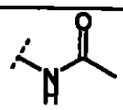
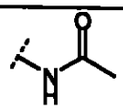
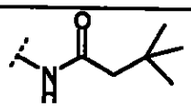
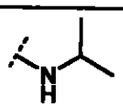
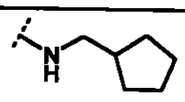
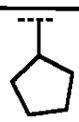
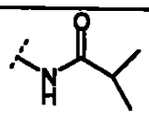
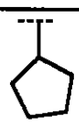
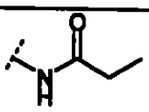
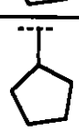
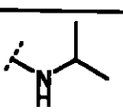
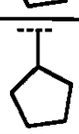
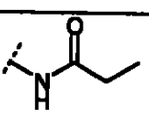
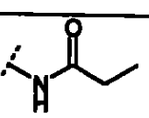
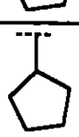
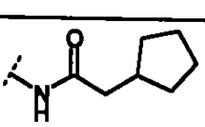
TABLA 1

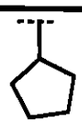
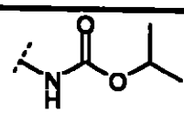
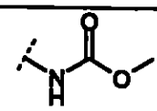
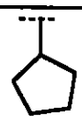
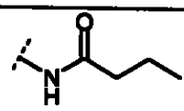
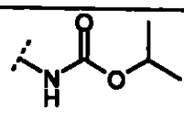
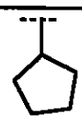
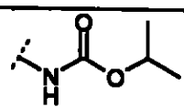
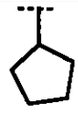
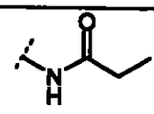
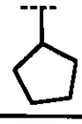
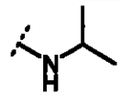
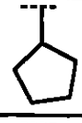
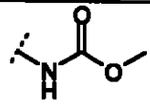
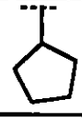
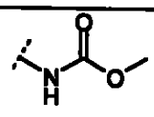
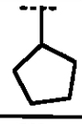
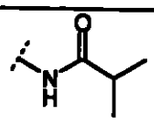
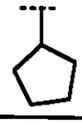
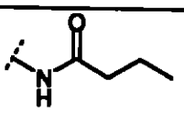
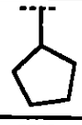
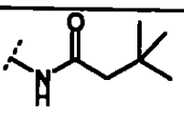
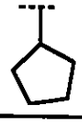
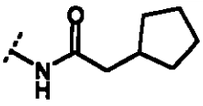


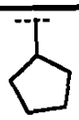
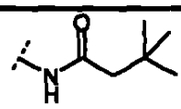
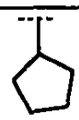
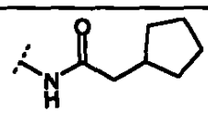
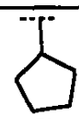
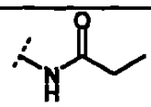
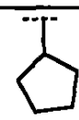
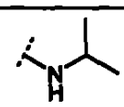
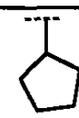
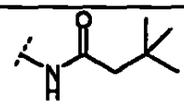
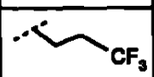
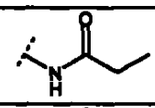
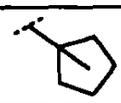
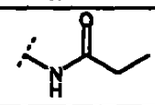
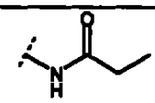
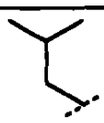
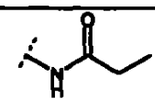
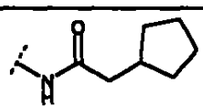
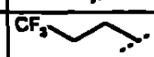
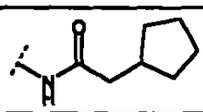
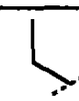
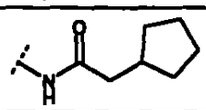
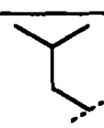
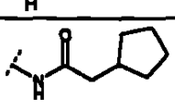
Comp.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1001		MeO-	MeO-		837,3
1002		MeO-	MeO-		835,3
1003		MeO-	MeO-		849,3
1004		MeO-	MeO-		863,4
1005		MeO-	Me-		831,4
1006		MeO-	Me-		819,5

Comp.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1007		MeO-	Me-		833,5
1008		MeO-	Me-		845,5
1009		Me_2N-	Me-		846,5
1010		Me_2N-	Me-		858,5
1011		Me_2N-	Me-		790,5
1012		Me_2N-	Me-		816,5
1013		MeO-	Me-		777,5
1014		MeO-	Me-		803,5
1015		MeO-	Me-		777,5
1016		MeO-	Me-		763,5
1017		MeO-	Me-		749,5
1018		MeO-	Me-		735,4
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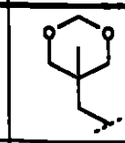
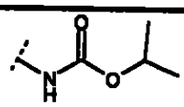
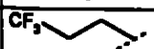
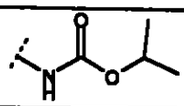
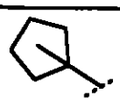
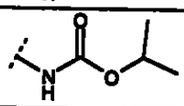
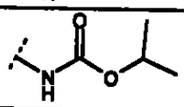
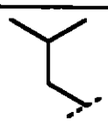
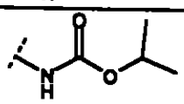
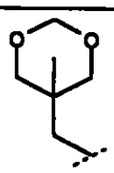
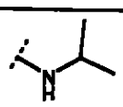
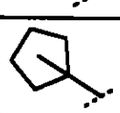
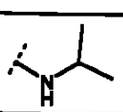
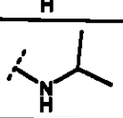
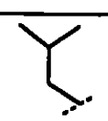
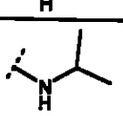
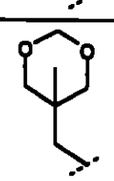
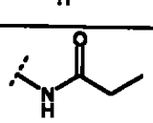
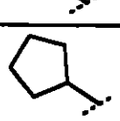
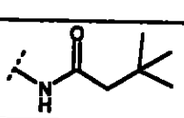
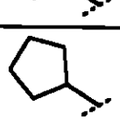
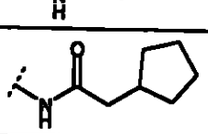
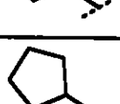
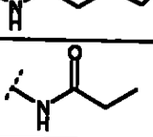
Comp.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1020		MeO-	Et-		847,5
1021		MeO-	Et-		791,4
1022		MeO-	Et-		859,5
1023		MeO-	Et-		791,4
1024		MeO-	Me-		811,4
1025		MeO-	Me-		755,5
1026		MeO-	Me-		835,4
1027		MeO-	Me-		779,3
1028		MeO-	Br-		841,3 843,2
1029		MeO-	Br-		911,3 909,3
1030		MeO-	Br-		841,3 843,3
1031		MeO-	Br-		897,3 899,3
1032		tBuO-	Me-		819,4

Comp.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1033		tBuO-	Me-		819,4
1034		HO-	Me-		763,4
1035		HO-	Me-		763,3
1036		MeO-	Me-		791,4
1037		MeO-	Me-		847,5
1038		MeO-	Me-		791,5
1039		MeO-	Me-		859,5
1040		MeO-	Me-		805,4
1041		MeO-	Me-		791,4
1042		MeO-	Cl		797,4 799,3
1043		MeO-	Br		855,2 857,2
1044		MeO-	Cl		811,3 813,3
1045		MeO-	Cl		865,4 867,4

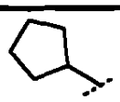
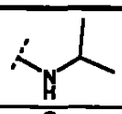
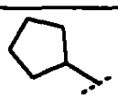
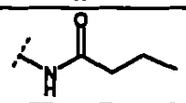
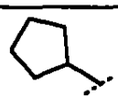
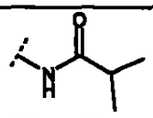
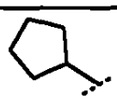
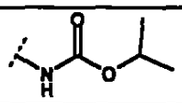
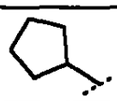
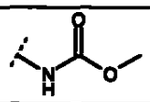
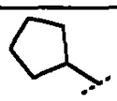
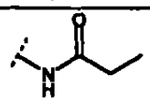
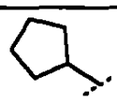
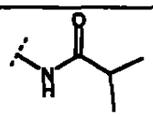
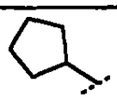
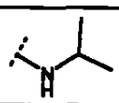
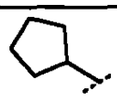
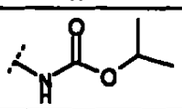
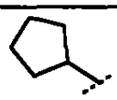
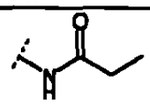
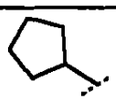
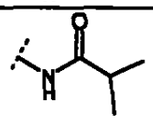
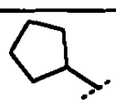
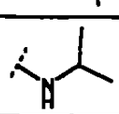
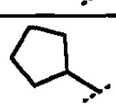
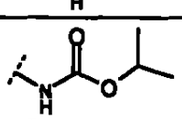
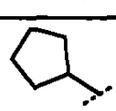
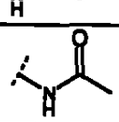
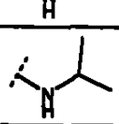
Comp.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1046		MeO-	Me-		821,4
1047		MeO-	Me-		793,4
1048		MeO-	Cl		825,3 827,3
1049		MeO-	Br		885,3 887,3
1050		MeO-	Cl		841,3 843,3
1051		MeO-	F		795,3
1052		MeO-	F		781,3
1053		MeO-	Cl		813,2 815,2
1054		MeO-	Br		857,2 859,2
1055		MeO-	Br		869 871,1
1056		MeO-	Br		869 871,1
1057		HO	Me		819,2
1058		HO	Me		831,2

Comp.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1059		H	Br		867 869
1060		H	Br		879 881
1061		H	Br		825 827
1062		H	Br		811 813
1063		F	Me		821,3
1064		MeO-	Br		883,2 885,2
1065		MeO-	Br		869,3 871,3
1066		MeO-	Br		815,2 817,2
1067		MeO-	Br		843,3 845,3
1068		MeO-	Br		955,3 957,3
1069		MeO-	Br		937,3 939,3
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1071		MeO-	Br		897,3 899,3

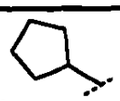
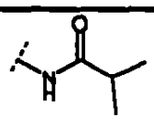
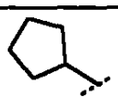
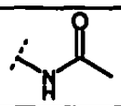
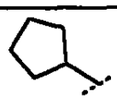
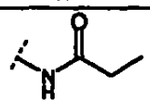
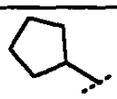
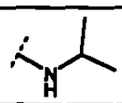
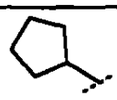
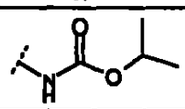
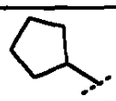
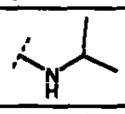
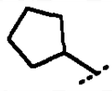
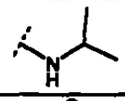
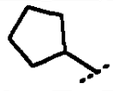
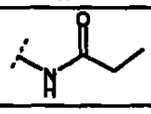
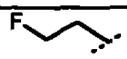
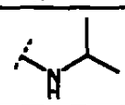
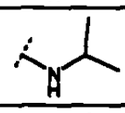
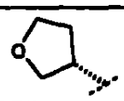
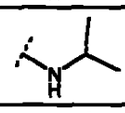
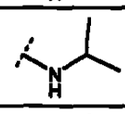
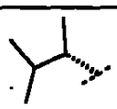
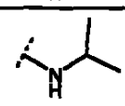
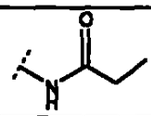
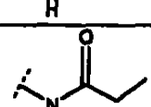
300
323

Comp.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1072		MeO-	Br		931,3 933,3
1073		MeO-	Br		913,2 915,2
1074		MeO-	Br		899,3 901,3
1075		MeO-	Br		845,2 847,2
1076		MeO-	Br		873,3 875,3
1077		MeO-	Br		887,2 889,2
1078		MeO-	Br		855,2 857,2
1079		MeO-	Br		801,2 803,2
1080		MeO	Br		829,2 831,2
1081		MeO	Br		901,3 903,3
1082		H	Cl		823,3 825,3
1083		H	Cl		835,3 837,3
1084		H	Cl		781,2 783,2

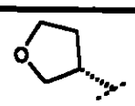
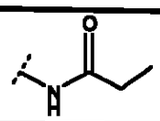
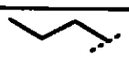
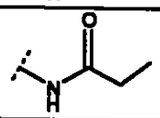
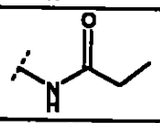
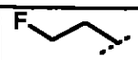
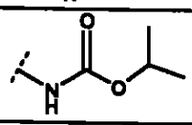
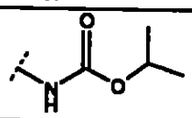
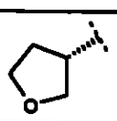
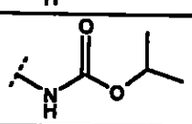
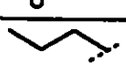
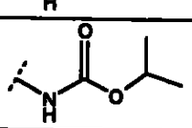
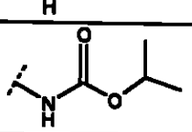
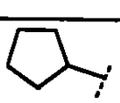
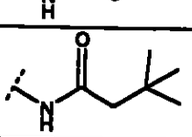
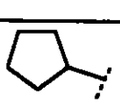
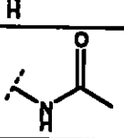
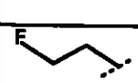
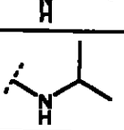
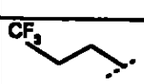
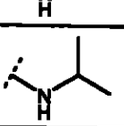
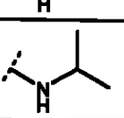
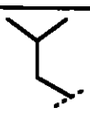
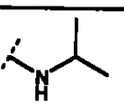
324

Comp.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1085		H	Cl		767,2 769,2
1086		H	Cl		795,2 797,2
1087		H	Cl		795,2 797,2
1088		H	Cl		811,2 813,2
1089		H	Cl		783,2
1090		EtO-	Br		869,2 871,2
1091		EtO-	Br		883,2 885,2
1092		EtO-	Br		855,2 857,2
1093		EtO-	Br		899,2 901,2
1094		PrO-	Br		883,2 885,2
1095		PrO-	Br		897,2 899,2
1096		PrO-	Br		869,2 871,2
1097		PrO-	Br		913,2 915,2
1098		H	Br		811 813
1099		MeO-	Br		869,2 871,1

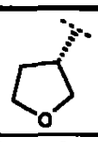
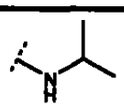
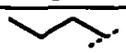
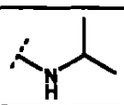
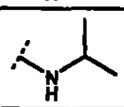
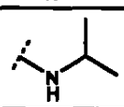
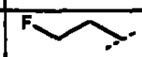
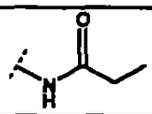
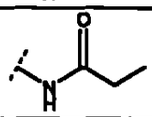
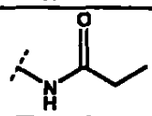
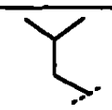
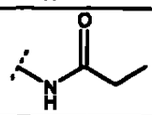
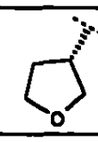
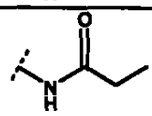
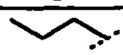
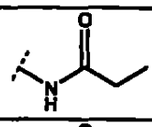
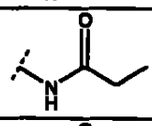
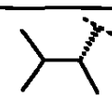
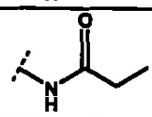
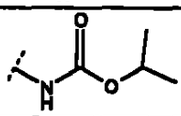
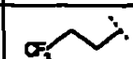
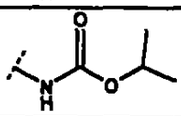
328
325

Comp.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1100		MeO-	Cl		825,2 827,2
1101		EtO-	Me		791,2
1102		EtO-	Me		805,2
1103		EtO-	Me		791,2
1104		EtO-	Me		835,3
1105		MeO-	CN		786,2
1106		Br	MeO-		841,2 843,2
1107		MeO-	CN		800,2
1108		MeO-	Br		819,1 821,1
1109		MeO	Br		833,1 835,2
1110		MeO-	Br		843,2 845,2
1111		MeO-	Br		815,2 817,2
1112		MeO-	Br		843,2 845,2
1113		MeO-	Br		833,1 835,1
1114		MeO	Br		847,2 849,2

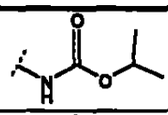
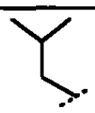
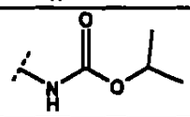
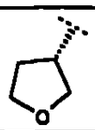
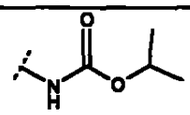
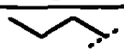
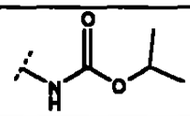
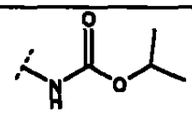
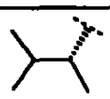
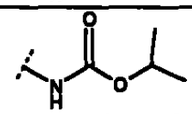
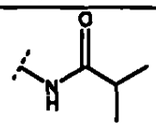
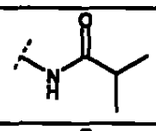
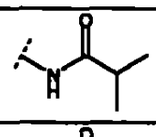
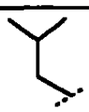
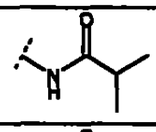
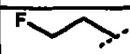
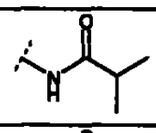
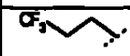
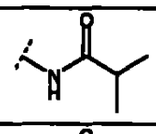
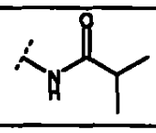
383
326

Comp.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1115		MeO-	Br		857,2 859,2
1116		MeO	Br		829,2 831,2
1117		MeO	Br		857,2 859,2
1118		MeO	Br		863,2 865,2
1119		MeO	Br		877,2 879,2
1120		MeO	Br		887,2 889,2
1121		MeO	Br		859,2 861,2
1122		MeO	Br		887,2 889,2
1123		MeO	CN		842,2
1124		MeO	CN		786,2
1125		MeO-	Cl		775,4 777,3
1126		MeO-	Cl		825,4 827,4
1127		MeO	Cl		757,4 759,4
1128		MeO	Cl		785,4 787,4

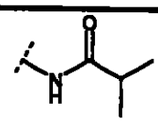
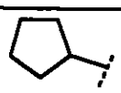
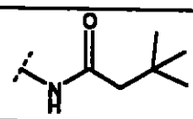
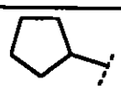
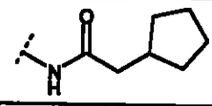
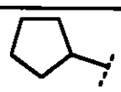
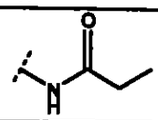
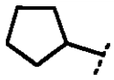
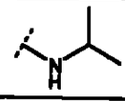
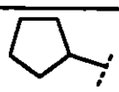
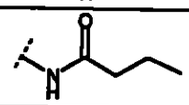
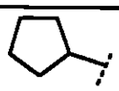
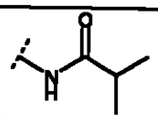
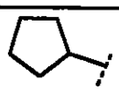
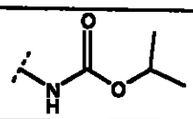
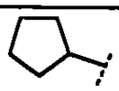
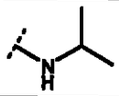
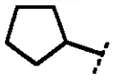
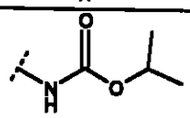
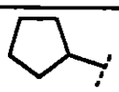
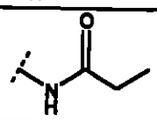
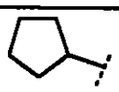
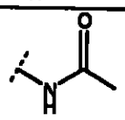
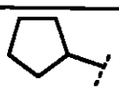
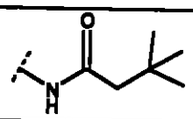
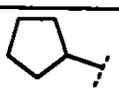
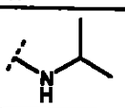
324
327

Comp.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1129		MeO	Cl		799,3 801,3
1130		MeO	Cl		771,3 773,3
1131		MeO	Cl		789,3 791,3
1132		MeO	Cl		799,5 801,4
1133		MeO	Cl		789,4 791,4
1134		MeO	Cl		839,4 841,4
1135		MeO	Cl		771,4 773,4
1136		MeO	Cl		799,4 801,4
1137		MeO	Cl		813,3 815,3
1138		MeO	Cl		785,3 787,3
1139		MeO	Cl		803,3 805,3
1140		MeO	Cl		813,5 815,4
1141		MeO	Cl		819,4 821,4
1142		MeO	Cl		869,4 871,4

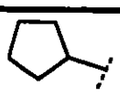
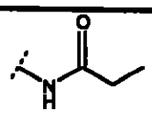
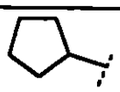
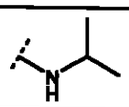
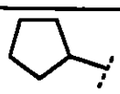
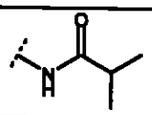
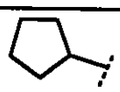
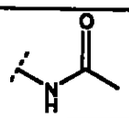
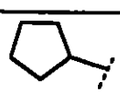
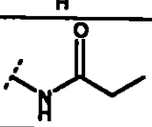
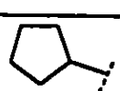
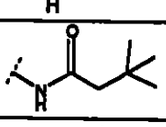
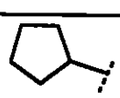
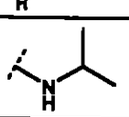
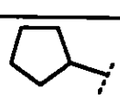
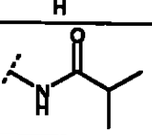
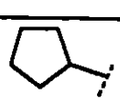
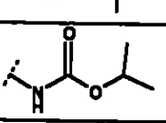
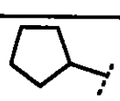
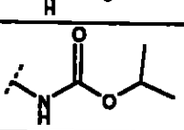
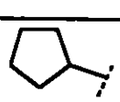
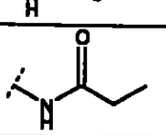
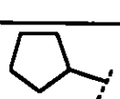
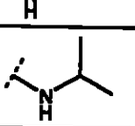
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Comp.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1143		MeO	Cl		801,4 803,4
1144		MeO	Cl		829,5 831,5
1145		MeO	Cl		843,4 845,3
1146		MeO	Cl		815,3 817,3
1147		MeO	Cl		833,3 835,3
1148		MeO	Cl		843,5 845,5
1149		MeO	Cl		803,2 805,2
1150		MeO	Cl		853,2 855,2
1151		MeO	Cl		785,2
1152		MeO	Cl		813,3
1153		MeO	Cl		817,2
1154		MeO	Br		897,3 899,2
1155		MeO	Br		829,2 831,2

329

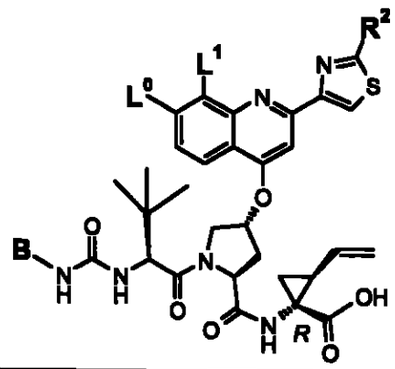
Comp.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1156		MeO	Br		847,3 849,2
1157		H	-SMe		835,4
1158		H	-SMe		847,4
1159		H	-SMe		79,3,
1160		H	-SMe		779,3
1161		H	-SMe		807,3
1162		H	-SMe		807,3
1163		H	-SMe		823,3
1164		H	$-CF_3$		801,4
1165		H	$-CF_3$		845,4
1166		H	$-CF_3$		815,4
1167		Cl	Cl		801,3 803,3 805,3
1168		Cl	Cl		857,2
1169		Cl	Cl		801,3

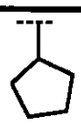
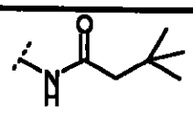
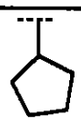
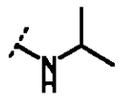
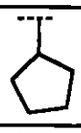
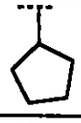
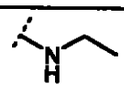
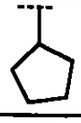
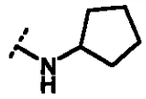
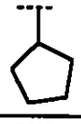
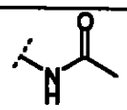
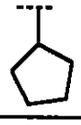
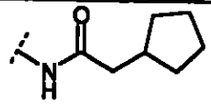
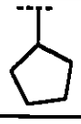
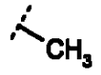
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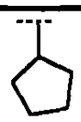
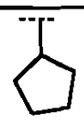
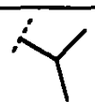
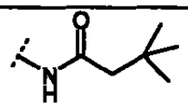
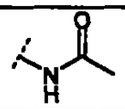
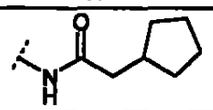
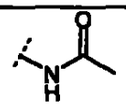
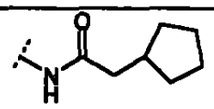
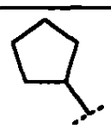
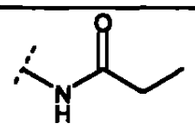
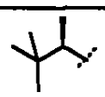
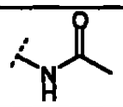
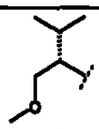
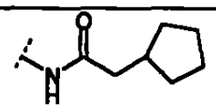
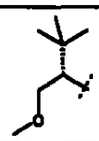
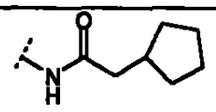
Comp.	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
1170		Cl	Cl		815,3 817,3 819,3
1171		H	$-SO_2Me$		811,3
1172		H	$-SO_2Me$		839,3
1173		H	Me-		747,3
1174		H	Me-		761,4
1175		H	Me-		803,4
1176		H	Me-		747,4
1177		H	Me-		775,4
1178		H	Me-		791,4
1179		H	$-SO_2Me$		855,3
1180		H	$-SO_2Me$		825,2
1181		H	-OMe		763,4

328
331

TABLA 2

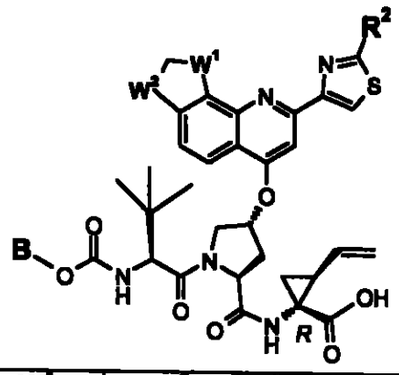


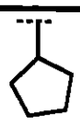
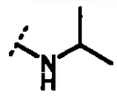
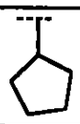
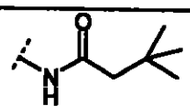
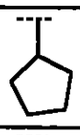
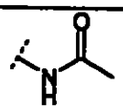
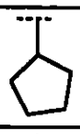
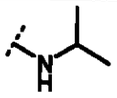
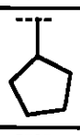
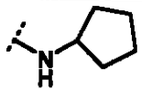
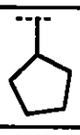
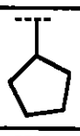
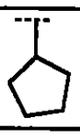
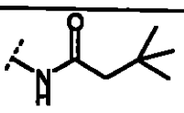
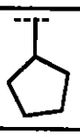
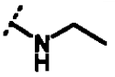
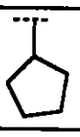
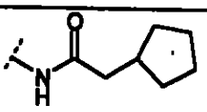
Comp. #	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
2001		MeO-	Me-		832,6
2002		MeO-	Me-		776,5
2003		MeO-	Me-		734,4
2004		MeO-	Me-		748,5
2005		MeO-	Me-		762,5
2006		MeO-	Me-		802,5
2007		MeO-	Me-		776,4
2008		MeO-	Me-		844,5
2009		MeO-	Me-		733,4

Comp. #	B	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
2010		MeO-	Me-		747,4
2011		MeO-	Me-		761,4
2012		MeO-	Me-		846,5
2013		MeO-	Me-		764,4
2014		MeO-	Me-		832,5
2015		MeO-	Me-		790,4
2016		MeO-	Me-		858,5
2017		MeO-	Br-		854,3 856,3
2018		MeO-	Me-		792,4
2019		MeO-	Me		876,5
2020		MeO-	Me		890,5

3RD 333

TABLA 3



Comp. #	B	W^1	W^2	R^2	m/z $(M+H)^+$ $(MH+2)^+$
3001		-O-	-O-		777,6
3002		-O-	-O-		833,6
3003		$-CH_2-$	-O-		775,4
3004		$-CH_2-$	-O-		775,4
3005		$-CH_2-$	-O-		801,4
3006		$-CH_2-$	-O-		747,3
3007		$-CH_2-$	-O-		733,3
3008		$-CH_2-$	-O-		831,5
3009		$-CH_2-$	-O-		761,5
3010		$-CH_2-$	-O-		843,3

334

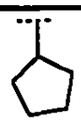
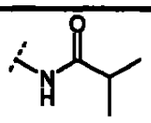
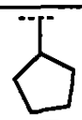
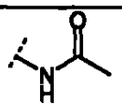
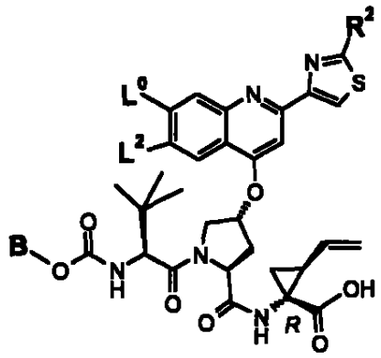
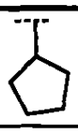
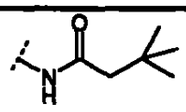
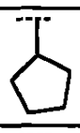
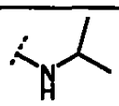
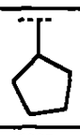
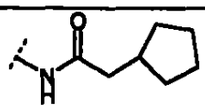
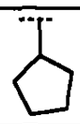
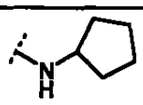
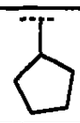
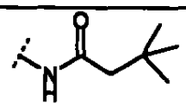
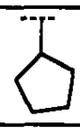
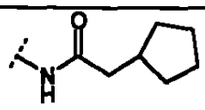
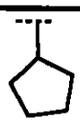
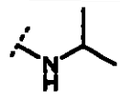
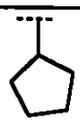
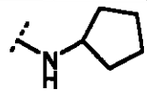
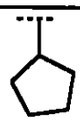
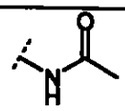
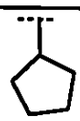
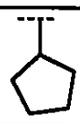
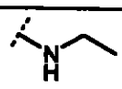
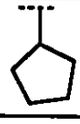
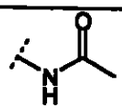
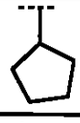
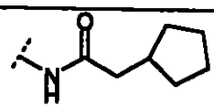
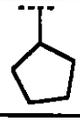
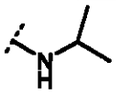
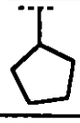
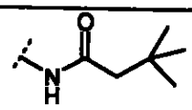
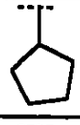
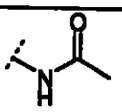
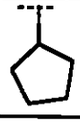
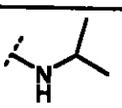
Comp. #	B	W^1	W^2	R^2	m/z $(M+H)^+$ $(MH+2)^+$
3011		$-CH_2-$	$-CH_2-$		801,5
3012		$-CH_2-$	$-CH_2-$		745,4
3013		$-CH_2-$	$-CH_2-$		773,4

TABLA 4



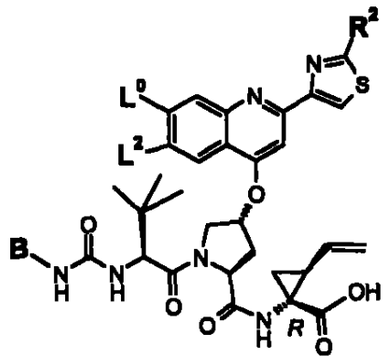
Comp. #	B	L^0	L^2	R^2	m/z $(M+H)^+$ $(MH+2)^+$
4001		MeO-	Me-		833,5
4002		MeO-	Me-		777,5
4003		MeO-	Me-		845,5
4004		MeO-	Me-		803,5
4005		Me_2N-	Me-		846,5
4006		Me_2N-	Me-		858,5

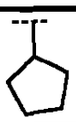
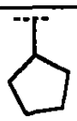
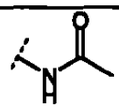
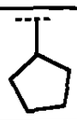
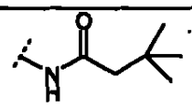
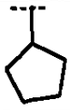
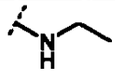
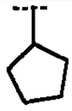
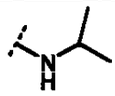
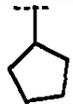
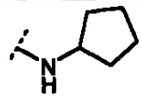
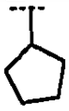
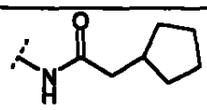
335

Comp. #	B	L^0	L^2	R^2	m/z $(M+H)^+$ $(MH+2)^+$
4007		Me_2N-	Me-		790,5
4008		Me_2N-	Me-		816,5
4009		MeO-	Me-		777,4
4010		MeO-	Me-		749,4
4011		MeO-	Me-		763,4
4012		MeO-	MeO-		793,3
4013		MeO-	MeO-		861,4
4014		MeO-	MeO-		793,4
4015		MeO-	MeO-		849,4
4016		Me-	MeO-		777,4
4017		Me-	MeO-		777,5

333
336

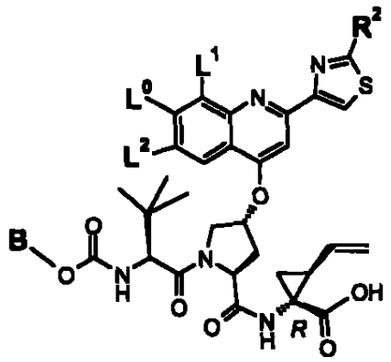
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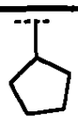
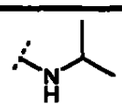
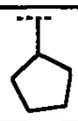
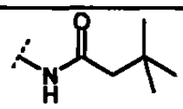
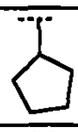
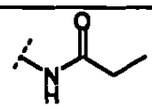
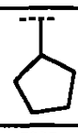
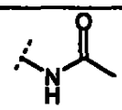
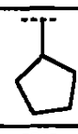
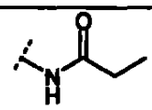
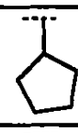
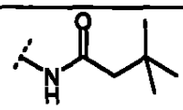
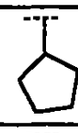
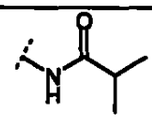
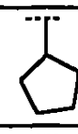
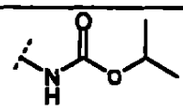
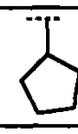
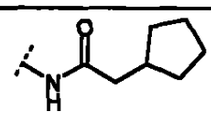
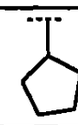
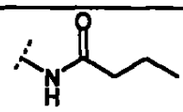


Comp. #	B	L^0	L^2	R^2	m/z $(M+H)^+$ $(MH+2)^+$
5001		MeO-	Me-		748,4
5002		MeO-	Me-		776
5003		MeO-	Me-		832,5
5004		MeO-	Me-		762
5005		MeO-	Me-		776,5
5006		MeO-	Me-		802,5
5007		MeO-	Me-		844,5

334
337

TABLA 6



Comp. #	B	L^2	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
6001		MeO-	H	Me		777,3
6002		MeO-	H	Me		833,4
6003		MeO-	H	Me		791,3
6004		MeO-	H	Me		777,2
6005		Me	H	Br		839,2 841,2
6006		Me	H	Br		881,2 883,2
6007		Me	H	Br		853,2 855,2
6008		Me	H	Br		869,2 871,2
6009		Me	H	Br		893,2 895,2
6010		Me	H	Br		853,2 855,2

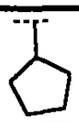
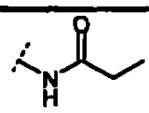
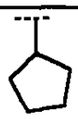
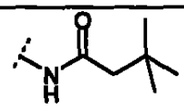
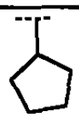
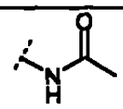
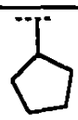
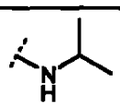
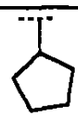
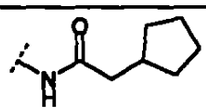
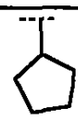
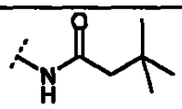
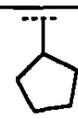
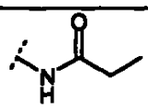
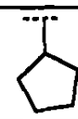
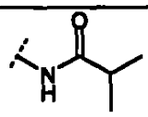
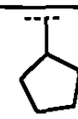
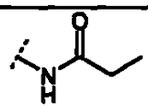
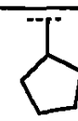
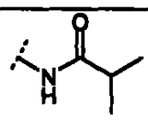
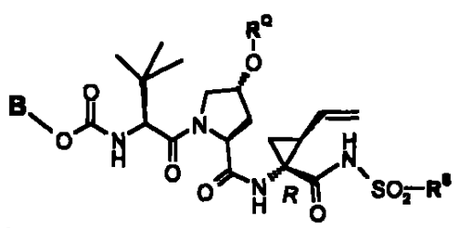
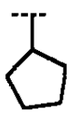
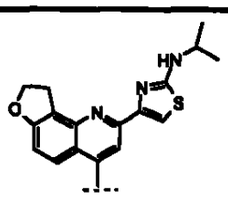
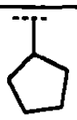
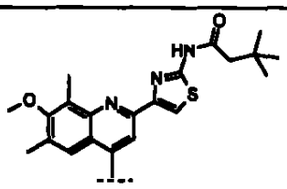
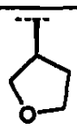
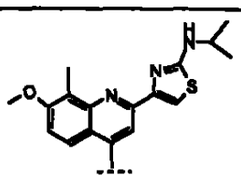
Comp. #	B	L^2	L^0	L^1	R^2	m/z $(M+H)^+$ $(MH+2)^+$
6011		Me	H	Me		775,3
6012		Me	H	Me		817,3
6013		Me	H	Me		761,3
6014		Me	H	Me		761,4
6015		Me	MeO-	Me		859,5
6016		Me	MeO-	Me		847,5
6017		Br	H	Br		905,2
6018		Br	H	Br		919,2
6019		Br	H	Cl		861,2
6020		Br	H	Cl		875,2

TABLA 7



Comp. #	B	R^Q	R^S	m/z $(M+H)^+$ $(MH+2)^+$

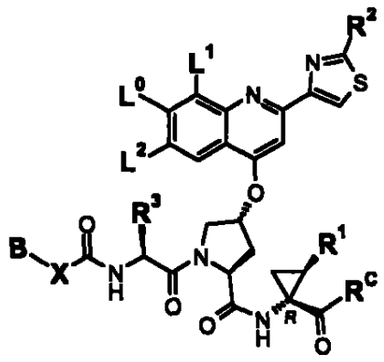
339

Comp. #	B	R^Q	R^S	m/z $(M+H)^+$ $(MH+2)^+$
7001				878,8
7002				950,4
7003				885,4

337
340

REIVINDICACIONES

1. Un racemato, un diasteroisómero o isómero óptico de un compuesto de fórmula (I):



I

donde

B es alquilo (C_{1-10}), cicloalquilo (C_{3-7}), o alquil (C_{1-4})-cicloalquilo (C_{3-7}),

a) donde dicho alquilo, cicloalquilo y alquil-cicloalquilo pueden estar mono-, di- o tri-sustituidos con alquilo (C_{1-3}); y

b) donde dicho alquilo, cicloalquilo y alquil-cicloalquilo pueden estar mono-sustituidos o disustituidos con sustituyentes seleccionados de hidroxi y O-alquilo (C_{1-4}); y

c) donde cada uno de dichos grupos alquilo puede estar mono-sustituido, disustituido o tri-sustituido con halógeno; y

d) donde cada uno de dichos grupos cicloalquilo que es de 4, 5, 6 o 7 miembros posee opcionalmente uno (para los de 4, 5, 6, o 7 miembros) o dos (para los de 5, 6, o 7 miembros) grupos $-CH_2-$ que no se encuentran unidos entre sí directamente se reemplazan por -O- de manera que el átomo de O se encuentra unido al grupo **X** mediante al menos dos átomos de C;

X es O o NH;

R^3 es alquilo (C_{2-8}), cicloalquilo (C_{3-7}) o alquil (C_{1-3})-cicloalquilo (C_{3-7}), donde dichos grupos alquilo, cicloalquilo y alquil-cicloalquilo pueden estar mono-, di- o tri-sustituidos con alquilo (C_{1-4});

L^0 es H, halógeno, alquilo (C_{1-4}), –OH, –O-alquilo (C_{1-4}), $-NH_2$, –NHalquilo (C_{1-4}) o -N(alquil (C_{1-4}))$_2$;

L^1, L^2 son cada uno independientemente halógeno, ciano, alquilo (C_{1-4}), -O-alquilo (C_{1-4}), -S-alquilo (C_{1-4}), -SO-alquilo (C_{1-4}), o $-SO_2$-alquilo (C_{1-4}), donde cada uno de dichos grupos alquilo está sustituido opcionalmente con de uno a tres átomos de halógeno; y cualquiera de L^1 o L^2 (pero no los dos al mismo tiempo) también puede ser H; o

336
341

L^0 y L^1 o

L^0 y L^2 pueden estar unidos covalentemente para formar, junto con los dos átomos de C a los cuales están unidos, un anillo carbocíclico de 5 o 6 miembros donde uno o dos grupos $-CH_2-$ que no están unidos entre sí directamente se pueden reemplazar cada uno independientemente por -O- o NR^8, donde R^8 es H o alquilo (C_{1-4}) y donde dicho anillo carbocíclico o heterocíclico está opcionalmente mono-sustituido o disustituido con alquilo (C_{1-4});

R^2 es R^{20}, $-NR^{22}COR^{20}$, $-NR^{22}COOR^{20}$ $-NR^{22}R^{21}$ o $-NR^{22}CONR^{21}R^{23}$, donde R^{20} se selecciona de alquilo (C_{1-6}), cicloalquilo (C_{3-7}) y alquil (C_{1-4})-cicloalquilo (C_{3-7}), donde dichos cicloalquilo y alquil-cicloalquilo pueden estar mono-, di- o tri-sustituidos con alquilo (C_{1-3});

R^{21} es H o R^{20} según se definió anteriormente,

R^{22} y R^{23} se seleccionan independientemente de H y metilo,

R^1 es etilo o vinilo;

R^C es hidroxi o $NHSO_2R^8$, donde R^8 es alquilo (C_{1-6}), cicloalquilo (C_{3-7}), alquil (C_{1-6})-cicloalquilo (C_{3-7}), fenilo, naftilo, piridinilo, alquil (C_{1-4})-fenilo, alquil (C_{1-4})-naftilo o alquil (C_{1-4})-piridinilo; estando cada uno de los cuales mono-sustituido, disustituido o tri-sustituido con sustituyentes seleccionados de halógeno, hidroxi, ciano, alquilo (C_{1-4}), O-alquilo (C_{1-6}), -CO-NH_2, -CO-NHalquilo (C_{1-4}), -CO-N(alquil (C_{1-4}))$_2$, -NH_2, -NHalquilo (C_{1-4}) y -N(alquil (C_{1-4}))$_2$, donde alquilo (C_{1-4}) y O-alquilo (C_{1-6}) están sustituidos opcionalmente con uno a tres átomos de halógeno; y estando cada uno de los cuales mono-sustituido con nitro;

o R^8 es $-N(R^{N2})R^{N1})$, donde R^{N1} y R^{N2} se seleccionan independientemente de H, alquilo (C_{1-6}), cicloalquilo (C_{3-7}), alquil (C_{1-6})-cicloalquilo (C_{3-7}), arilo y alquil (C_{1-6})-arilo; donde dicho alquilo (C_{1-6}), cicloalquilo (C_{3-7}), alquil (C_{1-6})-cicloalquilo (C_{3-7}), arilo y alquil (C_{1-6})-arilo están sustituidos opcionalmente con uno o más sustituyentes seleccionados independientemente de halógeno, alquilo (C_{1-6}), hidroxi, ciano, O-alquilo (C_{1-6}), -NH_2, -NHalquilo (C_{1-4}), -N(alquil (C_{1-4}))$_2$, -CO-NH_2, -CO-NHalquilo (C_{1-4}), -CO-N(alquil (C_{1-4}))$_2$, -COOH y –COO-alquilo (C_{1-6}); o

R^{N2} y R^{N1} se unen, junto con el nitrógeno con el cual están unidos, para formar un heterociclo monocíclico saturado o no saturado de 3 a 7 miembros o un heterociclo bicíclico saturado o no saturado de 9 o 10 miembros, cada uno de los cuales contiene opcionalmente de uno a tres heteroátomos adicionales seleccionados independientemente de N, S y O y estando cada uno de los cuales sustituido opcionalmente con uno o más sustituyentes seleccionados independientemente de

337
342

halógeno, alquilo (C_{1-6}), hidroxi, ciano, O-alquilo (C_{1-6}), $-NH_2$, -NHalquilo (C_{1-4}), -N(alquil (C_{1-4}))$_2$, $-CO-NH_2$, -CO-NHalquilo (C_{1-4}), -CO-N(alquil (C_{1-4}))$_2$, –COOH y –COOalquilo (C_{1-6});

o una sal o éster aceptable para uso farmacéutico del mismo.

2. El compuesto de acuerdo con la reivindicación 1 en el cual

B es alquilo (C_{1-10}), cicloalquilo (C_{3-7}), o alquil (C_{1-4})-cicloalquilo (C_{3-7}),

a) donde dicho cicloalquilo y alquil-cicloalquilo pueden estar mono-, di- o tri-sustituidos con alquilo (C_{1-3}); y

b) donde dicho alquilo, cicloalquilo y alquil-cicloalquilo pueden estar mono-sustituidos o disustituidos con sustituyentes seleccionados de hidroxi y O-alquilo (C_{1-4}); y

c) donde todos los grupos alquilo mencionados pueden estar mono-, di- o tri-sustituidos con halógeno; y

d) donde todos los grupos cicloalquilo que son de 4, 5, 6, o 7 miembros que poseen opcionalmente uno (para los de 4, 5, 6, o 7 miembros) o dos (para los de 5, 6, o 7 miembros) grupos $-CH_2-$ que no se encuentran unidos entre sí directamente por se reemplazan por -O- de manera que el átomo de O está unido al grupo **X** mediante al menos dos átomos de C;

X es O o NH;

R^3 es alquilo (C_{2-6}), cicloalquilo (C_{3-7}) o alquil (C_{1-3})-cicloalquilo (C_{3-7}), donde dichos grupos cicloalquilo pueden estar mono-, di- o tri-sustituidos con alquilo (C_{1-4});

L^0 es H, –OH, –O-alquilo (C_{1-4}), $-NH_2$, –NHalquil (C_{1-4}) o –N(alquil (C_{1-4}))$_2$;

L^1, L^2 son cada uno independientemente halógeno, alquilo (C_{1-4}), -O-alquilo (C_{1-4}) o -S-alquilo (C_{1-4}) (en cualquier estado de oxidación tal como SO o SO_2); y cualquiera de L^1 o L^2 (pero no los dos al mismo tiempo) también puede ser H; o

L^0 y L^1 o

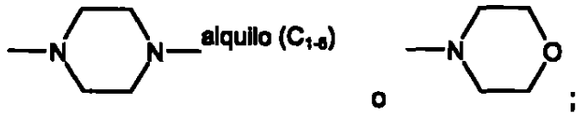
L^0 y L^2 pueden estar unidos covalentemente para formar, junto con los dos átomos de C a los cuales están unidos, un anillo carbocíclico de 5 o 6 miembros donde uno o dos grupos $-CH_2-$ que no se encuentran unidos entre sí directamente se pueden reemplazar cada uno independientemente por -O- o NR^a, donde R^a es H o alquilo (C_{1-4}) y donde dicho anillo carbocíclico o heterocíclico está opcionalmente mono-sustituido o disustituido con alquilo (C_{1-4});

R^2 es R^{20}, $-NR^{22}COR^{20}$, $-NR^{22}COOR^{20}$ $-NR^{22}R^{21}$ y $-NR^{22}CONR^{21}R^{23}$, donde R^{20} se selecciona de alquilo (C_{1-6}), cicloalquilo (C_{3-7}) y alquil (C_{1-4})-cicloalquilo (C_{3-7}), donde dichos cicloalquilo y alquil-cicloalquilo pueden estar mono-, di- o tri-sustituidos con alquilo (C_{1-3});

R^{21} es H o posee uno de los significados de R^{20} según se definió anteriormente, R^{22} y R^{23} se seleccionan independientemente de H y metilo,

R^1 es etilo o vinilo;

R^C es hidroxi o $NHSO_2R^8$ donde R^8 es alquilo (C_{1-6}), cicloalquilo (C_{3-7}), alquil (C_{1-6})-cicloalquilo (C_{3-7}), fenilo, naftilo, piridinilo, alquil (C_{1-4})-fenilo, alquil (C_{1-4})-naftilo o alquil (C_{1-4})-piridinilo; estando todos los cuales opcionalmente mono-, di- o tri-sustituidos con sustituyentes seleccionados de halógeno, hidroxi, ciano, alquilo (C_{1-4}), O-alquilo (C_{1-6}), -CO-NH_2, -CO-NHalquilo (C_{1-4}), -CO-N(alquil (C_{1-4}))$_2$, -NH_2, -NHalquilo (C_{1-4}) y -N(alquil (C_{1-4}))$_2$; y estando todos los cuales opcionalmente mono-sustituidos con nitro; o R^8 se puede seleccionar además de: -NHalquilo (C_{1-6}), N(alquilo (C_{1-6}))$_2$, -Het,



;

o una sal o éster aceptable para uso farmacéutico del mismo.

3. El compuesto de acuerdo con una o más de las reivindicaciones anteriores en el cual B se selecciona de alquilo (C_{2-8}), cicloalquilo (C_{3-7}) y alquil (C_{1-3})-cicloalquilo (C_{3-7}),

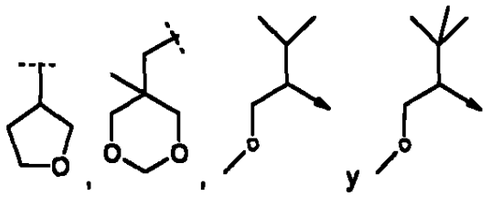
a) donde dichos alquilo, cicloalquilo y alquil-cicloalquilo pueden ser mono-, di- o tri-sustituidos con alquilo (C_{1-3}); y

b) donde dichos alquilo, cicloalquilo y alquil-cicloalquilo pueden estar mono-o di-sustituidos con sustituyentes seleccionados de hidroxi y O-alquilo (C_{1-4}); y

c) donde cada uno de dichos grupos alquilo puede estar mono-, di- o tri-sustituidos con flúor o mono-sustituido con cloro o bromo; y

d) donde en cada uno de dichos grupos cicloalquilo que son de 5, 6 o 7 miembros, uno o dos grupos -CH_2- que no se encuentran unidos directamente entre sí se pueden reemplazar por -O- de manera que el átomo de O se encuentra unido al grupo X mediante al menos dos átomos de C.

4. El compuesto de acuerdo con la reivindicación 3, donde B se selecciona de etilo, n-propilo, *ter*-butilo, 2-metilpropilo, 1,2-dimetilpropilo, 1,2,2-trimetilpropilo, 2-fluoroetilo, 3-fluoropropilo, 3,3,3-trifluoropropilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, 1-metilciclopentilo y 1-metilciclohexilo y un grupo seleccionado de:



y .

344

5. El compuesto de acuerdo con la reivindicación 4, donde **B** se selecciona de etilo, *n*-propilo, *ter*-butilo, ciclopentilo, 1-metilciclopentilo, 2-fluoroetilo o 3-fluoropropilo.

6. El compuesto de acuerdo con una o más de las reivindicaciones anteriores, en el cual X es O.

7. El compuesto de acuerdo con una o más de las reivindicaciones anteriores, en el cual X es NH.

8. El compuesto de acuerdo con una o más de las reivindicaciones anteriores, en el cual R^3 es alquilo (C_{2-6}), cicloalquilo (C_{3-7}) o alquil (C_{1-3})-cicloalquilo (C_{3-7}), estando cada uno de los cuales sustituido opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo (C_{1-4}).

9. El compuesto de acuerdo con la reivindicación 8, donde R^3 se selecciona de 1,1-dimetiletilo, ciclopentilo, ciclohexilo y 1-metilciclohexilo.

10. El compuesto de acuerdo con una o más de las reivindicaciones anteriores, en el cual L^0 se selecciona de H, halógeno, CH_3, -OH, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-OCH(CH_3)_2$, $-NHCH_3$, $-NHC_2H_5$, $-NHC_3H_7$, $-NHCH(CH_3)_2$, $-N(CH_3)_2$, $-N(CH_3)C_2H_5$, $-N(CH_3)C_3H_7$ y $-N(CH_3)CH(CH_3)_2$.

11. El compuesto de acuerdo con la reivindicación 10, donde L^0 se selecciona de H, -OH, $-OCH_3$, halógeno y $-N(CH_3)_2$.

12. El compuesto de acuerdo con la reivindicación 11, donde L^0 se selecciona de H, -OH u $-OCH_3$.

13. El compuesto de acuerdo con una o más de las reivindicaciones anteriores, en el cual L^1 y L^2 se seleccionan cada uno independientemente de: halógeno, $-CH_3$, $-C_2H_5$, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-OCH(CH_3)_2$, CF_3, -SMe, -SOMe y SO_2Me, por lo cual cualquiera de L^1 o L^2 puede ser H.

14. El compuesto de acuerdo con la reivindicación 13, donde cualquiera de L^1 y L^2 es $-CH_3$, -F, -Cl, -Br, -OMe, -SMe, o $-SO_2Me$ y el otro de L^1 y L^2 es H.

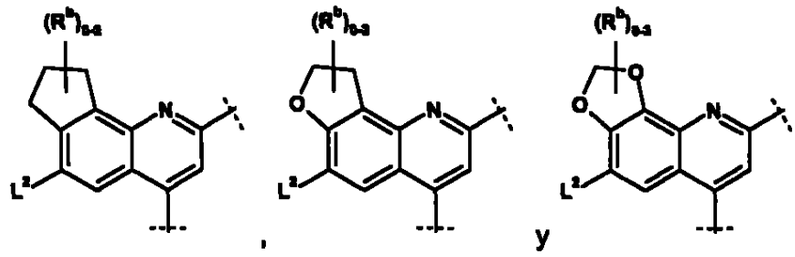
15. El compuesto de acuerdo con la reivindicación 14, donde L^1 es CH_3, -F, -Cl, -Br, -OMe, -SMe o $-SO_2Me$ y L^2 es H.

16. El compuesto de acuerdo con una o más de las reivindicaciones anteriores, en el cual L^0 se selecciona de H, -OH y $-OCH_3$; y cualquiera de L^1 y L^2 es CH_3, -F, -Cl, -Br, -OMe, -SMe, o $-SO_2Me$ y el otro de L^1 y L^2 es H.

17. El compuesto de acuerdo con la reivindicación 16, donde L^0 se selecciona de H, -OH y $-OCH_3$; L^1 es CH_3, -F, -Cl, -Br, -OMe, -SMe o $-SO_2Me$ y L^2 es H.

18. El compuesto de acuerdo con la reivindicación 17, donde L^0 se selecciona de H y $-OCH_3$; L^1 es CH_3, -Cl o -Br y L^2 es H.

19. El compuesto de acuerdo con una o más de las reivindicaciones anteriores, en el cual L^0 y L^1 están unidos covalentemente para formar, junto con el residuo de quinolina al cual están unidos, un sistema anular que se selecciona de:



y

donde cada R^b es independientemente alquilo (C_{1-4}) y L^2 se define como en la reivindicación 1.

20. El compuesto de acuerdo con la reivindicación 19, donde L^2 es H o metilo.

21. El compuesto de acuerdo con una o más de las reivindicaciones anteriores, en el cual R^2 es R^{20}, -NHCOR^{20}, -NHCOOR^{20}, -NHR^{21} o –NHCONR^{21}R^{23}, donde

R^{20} se selecciona de alquilo (C_{1-8}), cicloalquilo (C_{3-7}) y alquil (C_{1-3})-cicloalquilo (C_{3-7}), donde cada uno de dichos grupos cicloalquilo y alquil-cicloalquilo puede estar mono-, di- o tri-sustituido con alquilo (C_{1-3}); y

R^{21} es H o R^{20} según se definió anteriormente; y

R^{23} es H o metilo.

22. El compuesto de acuerdo con la reivindicación 21, donde R^2 es -NHCOR^{20}, -NHCOOR^{20} o -NHR^{21}.

23. El compuesto de acuerdo con la reivindicación 22 donde R^{20} y R^{21} se seleccionan independientemente de: metilo, etilo, *n*-propilo, *i*-propilo, *n*-butilo, 1-metilpropilo, 2-metilpropilo, *ter*-butilo, 2,2-dimetilpropilo, 1,1-dimetilpropilo, 1,2-dimetilpropilo, 1,2,2-trimetilpropilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclopropilmetilo, ciclobutilmetilo, ciclopentilmetilo, ciclohexilmetilo, estando cada uno de dichos grupos cicloalquilo o alquil-cicloalquilo opcionalmente mono- o di-sustituido con metil o etilo.

24. El compuesto de acuerdo con la reivindicación 23, donde R^{20} y R^{21} se seleccionan independientemente de metilo, etilo, *n*-propilo, *i*-propilo, 2,2-dimetilpropilo, ciclopentilo y ciclopentilmetilo.

25. El compuesto de acuerdo con una o más de las reivindicaciones anteriores, en el cual R^1 es vinilo.

26. El compuesto de acuerdo con una o más de las reivindicaciones anteriores, en el cual R^C es hidroxi, $NHSO_2$-metilo, $NHSO_2$-etilo, $NHSO_2$-(1-metil)etilo,

$NHSO_2$-propilo, $NHSO_2$-ciclopropilo, $NHSO_2$-CH_2-ciclopropilo, $NHSO_2$-ciclobutilo, $NHSO_2$-ciclopentilo o $NHSO_2$-fenilo.

27. El compuesto de acuerdo con la reivindicación 26, donde R^C es hidroxi.

28. El compuesto de acuerdo con la reivindicación 26, donde R^C es $NHSO_2$-ciclopropilo.

29. El compuesto de acuerdo con una o más de las reivindicaciones anteriores, en el cual R^C es $NHSO_2N(R^{N2})R^{N1}$), donde R^{N1} y R^{N2} se seleccionan independientemente de H, alquilo (C_{1-4}), cicloalquilo (C_{3-7}), alquil (C_{1-3})-cicloalquilo (C_{3-7}), fenilo y alquil (C_{1-3})-fenilo; donde dichos alquilo (C_{1-4}), cicloalquilo (C_{3-7}), alquil (C_{1-3})-cicloalquilo (C_{3-7}), fenilo y alquil (C_{1-3})-fenilo están sustituidos opcionalmente con uno, dos o tres sustituyentes seleccionados de halógeno, alquilo (C_{1-6}), hidroxi, ciano, O-alquilo (C_{1-6}), $-NH_2$, -NHalquilo (C_{1-4}), -N(alquilo (C_{1-4}))$_2$, $-CO-NH_2$, -CO-NH-alquilo (C_{1-4}), -CO-N(alquil (C_{1-4}))$_2$, –COOH y –COO(C_{1-6})alquilo; o

R^{N2} y R^{N1} se unen, junto con el nitrógeno al cual están unidos, para formar un heterociclo monocíclico de 5 o 6 miembros que puede ser saturado o no saturado, que contiene opcionalmente de uno a tres heteroátomos adicionales seleccionados independientemente de N, S y O y sustituido opcionalmente con uno, dos o tres sustituyentes seleccionados de halógeno, alquilo (C_{1-6}), hidroxi, ciano, O-alquilo (C_{1-6}), $-NH_2$, -NHalquilo (C_{1-4}), -N(alquil (C_{1-4}))$_2$, $-CO-NH_2$, -CO-NHalquilo (C_{1-4}), -CO-N(alquil (C_{1-4}))$_2$, –COOH y –COOalquilo (C_{1-6}).

30. El compuesto de acuerdo con la reivindicación 1, donde

B es alquilo (C_{2-6}), cicloalquilo (C_{3-7}) o alquil (C_{1-3})-cicloalquilo (C_{3-7}),

a) donde dichos alquilo, cicloalquilo y alquil-cicloalquilo pueden estar mono-, di- o tri-sustituidos con alquilo (C_{1-3}); y

b) donde dichos alquilo, cicloalquilo y alquil-cicloalquilo pueden estar mono- o disustituidos con sustituyentes seleccionados de hidroxi y O-alquilo (C_{1-4}); y

c) donde cada uno de dichos grupos alquilo puede estar mono-, di- o tri-sustituido con flúor o mono-sustituido con cloro o bromo; y

d) donde en cada uno de dichos grupos cicloalquilo que son de 5, 6 o 7 miembros, uno o dos grupos $-CH_2-$ que no se encuentran unidos directamente entre sí se pueden reemplazar por -O- de manera que el átomo de O se encuentra unido al grupo **X** mediante al menos dos átomos de C;

X es O o NH;

R^3 es alquilo (C_{2-6}) o cicloalquilo (C_{3-7}), estando ambos sustituidos opcionalmente con 1 a 3 sustituyentes seleccionados de alquilo (C_{1-4});

344
347

L^0 es H, -OH, $-OCH_3$, halógeno o $-N(CH_3)_2$;

L^1 y L^2 se seleccionan cada uno independientemente de: halógeno, $-CH_3$, $-C_2H_5$, $-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-OCH(CH_3)_2$, CF_3, -SMe, -SOMe y SO_2Me, por lo cual cualquiera de L^1 o L^2 puede ser H;

R^2 es R^{20}, $-NHCOR^{20}$, $-NHCOOR^{20}$, $-NHR^{21}$ y $-NHCONR^{21}R^{23}$,

donde

R^{20} se selecciona de alquilo (C_{1-6}), cicloalquilo (C_{3-7}), alquil (C_{1-3})-cicloalquilo (C_{3-7}), donde dichos cicloalquilo y alquil-cicloalquilo pueden estar mono-, di- o tri-sustituidos con alquilo (C_{1-3}); y

R^{21} es H o R^{20} según se definió anteriormente; y

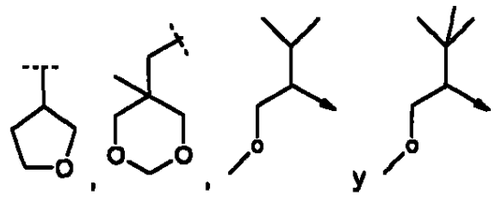
R^{23} es H o metilo;

R^1 es etilo o vinilo; y

R^C es hidroxi, $NHSO_2$-metilo, $NHSO_2$-etilo, $NHSO_2$-(1-metil)etilo, $NHSO_2$-propilo, $NHSO_2$-ciclopropilo, $NHSO_2$-CH_2-ciclopropilo, $NHSO_2$-ciclobutilo, $NHSO_2$-ciclopentilo o $NHSO_2$-fenilo.

31. El compuesto de acuerdo con la reivindicación 30, en el cual

B se selecciona de: etilo, n-propilo, *ter*-butilo, 2-metilpropilo, 1,2-dimetilpropilo, 1,2,2-trimetilpropilo, 2-fluoroetilo, 3-fluoropropilo, 3,3,3-trifluoropropilo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, 1-metilciclopentilo y 1-metilciclohexilo y un grupo seleccionado de:



R^3 se selecciona de 1,1-dimetiletilo, ciclopentilo, ciclohexilo y 1-metilciclohexilo; L^0 es H, -OH o $-OCH_3$; L^1 es CH_3, -F, -Cl, -Br, -OMe, -SMe, o $-SO_2Me$; L^2 es H;

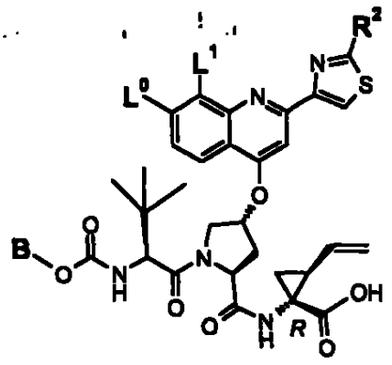
R^2 es $-NHCOR^{20}$, $-NHCOOR^{20}$ o $-NHR^{21}$, donde R^{20} y R^{21} se seleccionan independientemente de metilo, etilo, *n*-propilo, *i*-propilo, 2,2-dimetilpropilo, ciclopentilo y ciclopentilmetilo;

R^1 es vinilo; y R^C es hidroxi o $NHSO_2$-ciclopropilo.

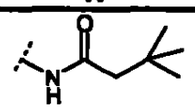
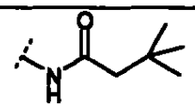
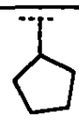
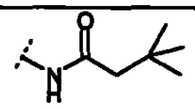
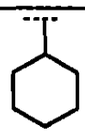
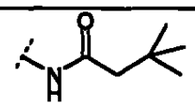
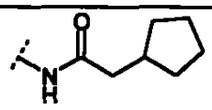
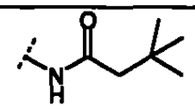
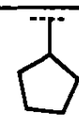
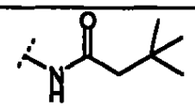
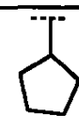
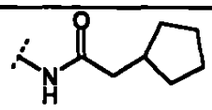
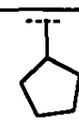
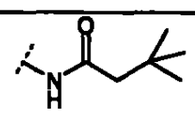
32. El compuesto de acuerdo con la reivindicación 31, donde B se selecciona de etilo, *n*-propilo, *ter*-butilo, ciclopentilo, 1-metilciclopentilo, 2-fluoroetilo y 3-fluoropropilo; R^3 se selecciona de 1,1-dimetiletilo y ciclohexilo; L^0 es H o $-OCH_3$; L^1 es $-CH_3$, -Cl, o -Br; L^2 es H; y R^C es hidroxi.

346
348

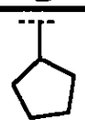
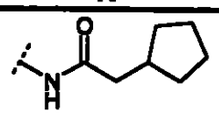
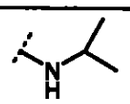
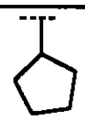
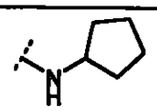
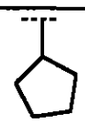
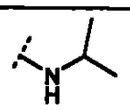
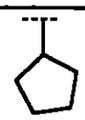
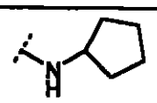
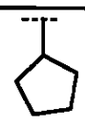
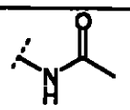
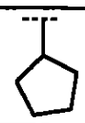
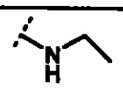
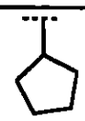
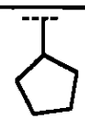
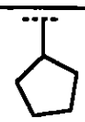
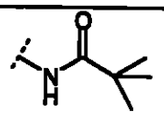
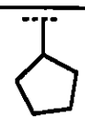
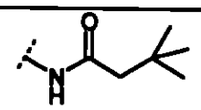
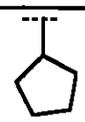
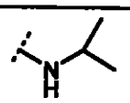
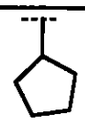
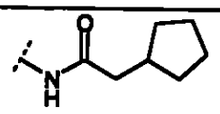
33. El compuesto de acuerdo con la reivindicación 1, de fórmula

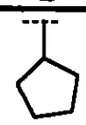
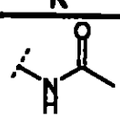
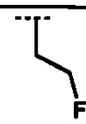
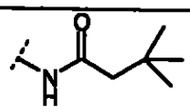
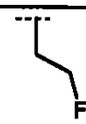
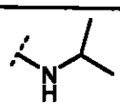
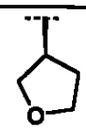
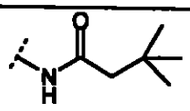
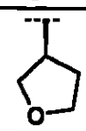
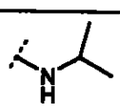
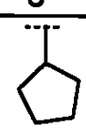
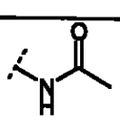
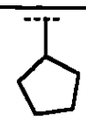
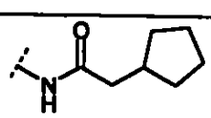
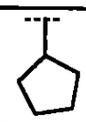
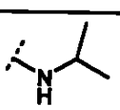
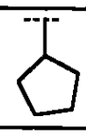
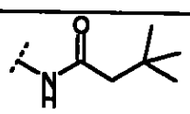
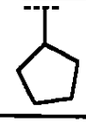
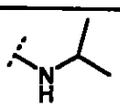
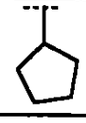
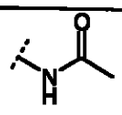
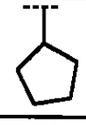
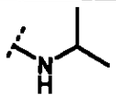
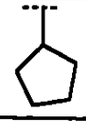
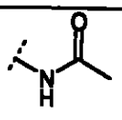


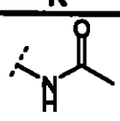
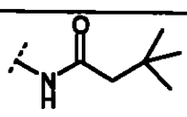
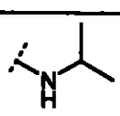
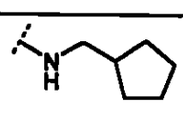
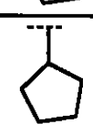
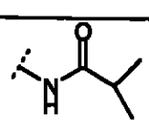
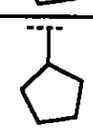
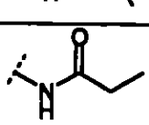
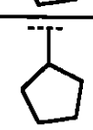
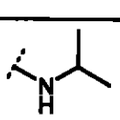
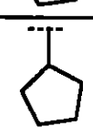
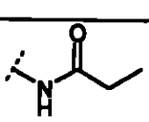
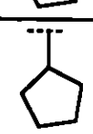
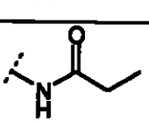
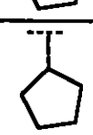
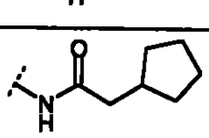
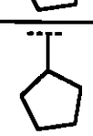
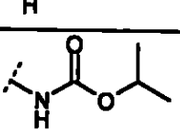
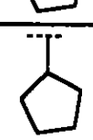
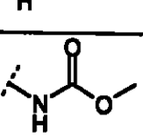
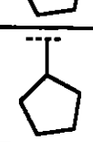
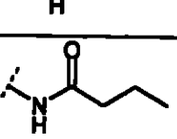
donde B, L^0, L^1 y R^2 se definen como en la siguiente tabla

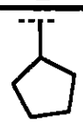
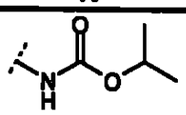
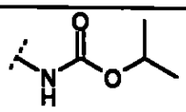
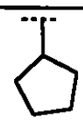
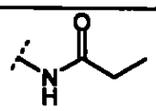
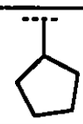
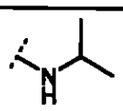
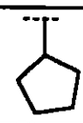
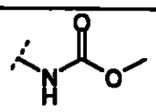
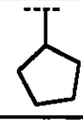
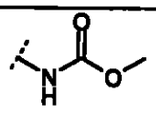
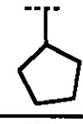
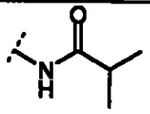
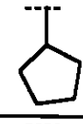
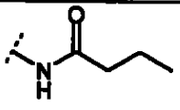
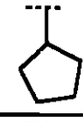
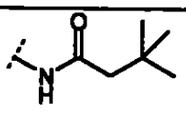
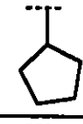
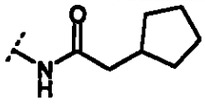
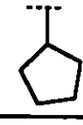
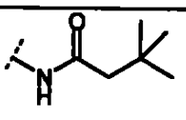
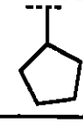
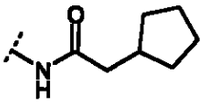
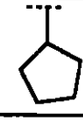
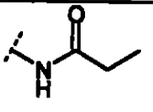
Comp.	B	L^0	L^1	R^2
1001		MeO-	MeO-	
1002		MeO-	MeO-	
1003		MeO-	MeO-	
1004		MeO-	MeO-	
1005		MeO-	Me-	
1006		MeO-	Me-	
1007		MeO-	Me-	
1008		MeO-	Me-	
1009		Me_2N-	Me-	

346
349

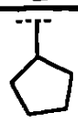
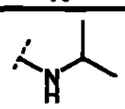
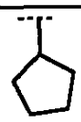
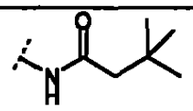
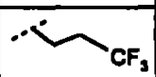
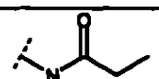
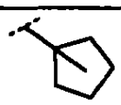
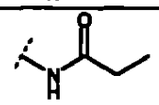
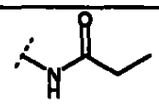
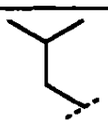
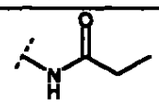
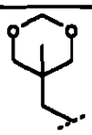
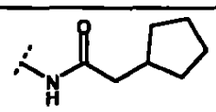
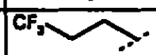
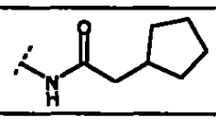
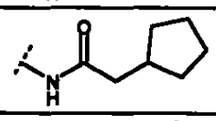
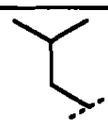
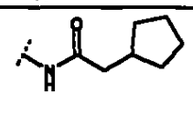
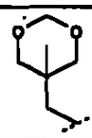
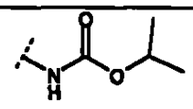
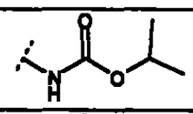
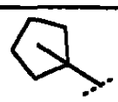
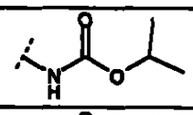
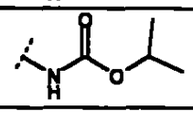
Comp.	B	L^0	L^1	R^2
1010		Me_2N-	Me-	
1011		Me_2N-	Me-	
1012		Me_2N-	Me-	
1013		MeO-	Me-	
1014		MeO-	Me-	
1015		MeO-	Me-	
1016		MeO-	Me-	
1017		MeO-	Me-	
1018		MeO-	Me-	
1019		MeO-	Me-	
1020		MeO-	Et-	
1021		MeO-	Et-	
1022		MeO-	Et-	

Comp.	B	L^0	L^1	R^2
1023		MeO-	Et-	
1024		MeO-	Me-	
1025		MeO-	Me-	
1026		MeO-	Me-	
1027		MeO-	Me-	
1028		MeO-	Br-	
1029		MeO-	Br-	
1030		MeO-	Br-	
1031		MeO-	Br-	
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1034		HO-	Me-	
1035		HO-	Me-	

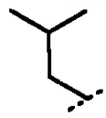
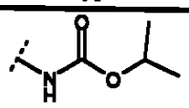
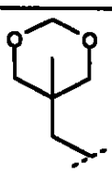
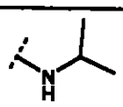
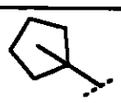
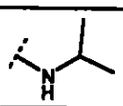
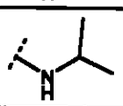
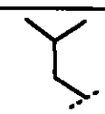
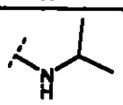
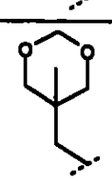
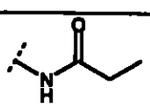
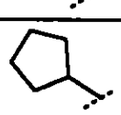
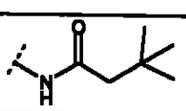
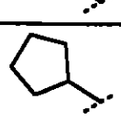
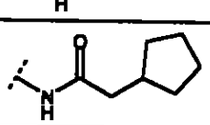
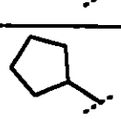
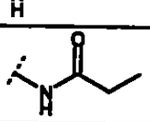
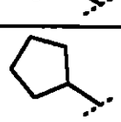
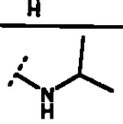
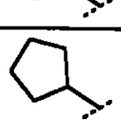
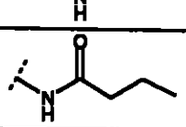
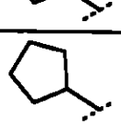
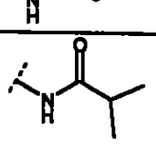
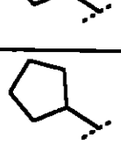
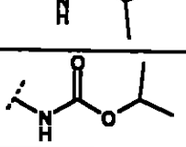
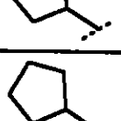
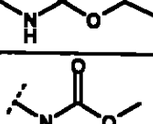
Comp.	B	L^0	L^1	R^2
1036		MeO-	Me-	
1037		MeO-	Me-	
1038		MeO-	Me-	
1039		MeO-	Me-	
1040		MeO-	Me-	
1041		MeO-	Me-	
1042		MeO-	Cl	
1043		MeO-	Br	
1044		MeO-	Cl	
1045		MeO-	Cl	
1046		MeO-	Me-	
1047		MeO-	Me-	
1048		MeO-	Cl	

Comp.	B	L^0	L^1	R^2
1049		MeO-	Br	
1050		MeO-	Cl	
1051		MeO-	F	
1052		MeO-	F	
1053		MeO-	Cl	
1054		MeO-	Br	
1055		MeO-	Br	
1056		MeO-	Br	
1057		HO	Me	
1058		HO	Me	
1059		H	Br	
1060		H	Br	
1061		H	Br	

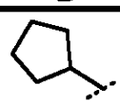
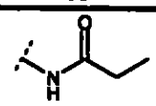
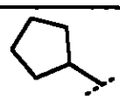
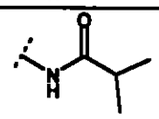
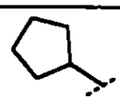
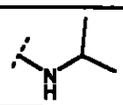
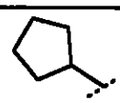
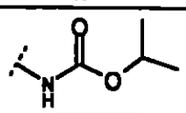
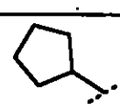
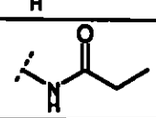
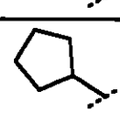
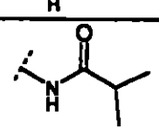
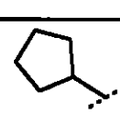
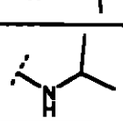
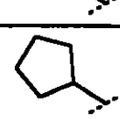
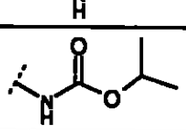
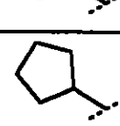
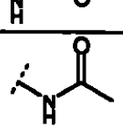
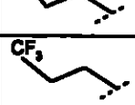
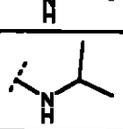
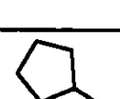
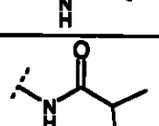
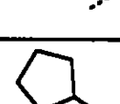
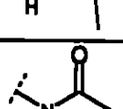
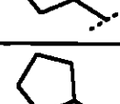
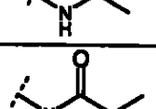
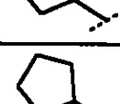
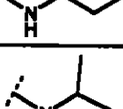
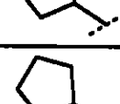
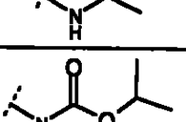
350
353

Comp.	B	L^0	L^1	R^2
1062		H	Br	
1063		F	Me	
1064		MeO-	Br	
1065		MeO-	Br	
1066		MeO-	Br	
1067		MeO-	Br	
1068		MeO-	Br	
1069		MeO-	Br	
1070		MeO-	Br	
1071		MeO-	Br	
1072		MeO-	Br	
1073		MeO-	Br	
1074		MeO-	Br	
1075		MeO-	Br	

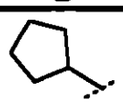
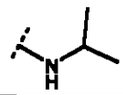
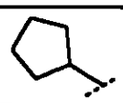
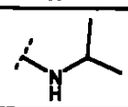
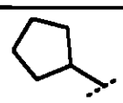
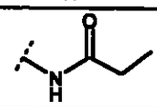
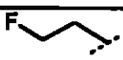
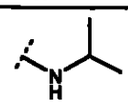
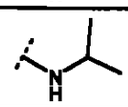
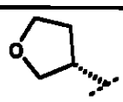
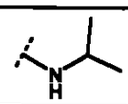
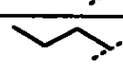
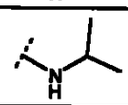
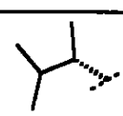
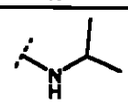
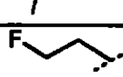
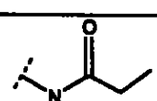
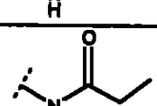
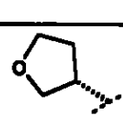
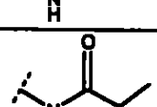
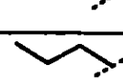
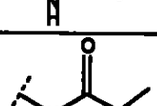
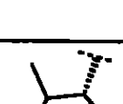
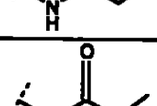
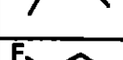
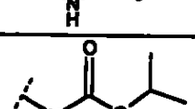
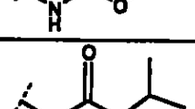
354
354

Comp.	B	L^0	L^1	R^2
1076		MeO-	Br	
1077		MeO-	Br	
1078		MeO-	Br	
1079		MeO-	Br	
1080		MeO	Br	
1081		MeO	Br	
1082		H	Cl	
1083		H	Cl	
1084		H	Cl	
1085		H	Cl	
1086		H	Cl	
1087		H	Cl	
1088		H	Cl	
1089		H	Cl	

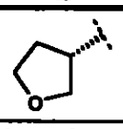
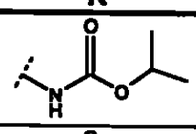
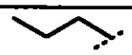
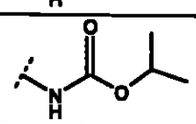
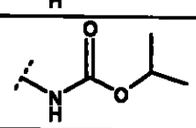
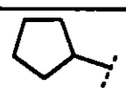
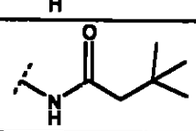
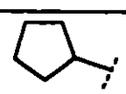
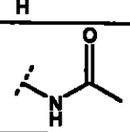
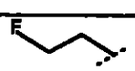
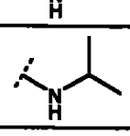
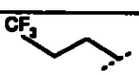
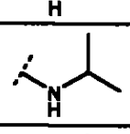
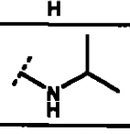
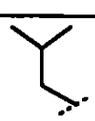
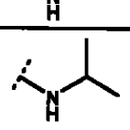
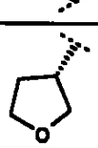
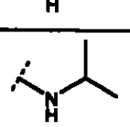
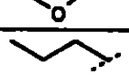
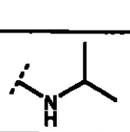
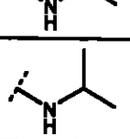
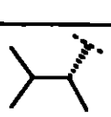
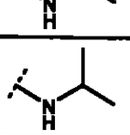
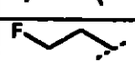
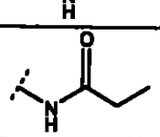
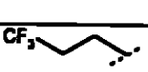
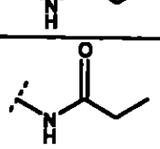
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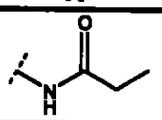
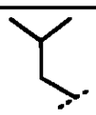
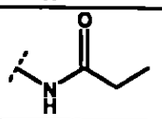
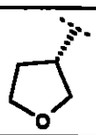
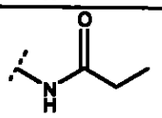
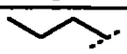
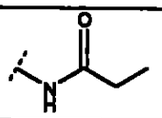
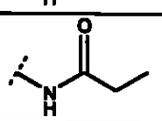
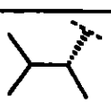
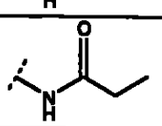
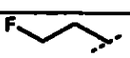
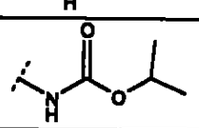
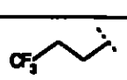
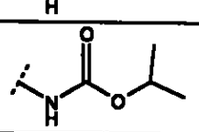
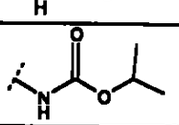
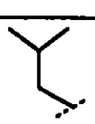
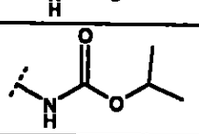
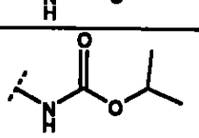
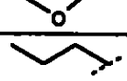
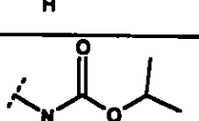
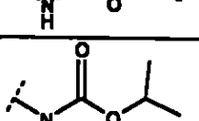
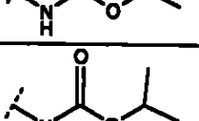
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1094		PrO-	Br	
1095		PrO-	Br	
1096		PrO-	Br	
1097		PrO-	Br	
1098		H	Br	
1099		MeO-	Br	
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1103		EtO-	Me	
1104		EtO-	Me	

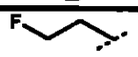
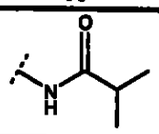
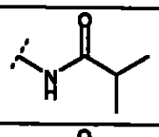
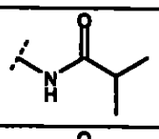
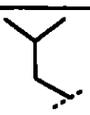
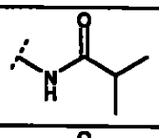
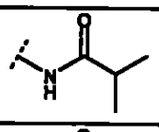
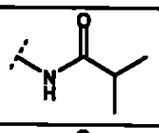
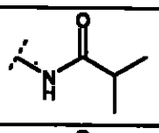
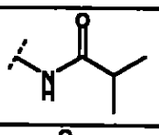
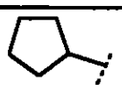
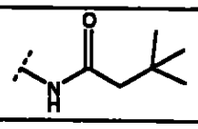
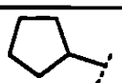
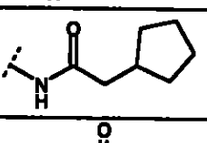
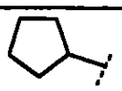
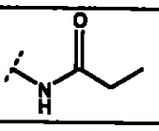
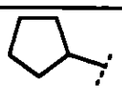
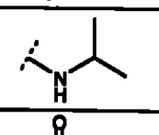
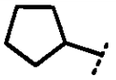
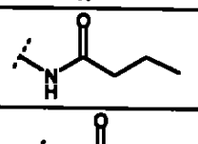
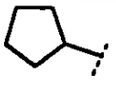
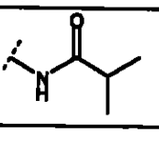
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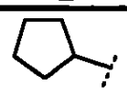
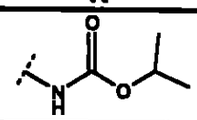
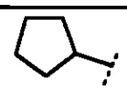
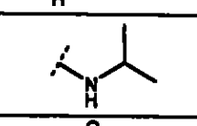
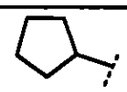
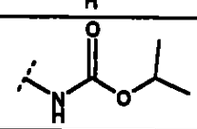
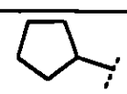
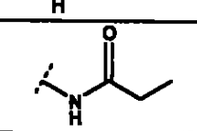
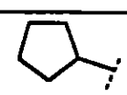
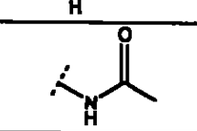
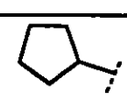
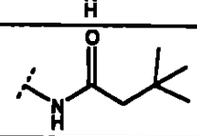
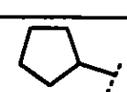
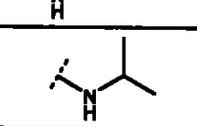
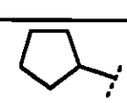
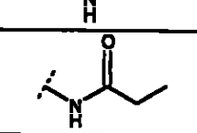
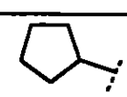
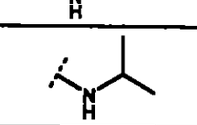
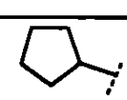
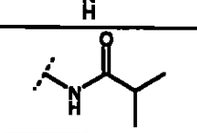
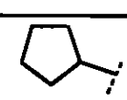
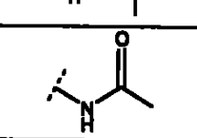
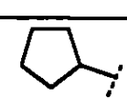
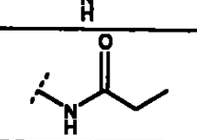
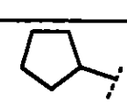
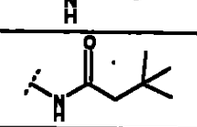
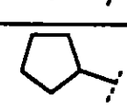
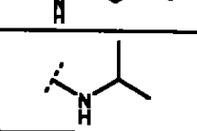
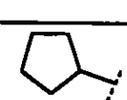
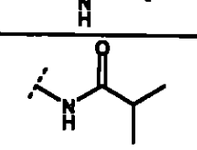
Comp.	B	L^0	L^1	R^2
1105		MeO-	CN	
1106		Br	MeO-	
1107		MeO-	CN	
1108		MeO-	Br	
1109		MeO	Br	
1110		MeO-	Br	
1111		MeO-	Br	
1112		MeO-	Br	
1113		MeO-	Br	
1114		MeO	Br	
1115		MeO-	Br	
1116		MeO	Br	
1117		MeO	Br	
1118		MeO	Br	
1119		MeO	Br	

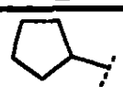
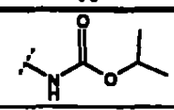
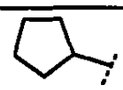
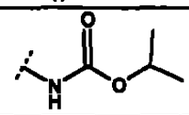
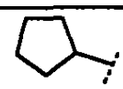
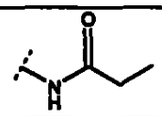
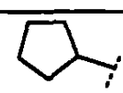
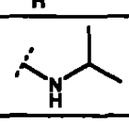
357

Comp.	B	L^0	L^1	R^2
1120		MeO	Br	
1121		MeO	Br	
1122		MeO	Br	
1123		MeO	CN	
1124		MeO	CN	
1125		MeO-	Cl	
1126		MeO-	Cl	
1127		MeO	Cl	
1128		MeO	Cl	
1129		MeO	Cl	
1130		MeO	Cl	
1131		MeO	Cl	
1132		MeO	Cl	
1133		MeO	Cl	
1134		MeO	Cl	

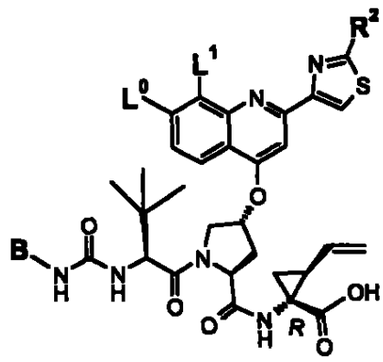
Comp.	B	L^0	L^1	R^2
1135		MeO	Cl	
1136		MeO	Cl	
1137		MeO	Cl	
1138		MeO	Cl	
1139		MeO	Cl	
1140		MeO	Cl	
1141		MeO	Cl	
1142		MeO	Cl	
1143		MeO	Cl	
1144		MeO	Cl	
1145		MeO	Cl	
1146		MeO	Cl	
1147		MeO	Cl	
1148		MeO	Cl	

Comp.	B	L^0	L^1	R^2
1149		MeO	Cl	
1150		MeO	Cl	
1151		MeO	Cl	
1152		MeO	Cl	
1153		MeO	Cl	
1154		MeO	Br	
1155		MeO	Br	
1156		MeO	Br	
1157		H	-SMe	
1158		H	-SMe	
1159		H	-SMe	
1160		H	-SMe	
1161		H	-SMe	
1162		H	-SMe	

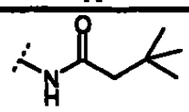
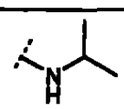
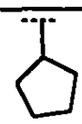
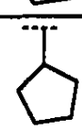
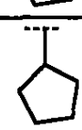
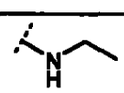
Comp.	B	L^0	L^1	R^2
1163		H	-SMe	
1164		H	$-CF_3$	
1165		H	$-CF_3$	
1166		H	$-CF_3$	
1167		Cl	Cl	
1168		Cl	Cl	
1169		Cl	Cl	
1170		Cl	Cl	
1171		H	$-SO_2Me$	
1172		H	$-SO_2Me$	
1173		H	Me-	
1174		H	Me-	
1175		H	Me-	
1176		H	Me-	
1177		H	Me-	

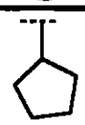
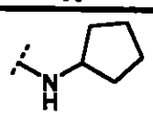
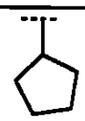
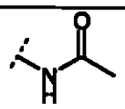
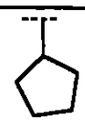
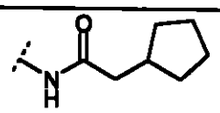
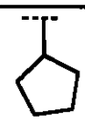
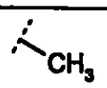
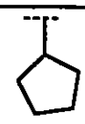
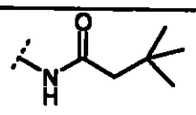
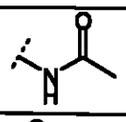
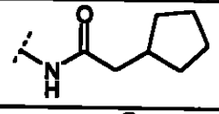
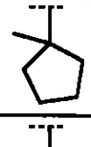
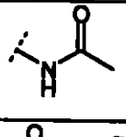
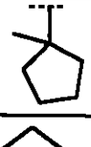
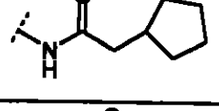
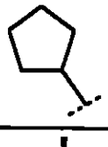
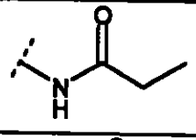
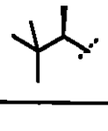
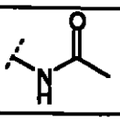
Comp.	B	L^0	L^1	R^2
1178		H	Me-	
1179		H	$-SO_2Me$	
1180		H	$-SO_2Me$	
1181		H	-OMe	

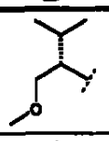
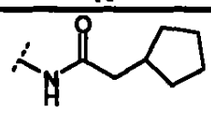
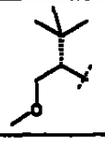
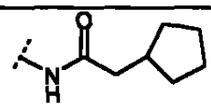
34. El compuesto de acuerdo con la reivindicación 1, de fórmula



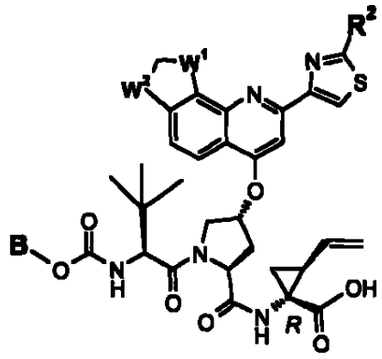
donde B, L^0, L^1 y R^2 se definen como en la siguiente tabla

Comp. #	B	L^0	L^1	R^2
2001		MeO-	Me-	
2002		MeO-	Me-	
2003		MeO-	Me-	
2004		MeO-	Me-	
2005		MeO-	Me-	

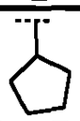
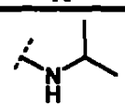
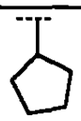
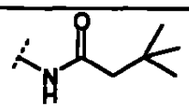
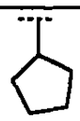
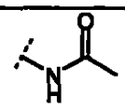
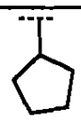
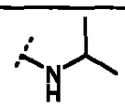
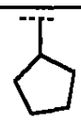
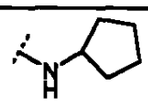
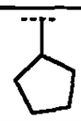
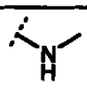
Comp. #	B	L^0	L^1	R^2
2006		MeO-	Me-	
2007		MeO-	Me-	
2008		MeO-	Me-	
2009		MeO-	Me-	
2010		MeO-	Me-	
2011		MeO-	Me-	
2012		MeO-	Me-	
2013		MeO-	Me-	
2014		MeO-	Me-	
2015		MeO-	Me-	
2016		MeO-	Me-	
2017		MeO-	Br-	
2018		MeO-	Me-	

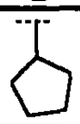
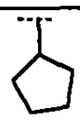
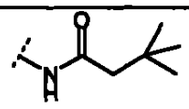
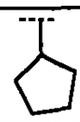
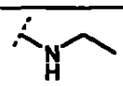
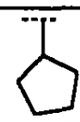
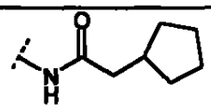
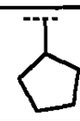
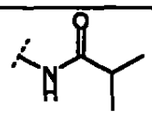
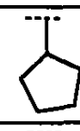
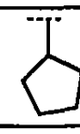
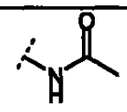
Comp. #	B	L^0	L^1	R^2
2019		MeO-	Me	
2020		MeO-	Me	

35. El compuesto de acuerdo con la reivindicación 1, de fórmula

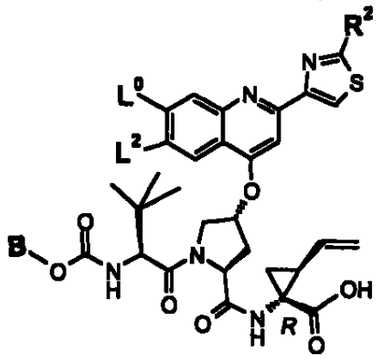


donde B, W^1, W^2 y R^2 se definen como en la siguiente tabla

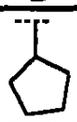
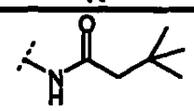
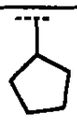
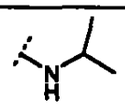
Comp. #	B	W^1	W^2	R^2
3001		-O-	-O-	
3002		-O-	-O-	
3003		-CH_2-	-O-	
3004		-CH_2-	-O-	
3005		-CH_2-	-O-	
3006		-CH_2-	-O-	

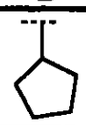
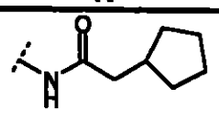
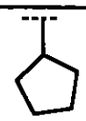
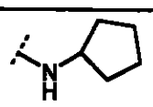
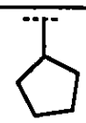
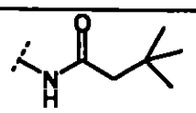
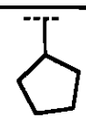
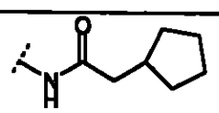
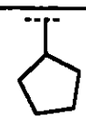
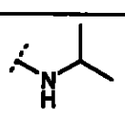
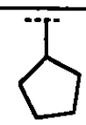
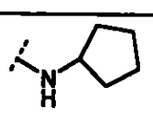
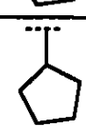
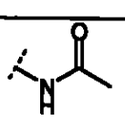
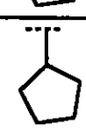
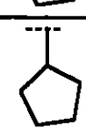
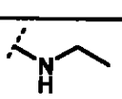
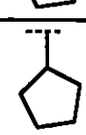
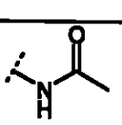
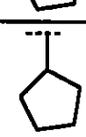
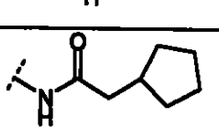
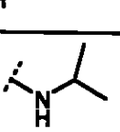
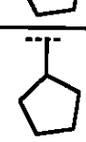
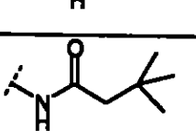
Comp. #	B	W^1	W^2	R^2
3007		-CH_2-	-O-	
3008		-CH_2-	-O-	
3009		-CH_2-	-O-	
3010		-CH_2-	-O-	
3011		-CH_2-	-CH_2-	
3012		-CH_2-	-CH_2-	
3013		-CH_2-	-CH_2-	

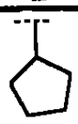
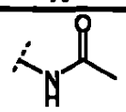
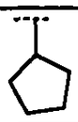
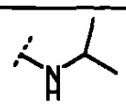
36. El compuesto de acuerdo con la reivindicación 1, de fórmula



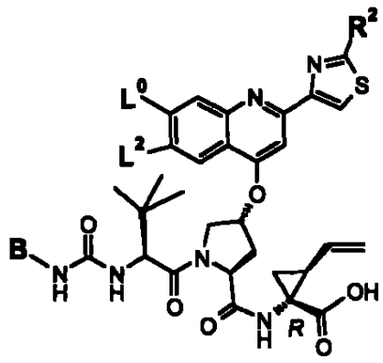
donde B, L^0, L^2 y R^2 se definen como en la siguiente tabla

Comp. #	B	L^0	L^2	R^2
4001		MeO-	Me-	
4002		MeO-	Me-	

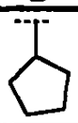
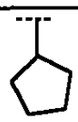
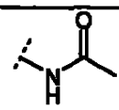
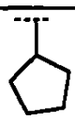
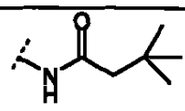
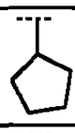
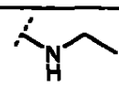
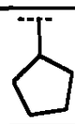
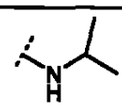
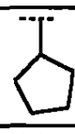
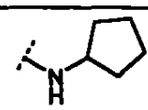
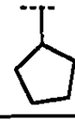
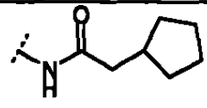
Comp. #	B	L^0	L^2	R^2
4003		MeO-	Me-	
4004		MeO-	Me-	
4005		Me_2N-	Me-	
4006		Me_2N-	Me-	
4007		Me_2N-	Me-	
4008		Me_2N-	Me-	
4009		MeO-	Me-	
4010		MeO-	Me-	
4011		MeO-	Me-	
4012		MeO-	MeO-	
4013		MeO-	MeO-	
4014		MeO-	MeO-	
4015		MeO-	MeO-	

Comp. #	B	L^0	L^2	R^2
4016		Me-	MeO-	
4017		Me-	MeO-	

37. El compuesto de acuerdo con la reivindicación 1, de fórmula

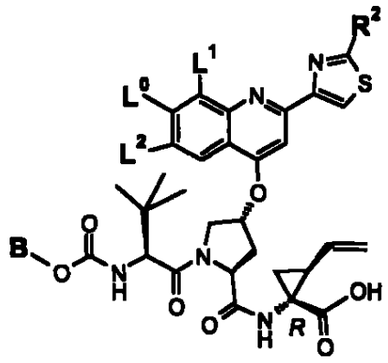


donde B, L^0, L^2 y R^2 se definen como en la siguiente tabla

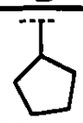
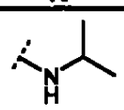
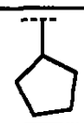
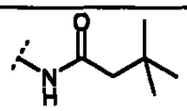
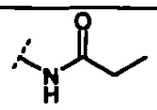
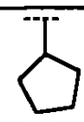
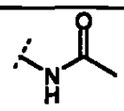
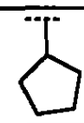
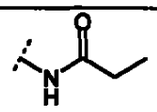
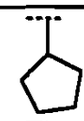
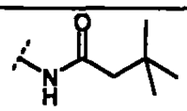
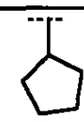
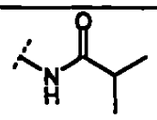
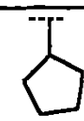
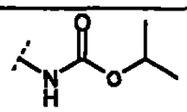
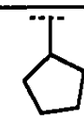
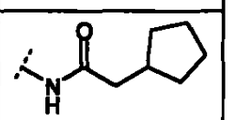
Comp. #	B	L^0	L^2	R^2
5001		MeO-	Me-	
5002		MeO-	Me-	
5003		MeO-	Me-	
5004		MeO-	Me-	
5005		MeO-	Me-	
5006		MeO-	Me-	
5007		MeO-	Me-	

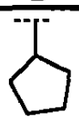
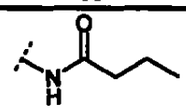
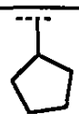
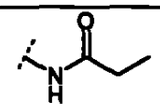
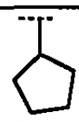
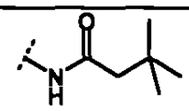
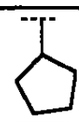
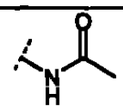
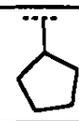
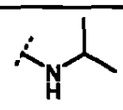
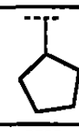
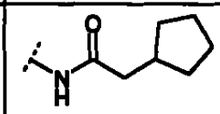
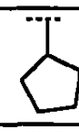
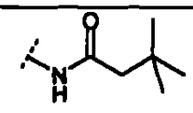
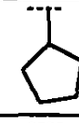
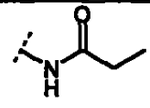
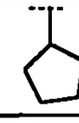
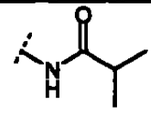
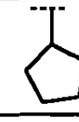
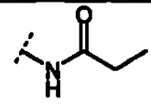
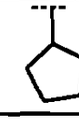
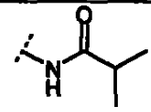
364
367

38. El compuesto de acuerdo con la reivindicación 1, de fórmula

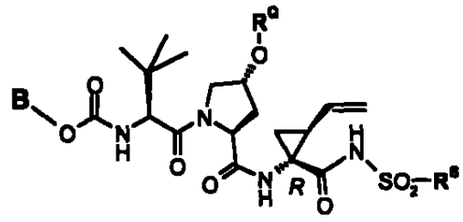


donde B, L^0, L^1, L^2 y R^2 se definen como en la siguiente tabla

Comp. #	B	L^2	L^0	L^1	R^2
6001		MeO-	H	Me	
6002		MeO-	H	Me	
6003		MeO-	H	Me	
6004		MeO-	H	Me	
6005		Me	H	Br	
6006		Me	H	Br	
6007		Me	H	Br	
6008		Me	H	Br	
6009		Me	H	Br	

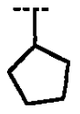
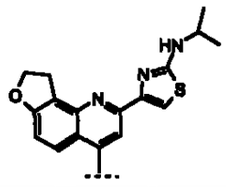
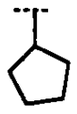
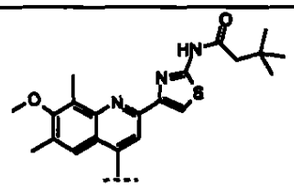
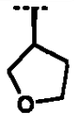
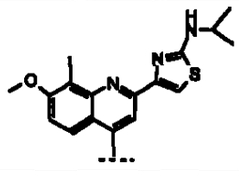
Comp. #	B	L^2	L^0	L^1	R^2
6010		Me	H	Br	
6011		Me	H	Me	
6012		Me	H	Me	
6013		Me	H	Me	
6014		Me	H	Me	
6015		Me	MeO-	Me	
6016		Me	MeO-	Me	
6017		Br	H	Br	
6018		Br	H	Br	
6019		Br	H	Cl	
6020		Br	H	Cl	

39. El compuesto de acuerdo con la reivindicación 1, de fórmula



366
369

donde B, R^Q y R^S se definen como en la siguiente tabla

Comp. #	B	R^Q	R^S
7001			
7002			
7003			

40. Una composición farmacéutica que comprende una cantidad anti-hepatitis C efectiva para combatir virus de un compuesto de fórmula I de acuerdo con una o más de las reivindicaciones 1 a 39 o una sal o éster aceptable para uso farmacéutico del mismo, en mezcla con un medio de vehículo o agente auxiliar aceptables para uso farmacéutico.

41. La composición farmacéutica de acuerdo con la reivindicación 40, que comprende además una cantidad terapéuticamente efectiva de al menos otro agente antiviral.

42. La composición farmacéutica de acuerdo con la reivindicación 41, donde dicho agente antiviral es ribavirin.

43. La composición farmacéutica de acuerdo con la reivindicación 41, donde dicho agente antiviral se selecciona de otro agente anti-VHC, un inhibidor de VIH, un inhibidor de VHA y un inhibidor de VHB.

44. La composición farmacéutica de acuerdo con la reivindicación 43, donde dicho otro agente anti-VHC se selecciona de agentes inmunomoduladores, otros inhibidores de proteasa NS3 del VHC, inhibidores de la polimerasa del VHC e inhibidores de otro blanco en el ciclo de vida del VHC.

45. La composición farmacéutica de acuerdo con la reivindicación 44, donde dicho agente inmunomodulador se selecciona de α-interferón y α-interferón pegilado.

46. La composición farmacéutica de acuerdo con la reivindicación 44, donde dicho inhibidor de otro blanco en el ciclo de vida del VHC se selecciona de inhibidores de: helicasa, proteasa NS2/3 y sitio interno de entrada del ribosoma (IRES).

47. Un método para el tratamiento o prevención de una infección viral de hepatitis C en un mamífero administrando al mamífero una cantidad anti-hepatitis C efectiva para combatir virus de un compuesto de fórmula I de acuerdo con una o más de las reivindicaciones 1 a 39, o una sal o éster aceptable para uso farmacéutico del mismo.

48. Un método para el tratamiento o prevención de una infección viral de hepatitis C en un mamífero administrando al mismo una cantidad anti-hepatitis C efectiva para combatir virus de un compuesto de fórmula I de acuerdo con una o más de las reivindicaciones 1 a 39, o una sal o éster aceptable para uso farmacéutico del mismo en combinación con al menos otro agente antiviral .

49. El método de acuerdo con la reivindicación 48, donde dicho agente antiviral es ribavirin.

50. El método de acuerdo con la reivindicación 48, donde dicho otro agente antiviral se selecciona de otro agente anti-VHC, un inhibidor de VIH, un inhibidor del VHA y un inhibidor de VHB.

51. El método de acuerdo con la reivindicación 50, donde dicho otro agente anti-VHC se selecciona de agentes inmunomoduladores, otros inhibidores de proteasa NS3 del VHC, inhibidores de la polimerasa del VHC e inhibidores de otro blanco en el ciclo de vida del VHC.

52. El método de acuerdo con la reivindicación 51, donde dicho agente inmunomodulador se selecciona de α-interferón y α-interferón pegilado.

53. El método de acuerdo con la reivindicación 51, donde dicho inhibidor de otro blanco en el ciclo de vida del VHC se selecciona de inhibidores de: helicasa, proteasa NS2/3 y sitio interno de entrada del ribosoma (IRES).

54. Uso de un compuesto de fórmula I, incluyendo una sal o éster aceptable para uso farmacéutico del mismo, de acuerdo con una o más de las reivindicaciones 1 a 39, para la fabricación de un medicamento para el tratamiento o prevención de infección viral de hepatitis C en un mamífero.

55. Un método para inhibir la replicación del virus de la hepatitis C exponiendo el virus a una cantidad inhibidora de la proteasa NS3 del virus de la hepatitis C del compuesto de fórmula (I) de acuerdo con una o más de las reivindicaciones 1 a 39, o una sal o éster aceptable para uso farmacéutico del mismo.

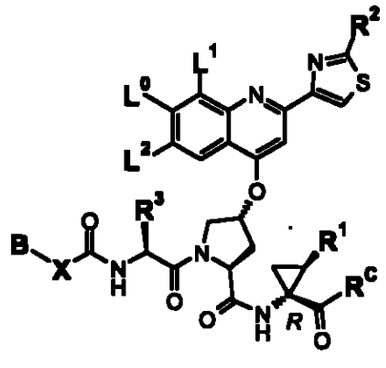
371

56. Un artículo de fabricación que comprende material de embalaje contenido en el mismo, que es una composición efectiva para el tratamiento de una infección por VHC o para inhibir la proteasa NS3 del VHC y el material de embalaje comprende un rótulo que indica que la composición se puede emplear para tratar la infección por el virus de la hepatitis C, y donde dicha composición comprende un compuesto de fórmula (I) de acuerdo con una o más de las reivindicaciones 1 a 39 o una sal o éster aceptable para uso farmacéutico del mismo.

369
372

RESUMEN

Compuestos de fórmula (I):



(I)

donde B, X, R^3, L^0, L^1, L^2, R^2, R^1 y R^C se definen en la presente. Los compuestos son útiles como inhibidores de proteasa NS3 del VHC para el tratamiento de la infección por el virus de la hepatitis C.

370
373

LISTADO DE SECUENCIAS

<110> BOEHRINGER INGELHEIM INTERNATIONAl GmbH

<120> COMPUESTOS INHIBIDORES DE HEPATITIS C

<130> 13/119 WO

<140> 60/472709
<141> 2003-05-21

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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.
13/119WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA2004/000750	19/05/2004	21/05/2003

Applicant

BOEHRINGER INGELHEIM INTERNATIONAL GMBH

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 the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. [X] Certain claims were found unsearchable (See Box II).

3. [ ] Unity of invention is lacking (see Box III).

4. With regard to the title,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regards to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] as selected by this Authority, because the applicant failed to suggest a figure.

[ ] as selected by this Authority, because this figure better characterizes the invention.

b. [ ] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA2004/000750

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/04 C07K5/08 A61P31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07K 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, PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/09543 A (BOEHRINGER INGELHEIM CA LTD ; GOUDREAU NATHALIE (CA); GHIRO ELISE (CA)) 24 February 2000 (2000-02-24) cited in the application page 1, line 3 - page 1, line 8; claims; examples 333,334,616,628-630,709,711,713,714,717,719,722	1-56

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 September 2004	15/09/2004

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	Schmid, A

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2004/000750

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 47-55 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

International Application No
PCT/CA2004/000750

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0009543 A	24-02-2000	AU 769738 B2	05-02-2004
		AU 5273199 A	06-03-2000
		BG 105232 A	30-11-2001
		BR 9913646 A	05-06-2001
		CA 2338946 A1	24-02-2000
		CA 2445938 A1	24-02-2000
		WO 0009543 A2	24-02-2000
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		EA 3906 B1	30-10-2003
		EE 200100081 A	15-08-2002
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		HU 0105144 A2	29-04-2002
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		TR 200100432 T2	21-09-2001
		TR 200200129 T2	21-06-2002
		US 6534523 B1	18-03-2003
		US 6323180 B1	27-11-2001
		US 6268207 B1	31-07-2001
		US 6329379 B1	11-12-2001
		US 6329417 B1	11-12-2001
		US 2002016442 A1	07-02-2002
		US 2002037998 A1	28-03-2002

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/CA2004/000750	19.05.2004	21.05.2003

International Patent Classification (IPC) or both national classification and IPC
C07D417/04, C07K5/08, A61P31/00

Applicant
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

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"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified 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 three 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:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Schmid, A

Telephone No. +49 89 2399-8591

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 field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

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:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable 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:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 47-55

because:

☒ the said international application, or the said claims Nos. 47-55 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

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	1-56
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-56
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-46,56
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1) Claims 47-55 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) Reference is made to the following document/s/:
   D1: WO 00/09543 A (BOEHRINGER INGELHEIM CA LTD ; GOUDREAU NATHALIE (CA); GHIRO ELISE (CA)) 24 February 2000 (2000-02-24)

   Document D1, which is considered to represent the most relevant state of the art, discloses in the examples as mentioned in the search report compounds which differs from the present compounds in a carboxy or substituted carboxy group attached to the cyclopropyl residue.

   Accordingly, the subject-matter of the present claims therefore new (Article 33(2) PCT).

2) A skilled person looking for alternative hepapitis C inhibitors would surely not try to remove just the carboxyl group found to be essential for the known compounds with a reasonable expectation of success to obtain compounds with the desired properties as could be proved by the applicant on pages 110 - 112.

   Therefore the present subject-matter also involves an inventive step with regard Article 33(3) PCT.

3) For the assessment of the present claims 47-55 on the question whether they are

industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

382

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below: 385

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference: 13/119WO
International application No.: PCT/CA2004/000750	International filing date *(day/month/year)*: 19/05/2004	(Earliest) Priority date *(day/month/year)*: 21/05/2003
Title of invention: HEPATITIS C INHIBITOR COMPOUNDS		

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	Telephone No. / Facsimile No. / Telegraphic No. / Applicant's registration No. with the Office
BOEHRINGER INGELHEIM INTERNATIONAL GmbH Binger Strasse 173 55118 Ingelheim Germany	Telephone No.: 011 49 6132 77 2326 Facsimile No.: 011 49 6132 77 3000 Telegraphic No.: Applicant's registration No. with the Office:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
DE	DE

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BOEHRINGER INGELHEIM PHARMA GmbH & CO KG
Binger Strasse 173
55118 Ingelheim
Germany

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
DE	DE

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

LLINAS-BRUNET, Montse
2100 Cunard Street
Laval, Québec
H7S 2G5
CANADA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CA	CA

☒ Further applicants are indicated on a continuation sheet.

International application No.
PCT/CA2004/000750

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BAILEY, Murray, D.
2100 Cunard Street
Laval, Québec
H7S 2G5
CANADA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CA	CA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BHARDWAJ, Punit
2100 Cunard Street
Laval, Québec
H7S 2G5
CANADA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
IN	CA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BORDELEAU, Josée
2100 Cunard Street
Laval, Québec
H7S 2G5
CANADA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CA	CA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

FORGIONE, Pasquale
2100 Cunard Street
Laval, Québec
H7S 2G5
CANADA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CA	

☒ Further applicants are indicated on another continuation sheet.

International application No.
PCT/CA2004/000750

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GHIRO, Elise
2100 Cunard Street
Laval, Québec
H7S 2G5
CANADA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CA	CA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GORYS, Vida
2100 Cunard Street
Laval, Québec
H7S 2G5
CANADA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CA	CA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GOUDREAU, Nathalie
2100 Cunard Street
Laval, Québec
H7S 2G5
CANADA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CA	CA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GOULET, Sylvie
2100 Cunard Street
Laval, Québec
H7S 2G5
CANADA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CA	

☒ Further applicants are indicated on another continuation sheet.

Sheet No. 4.

International application No.
PCT/CA2004/000750

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HALMOS, Teddy
2100 Cunard Street
Laval, Québec
H7S 2G5
CANADA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CA	CA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RANCOURT, Jean
2100 Cunard Street
Laval, Québec
H7S 2G5
CANADA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CA	CA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

Sheet No. 5

International application No.
PCT/CA2004/000750

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

OGILVY RENAULT / Victoria Heppell, Agent
c/o BOEHRINGER INGELHEIM (CANADA) LTD.
2100 Cunard Street
Laval, Québec
H7S 2G5
CANADA

Telephone No.
(450) 682-4640

Facsimile No.
(450) 682-8434

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☒ as originally filed
☐ as amended under Article 34

the claims ☒ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☒ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of the applicable time limit under Rule 69.1(d).

4. ☐ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54*bis*.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☐ which is the language of publication of the international application.

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

International application No.
PCT/CA2004/000750

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☐ tables in computer readable form related to a sequence listing
8. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Victoria Heppell

Ogilvy Renault
Victoria Heppell, registration no. 11270

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
   ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.
6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54*bis*.1(a) and item 7 or 8, below, does not apply.
7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54*bis*.1(a) as extended by virtue of Rule 80.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54*bis*.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 13/119WO	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/CA2004/000750	International filing date *(day/month/year)* 19.05.2004	Priority date *(day/month/year)* 21.05.2003
International Patent Classification (IPC) or national classification and IPC C07D417/04, C07K5/08, A61P31/00		
Applicant BOEHRINGER INGELHEIM INTERNATIONAL GMBH et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.11.2004	04.04.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Telephone No. +49 89 2399-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No. PCT/CA2004/000750

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-141 as originally filed

   Claims, Numbers

   1-56 as originally filed

   Drawings, Sheets

   1/1 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT N PATENTABILITY

International application No. PCT/CA2004/000750

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 47-55

because:

☒ the said international application, or the said claims Nos. 47-55 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CA2004/000750

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-56
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-56
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-46,56
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1) Claims 47-55 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) Reference is made to the following document/s/:
   D1: WO 00/09543 A (BOEHRINGER INGELHEIM CA LTD ; GOUDREAU NATHALIE (CA); GHIRO ELISE (CA)) 24 February 2000 (2000-02-24)

   Document D1, which is considered to represent the most relevant state of the art, discloses in the examples as mentioned in the search report compounds which differs from the present compounds in a carboxy or substituted carboxy group attached to the cyclopropyl residue.

   Accordingly, the subject-matter of the present claims therefore new (Article 33(2) PCT).

2) A skilled person looking for alternative hepapitis C inhibitors would surely not try to remove just the carboxyl group found to be essential for the known compounds with a reasonable expectation of success to obtain compounds with the desired properties as could be proved by the applicant on pages 110 - 112.

   Therefore the present subject-matter also involves an inventive step with regard Article 33(3) PCT.

3) For the assessment of the present claims 47-55 on the question whether they are

industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Industria y Comercio

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS

Royal Technologies S.A.

Item		Expediente No 05-117348. No de unidades	No de Folio √
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA X0	1	✓
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones:

CONTIENE ANEXO FINAL

346
348

SUPERINTENDENCIA Y COMERCIO
Radicacion : 05117348 [illegible] Folios: 397
Fecha (AMD): 2005-11-18 17:35:08
Tramite : 411 PCT-PRIORI 379 FASE MACI 411 PRESENTAC
Procedencia: 2050 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 87,641
FECHA : NOVIEMBRE 15 DE 2005

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	27496710	15/11/2005	56,100,000.00

***** C O N C E P T O *****

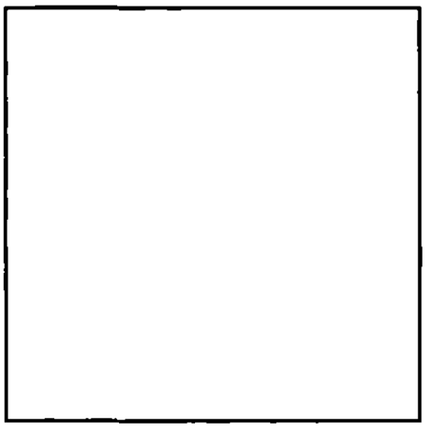
CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	443,000.00
		TOTAL : $	443,000.00

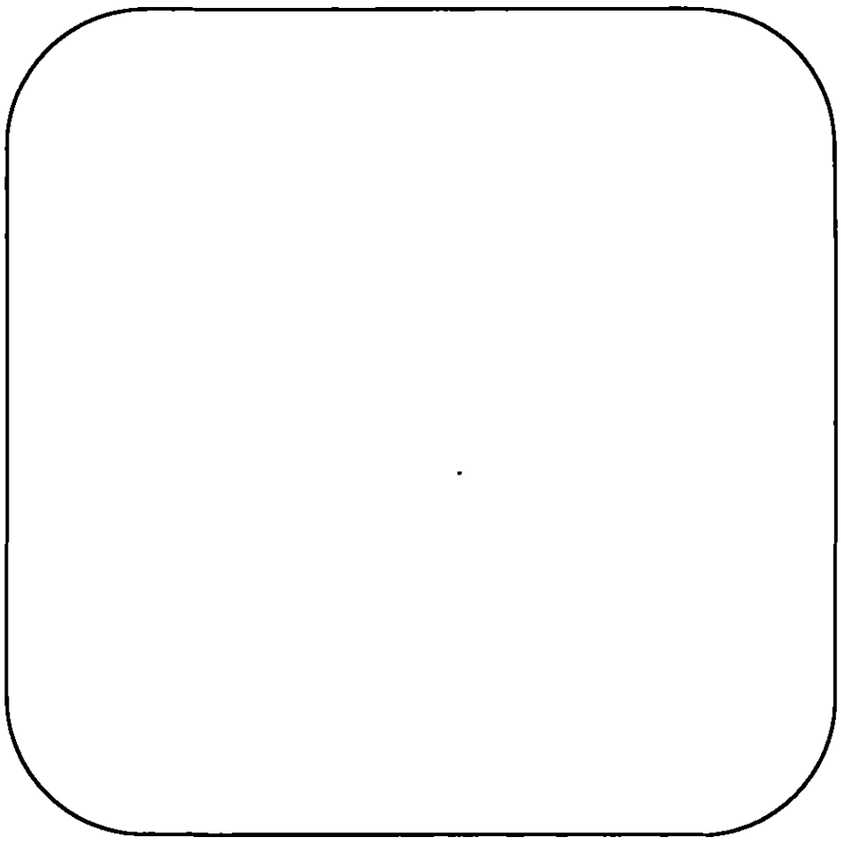
SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

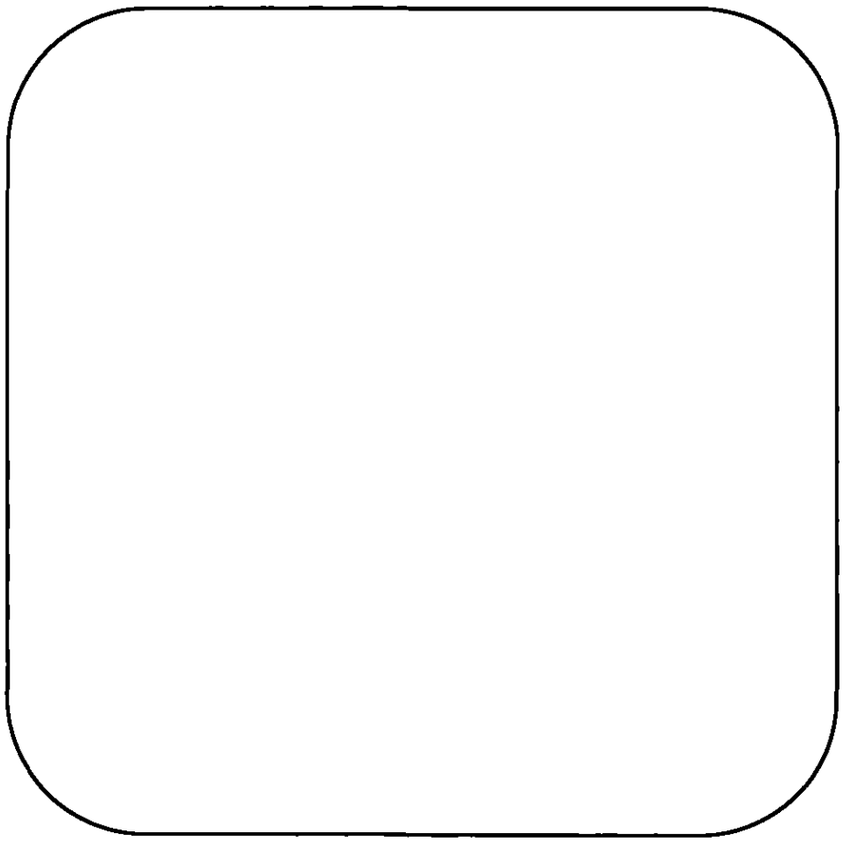
RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Cdo 0925-891-0301







399
400

SUPERINTENDENCIA Y COMERCIO
Radicacion 02-11/348 [illegible] Folios: 39/
Fecha (MM/DD) 2002-11-18 17:25:08
Tramite 011 PCT-PATENT 379 FINAL MAIL 411 PRESENTAL
Procedencia 2400 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

		USUARIO	RADICADOR
PATENTE DE INVENCIÓN	MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente		( )	( )
- Datos de identificacion del solicitante o de la persona que se presenta la solicitud.		( )	( )
- Descripción de la invención		( )	( )
- Dibujos de ser estos pertinentes.		( )	( )
- Comprobante de Pago de las tasas establecidas.			
COMPLETA	( )	INCOMPLETA ( )	( )
DISEÑO INDUSTRIAL ( )			
- Indicación de que se solicita el registro de Diseño Industrial		( )	( )
- Datos de identificación del solicitante o de la persona que presenta		( )	( )
- la solicitud			
- Representación gráfica o fotografica 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 solicita el registro de un Esquema de trazado		( )	( )
- Datos de identificación del solcitante o de la persona que presenta La solicitud		( )	( )
Representación gráfica del esquema de trazado		( )	( )
Comprobante de pago de las tasas establecidas		( )	( )
COMPLETA		INCOMPLETA ( )	( )

Firma Responsable

Fecha